NEW THERAPEUTIC OPTION AND INSIGHTS INTO THE IMPACT OF SYMPTOM SEVERITY ON QUALITY OF LIFE IN WOMEN WITH INTERSTITIAL CYSTITIS

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Background: Interstitial Cystitis (IC) is a poorly understood condition of urinary bladder characterized by pelvic pain, urinary frequency, urgency and nocturia in the absence of other obvious pathology. The public health significance of IC is related to its profound impact on patients' physical and emotional Quality of Life (QOL). The actual prevalence rate is unknown, and estimates range widely from 67/100,000 to 575/100,000. The majority of IC cases are females in the midlife age. This research addressed 1) the extent to which socio-demographic and clinical factors affect both symptom severity and QOL in IC patients, 2) the impact of symptom severity on QOL and 3) the efficacy of a combination of oral and intravesical Pentosan Polysulfate Sodium (PPS) as a new therapeutic option for IC. **Methods:** Forty one women with IC (age 20-71 years) were studied. Demographic, reproductive and clinical characteristics as well as QOL measures were evaluated in a cross-sectional design to assess the first two aims. To examine the third aim, participants were randomized to receive either a combination of oral plus intravesical PPS (treatment group) or oral PPS plus intravesical placebo (placebo group) in a clinical trial design. The main outcomes were the changes in subjective and objective measures of symptom severity, QOL and sexual functions. **Results**: Unmarried patients reported more severe symptoms compared to married patients. Being unemployed, obese, currently unmarried

and never pregnant were associated with a decrement in at least one QOL domain. Moreover, symptom severity was associated with worse QOL on 4 domains, ($p<0.05$). On the other hand, the results from the clinical trial showed a greater significant reduction in symptom severity among the treatment group compared to the placebo group (46% reduction vs. 24% reduction respectively, $p=0.04$) and significant improvement in all QOL domains in the treatment group compared to the baseline ($p<0.05$). **Conclusion:** Being unmarried and symptom severity are important factors that may disturb the QOL in IC patients. Moreover, the use of intravesical PPS simultaneously with oral PPS is an effective therapeutic option. The findings of this research will open a new option for IC patients to reduce their devastating symptoms and to improve their quality of life.

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PREFACE

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1.0 INTRODUCTION

1.1 RATIONALE AND SIGNIFICANCE OF PUBLIC HEALTH

Interstitial Cystitis (IC) is a chronic, severely debilitating disease of the urinary bladder. It affects the internal bladder wall and eventually disables its function. When a subject complains of urinary urgency, frequency, and/or pelvic/perineal pain in the absence of any identifiable cause, such as bacterial infection or carcinoma, a diagnosis of IC is likely. [1] Despite the long-standing recognition of interstitial cystitis, there are still no definitive answers to vital issues, such as the etiology, prevalence, diagnostic definition and therapy.

It was thought that IC was a very rare event; however, ongoing prevalence studies demonstrate the otherwise. Until 1999 in the United States (US) the prevalence rate ranged from 37 to 67 per 100,000. [2, 3] Since then, the prevalence of IC has been estimated at 575 to 12,600 per 100,000. [4] Such a dramatic increase in prevalence has also been observed in Europe, as the estimated prevalence rate currently ranges from 300 to 680 per 100,000 [5, 6] compared to 10.6 per 100,000 in 1975.[7] The explanations for this huge gap in estimating IC prevalence rate can be related to the absence of single diagnostic criterion and to the use of different methods in estimating the rate. An increasing awareness about IC among both patients and health workers might be another explanation that could lead to higher prevalence estimates. Moreover, earlier studies were based on already established diagnosed IC cases rather than evaluating the

prevalence of symptoms of IC in a general population, which may have underestimated the true prevalence rate, as both mild and early cases may not have been included in the earlier estimations.

IC affects women and men of any age or race, including children and the elderly. The majority of IC patients are white, [8, 9] female, [10] and premenopausal with a median age at diagnosis of 42-46 years. [3] Although IC can affect both men and women, it has been predominantly seen in women (historical female to male ratio is 9:1). [11] A recent study reports, however, that men currently account for higher proportion of IC patients (current female to male ratio is 5:1) compared to earlier estimates. [12] Whether this new estimate is correct, is still unclear. Well-designed epidemiological studies are necessary to determine the epidemiology of IC, which affects a wide variety of individuals and impairs their health related quality of life, as well as the magnitude of the problem.

Importantly, IC might have a significant influence on the national economy. For instance, the average cost of treating an IC patient is over $7,500 a year, based on the INGENIX (Eden Prairie, Minnesota) claims-based dataset, the economic impact in the United States is estimated at approximately $3 billion per year. [13]

The impact of IC on patients' Health Related Quality of Life (HRQL) is much more pervasive. It impairs physical, social, and emotional functions and well-being of the patients. It is a serious health problem that leaves many patients unable to cope with basic daily functions. Patient suffers 5 to 7 years on average and often visits as many as 8 physicians before the correct diagnosis is made. [2] IC patients often need to void more than 60 times a day, and experience severe pelvic pain and dyspareunia (pain with sexual activity), which can isolate them from social life, family relationships, work and can lead severe disability and depression. [14-16] IC

patients are 3 to 4 times more likely to report thoughts of suicide, and 5 times more likely to be treated for emotional problems as the general population. [2] Approximately, 30% of the patients reported that employment is impossible due to the severity of IC symptoms. [17, 18] Furthermore, an average of 50% of the patients are unable to work full time, and those who do work earn approximately $3.41 or less per hour. [19]

Several limitations were identified in earlier studies that assessed the impact of IC on patient's quality of life. Most of the findings originate from studies using specific questions rather than standardized instruments to assess HRQL. [2, 4, 6, 18, 20] In fact, there are few reports available that use universally validated instruments, [17, 21, 22] such as the SF-36 survey instrument. The limited existing studies indicate that IC patients reported a poorer HRQL than controls across all SF-36 domains (physical functioning, role limitations related to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health). [22] Moreover, women with IC experienced greater decrements in HRQL compared to those with hypertension, but not compared to those with rheumatoid arthritis. [21]

A first step towards improving the lives of IC patients is to learn more about how IC affects HRQL. It is crucial to determine the factors that are associated with the severity of symptoms and the impairments in HRQL in IC patients. Identifying these factors will enable us to investigate if symptom severity has significant independent effect on the HRQL in IC patients after adjusting for such factors. Moreover, it is of great interest to examine which domain of HRQL is most affected by the severity of symptoms. Also, it is important to identify which specific symptom (pain, urgency, urinary frequency, and/or nocturia) affects HRQL the greatest.

Answering all these questions will help to modify treatment options to focus on the main impaired domain of HRQL and the most devastating symptom.

Two studies have attempted to answer some of the above questions. Unfortunately, several limitations exist. [17, 22] Investigators in both studies used non validated, self-reported measures to classify the severity of pain, urgency and urinary frequency symptoms as mild, moderate, and severe without the use of any objective verification of disease severity. This, in fact, may be introduced misclassification bias and uncertainty into the classification of symptom severity. Currently there are two important standardized and validated instruments: O'Leary-Sant Interstitial Cystitis Symptom and Problem Index, and Pelvic Pain and Urgency/ Frequency Patient Symptom Scale (PUF) that have been created to either evaluate the development of established IC [23] or as a screening test of IC. [24] Both instruments can be used to classify the severity of IC symptoms in a more objective manner. Another limitation to be addressed; both studies did not identify the important covariates that may confound the association between symptom severity and HRQL. Furthermore, only the distributions of answers to selected items on the SF-36 questionnaire were reported in one of the two studies. [17] Given the above limitations, further studies are needed to more definitively evaluate the association between symptom severity and HRQL.

A second step in improving lives of IC patients is to determine the best treatment for the relief of IC symptoms. Several possible etiologies have been suggested for IC; for each etiological theory there are different treatment options tailored to the postulated mechanism of action. Because there is no single confirmed etiology of IC, treatment is currently prescribed on the basis of a patient's symptomatology. A total of 183 different therapeutic regimens currently

exist for IC; including cystoscopy and hydrodistension, amitriptyline, phenazopyridine, special diet and intravesical heparin. [25]

The bladder permeability theory is one of the most widely studied as a possible etiology of IC. In brief, it states that the epithelial lining of the bladder (the glycosaminoglycan or GAG layer) is deficient in IC patients, thus urine components can penetrate and irritate the bladder. [26] Using substances with the same chemical nature of the GAG layer can replace the defective glycosaminoglycan in the bladder epithelium, and relieve symptoms. Pentosan Polysulfate Sodium (PPS) (Elmiron®) is one of the main treatment options based on bladder permeability theory. PPS remains the only oral therapy for IC approved by the Food and Drug Administration (FDA). [27, 28] Its efficacy and safety as an oral treatment for IC have been documented in several randomized double blind clinical trials. [27-33] However, one important drawback of PPS as an oral treatment is the low amount of active drug reaching the bladder (only 1-3% of the oral dose is excreted in the urine) resulting in a long lag time before clinical improvement is expected. Approximately 3 to 6 months is usually required before symptoms improve. [34] If the oral therapy is not sufficient to improve symptoms, intravesical therapy (the direct instillation of medication into the bladder using a catheter inserted through the urethra) is an alternative. It is one of the mainstays for the treatment of interstitial cystitis. The main advantages of intravesical therapy over oral therapy include high concentration of the drug in the bladder, short dwell time in the bladder, lack of significant side effects and non-interference with renal or liver metabolism. [35] Currently, dimethyl sulfoxide (Rimso-50^{TM}) is the only intravesical therapy approved by FDA.

Because the efficacy of PPS as an oral therapy (response rate ranges from 27-42%) [36] is well-documented, [28-33] and the only important pitfall is related to its pharmacokinetic properties (only 3% of the oral dose reaches the bladder), researchers are now considering the use of PPS as

an intravesical therapy to overcome this drawback and to achieve higher efficacy. To the best of our knowledge, only one small randomized blind clinical trial assessed the efficacy of intravesical PPS compared to placebo. [37] This trial was conducted in the Netherlands and included 20 IC patients (10 patients per arm). Participants were randomized to receive either intravesical PPS (300 mg in 50 ml of 0.9% sodium chloride) applied twice a week for 3 months or a placebo. Significant symptomatic relief was reported in 4 of those who received the intravesical PPS compared to 2 of those receiving placebo. Furthermore, a significant increase in bladder capacity was reported among patients treated with PPS compared to placebo. However, one important limitation was that the intravesical instillation of PPS was done by a specialist only one time; after the first treatment, the patients had to perform self-catheterization. This self-catheterization might affect the validity and the repeatability of results, since patients may not perform all required instillations properly due to a lack of supervision.

In a small study in the US, Davis et al. [38] evaluated the effect of direct bladder application of PPS on the symptoms of IC among 31 female IC patients. The O'Leary-Sant's IC Symptom Problem Questionnaire, Parsons' Patient Symptom Scale (PUF), and the IC Network pain index were used to assess the efficacy of intravesical PPS. After receiving 5 instillations of PPS over a period of 21 months, participants reported 39.43% reduction in average pain score and 15% or more reduction in all the other three assessment scale scores.

Although the substantial effect of IC on HRQL is well recognized, very few clinical trials that assessed the efficacy of oral PPS considered quality of life one of its endpoints. All the studies focused on symptoms as primary endpoint. The present study is the first, randomized double blind clinical trial in the US that tests the efficacy of intravesical instillation of PPS in the

bladder, and uses HRQL as well as symptom severity as main outcomes. The following section specifies the main aims of the current study.

1.2 SPECIFIC AIMS

The following specific aims were addressed in this study:

1) To determine to what extent socio-demographic, lifestyle, reproductive and clinical factors are associated with symptom severity and impairment in HRQL in women diagnosed with IC.

We **hypothesize** that age, education, smoking history, menopausal status, and co-morbid conditions will be associated with symptom severity, and that the same factors, with the exception of smoking history, will also be associated with impairment in HRQL in women diagnosed with IC.

2) To determine if symptom severity is correlated with impairment in all HRQL domains after adjusting for confounders that will be identified from assessing the Specific Aim 1 of this study.

We **hypothesize** that symptom severity will be associated with impairment in physical function, social function and mental health domains of HRQL and that these associations will not be significantly altered after adjusting for lifestyle and socio-demographic factors.

3) To determine which symptom (pain, urinary frequency, nocturia and/or urgency) is most likely to impair IC patients' HRQL represented by Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36 instrument.

We **hypothesize** that there will be variability in the effect of each symptom on PCS and MCS scales, and that pain will be the symptom most likely to impair both summary components.

4) To determine if the intravesical instillation of PPS plus the administration of oral PPS will reduce symptom severity more than oral PPS plus intravesical placebo at the following endpoints: week 6, week 12, and/or week 18 of the trial.

We **hypothesize** that the use of both intravesical PPS and oral PPS for the first 6 weeks of the trial will improve IC symptoms significantly more than the use of oral PPS and intravesical placebo.

5) To determine which symptom (pain, urgency, nocturia and/or urinary frequency) is most likely to be improved as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at the following endpoints: week 6, week 12, and/or week 18 of the trial.

We **hypothesize** that pain will be the most improved symptom as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at each endpoint.

6) To determine if the proportion of responders (defined by those who reported any improvement through patient global assessment instrument) is significantly more among those who received both intravesical PPS and oral PPS (treatment group) in comparison to those who received intravesical placebo and oral PPS (placebo group) by the end of the study (at week 18).

We **hypothesize** that the proportion of responders will be significantly more among the treatment group compared to the placebo group at week 18 of the study.

7) To test if the intravesical instillation of PPS plus the administration of oral PPS will improve IC patients' HRQL represented by Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36 more than intravesical placebo plus oral PPS at week 4 and/or at the end of the trial (at week 18).

We **hypothesize** that the use of both intravesical PPS and oral PPS will improve HRQL in IC patients significantly more than the use of intravesical placebo plus oral PPS at both endpoints.

8) To determine which domain of HRQL is most likely to be improved as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at week 4 and/or at the end of the trial (at week 18).

We **hypothesize** that the use of either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS will not have the same improvement effect on all HRQL domains at both endpoints, and that administering intravesical PPS plus oral PPS will significantly improve all HRQL domains by the end of the trial.

9) To determine if the administration of both intravesical PPS and oral PPS will improve sexual function more than intravesical placebo and oral PPS at week 4 and/or at the end of the trial (at week 18).

We **hypothesize** that the use of both intravesical PPS and oral PPS will improve sexual function of IC patients more than the use of intravesical placebo and oral PPS at both endpoints.

2.0 GENERAL BACKGROUND AND LITERATURE REVIEW

2.1 HISTORICAL BACKGROUND

Interstitial Cystitis (IC), or as it is called today, Painful Bladder Syndrome (PBS), has been a relatively poorly recognized condition. Its etiology has remained obscure at least partly because of the lack of research on the disorder as well as a precise definition and diagnosis of the disease.

Historically, IC has been known since 1836. [39] At that time, IC was described as a spontaneous rupture of the urinary bladder secondary to ulceration. Later, Skene defined the term IC as the end stage of a disease that attacks the bladder. [40] In 1907, Nitze described IC as a condition of the bladder in which the frequency of micturation, pain, and mucosal ulceration are the most important features. [41] The concerns about IC have received much attention since Hunner associated IC with a rare type of bladder ulcer known as Hunner's ulcer and defined as a reddened area of the bladder wall that can be found on cystoscopy. [42] Unfortunately, this discovery led people to think that the disease might be focal and not a pancystitis (cystitis involving the entire thickness of the wall of the urinary bladder) even when in fact it is, and it also led physicians to look for an ulcer at cystoscopy to confirm the diagnosis of IC. [43] Later, new descriptive terms appeared and it became clear that Hunner ulceration is not the only feature of the disease.

2.2 CLINICAL PRESENTATION OF IC

2.2.1 Definition and Classification

Given the fact that there is no single theory that exhaustively explains the etiology of IC, several definitions were suggested. IC is defined as a chronic disease or syndrome characterized by the symptoms of urinary frequency, urgency, or pelvic pain in any combination in the absence of another well defined cause (Urinary tract infection or bladder cancer). [44] Pathoanatomically, IC is defined by an elevation of mast cell count in the detrusor muscle to more than 28 mast cell/mm^2. [45, 46, 47] Holm-Bentzen et al., define IC to include all the following: 1) chronic cystitis symptoms, including suprapubic pain, for at least one year, 2) sterile and cytological normal urine, 3) most often, but not necessarily, either an abnormal cystoscopy before distension or a petechial bleeding after distension, 4) an elevated mast cell count in the detrusor muscle. [48]

Based on cystoscopic findings, IC can be classified into two different types; either ulcerative (classic) or non-ulcerative (early). The classic type is characterized by the presence of granulation tissue; usually about 94% of classic cases have granulation. [49] On the other hand, the so-called strawberry-like hemorrhages (known as glomerulations) are seen in the early type. [49] In fact, the early type is the most common; approximately 90% of IC patients are classified as non-ulcerative cases. [9] Studies showed that patients with the classic type have a smaller bladder capacity (less than 450 ml) compared to patients with the early type. Another difference between the two types is the concentration of mononuclear cells (present in the mucosa) that represent the degree of inflammation. Patients with the classic type have higher mononuclear concentration compared to early type patients. [49]

2.2.2 Symptoms

The most prevalent symptoms of IC are urinary frequency, urgency, suprapubic and pelvic or perineal pain. The pain can occur in the lower abdomen, inguinal area, labia, vaginal-perineal region, lower back or medial aspect of the thighs, and its severity is not affected by filling or emptying the bladder. [44] The urgency is one of the most devastating symptoms. In some severe cases a patient may need to urinate over 60 times a day and to void up to 20 times during the night. [45]

Interestingly, most women report an increase of pelvic pain one week prior to menses; some women experience dysmenorrhea. Sexual intimacy was found to be associated with IC pain; the pain occurs before, during and/or after sexual intercourse in both women and men. Symptoms may also be exacerbated by specific foods, beverages, physical or emotional stress.[44]

2.2.3 Etiology

The etiology of IC is still not clear. Several theories have been postulated; however, none of them can stand alone. In 1986, Messing reviewed all the existing theories about the pathology and etiology of IC. These theories included infection, toxic agents in the urine, genetic or endocrinologic deficiencies, lymphatic or vascular obstruction, neurogenic, autoimmune causes and psychiatric causes. [50] In fact, there is a general agreement that IC etiology is multifactorial and that we are dealing with a syndrome, not just a single disease. [51] Major theories are presented in the following sections.

2.2.3.1 Epithelial Dysfunction Theory (Leaky Bladder Theory)

The mucous surface coat lining the urothelium, with its content of glycosaminoglycan (GAG), is thought of as playing an important protective role for the bladder wall. [26] There are seven major classes of GAG (called mucopolysaccharides): chondroitin 4- and 6-sulfate, dermatan sulfate, keratan sulfate, heparan sulfate, hyalouronic acid and heparin. In 1983, Parsons was the first who drew attention to the role of GAG layer in the development of IC. He hypothesized that IC patients do not have the GAG layer, or have a defective one and, therefore, they need to be treated using synthetic GAG. [52] Later, both Lilly and Parsons suggested that the GAG layer acts as an epithelial permeability barrier between the bladder wall and the urine. [53] They showed that the GAG layer prevents the small molecule urea from leaking across bladder wall, and this protective effect can be impaired by instilling a quaternary amine (protamine) into the bladder, and can be restored by instilling a sulfate polysaccharide (heparin) into the bladder.

In fact, GAG contains negatively charged, sulfated polysaccharide groups with hydrophilic property. This provides the hydrated surface layer (GAG) with the ability to prevent urinary solutes from damaging the bladder cells. Thus, if GAG is damaged, bladder cells will become subject to harmful solutes. One potentially damaging urinary solute is potassium which is found in high levels (40 to 140 mEq/L) in normal urine. Potassium in this concentration does not transfer through a healthy bladder. However, if there is a dysfunction in the bladder epithelium, potassium will diffuse into the bladder muscles. As a result, depolarization of nerve and muscle can take place, which can lead to an injury, and then, induce IC symptoms of urgency and pain. [54]

In 1994, Chelsky et al. published a paper that conflicted with the GAG theory (epithelial leak). They tested the bladder permeability through measuring the transvesical migration of the

radioisotope technetium99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) into the systemic circulation in 10 IC patients and 9 controls. The result of the study showed that there is a considerable variability in the absorption of ^{99m}Tc-DTPA in both IC patients and normal people. However, the differences between the two groups were not statistically significant. [55] This study suggests that the permeability spectrum of the bladder of normal people is not different from that in IC patients.

Although the previous study did not support the GAG theory, it may have lacked statistical power to detect a true difference because of its small sample size. Moreover, we cannot ignore all the clinical studies that reported synthetic polysaccharides as a successful treatment of IC. [28-30, 56] All these studies support the GAG theory, and suggest that the abnormality of GAG layer could be an important etiology of IC in a subset of patients, and that more than 50% of IC patients will get benefits from using synthetic polysaccharides.

In summary, it is important to mention that this theory has not been completely proven; therefore, it remains an area of active research. We still need to identify the reasons that lead to the changes in the permeability of the urothelium, and how these changes correlate with bladder permeability.

2.2.3.2 Mast Cell Theory and Neurogenic Inflammation

Mast cells are inflammatory cells that secrete a variety of mediators (histamine, prostaglandins, leukotrienes, cytokines, and chemotactic factors) relevant to IC symptoms. These mediators are either synthesized *de novo* or released from the intracellular granules, when the mast cells are activated (degranulated). The main triggers of mast cells degranulation are antigen binding to IgE on mast cell surface, cholinergic agonists, hormones, stress, and trauma. [57]

When mast cells are activated, they release inflammatory mediators (such as histamine) which in turn induce IC symptoms (pain, hyperemia, and fibrosis). Several studies support this theory. Simmons et al. are the first to outline the role of mast cells as a cause of IC. [58] They found mast cells in the wall of the normal bladder secreting histamine, and they reported improvement in IC symptoms among IC patients who received antihistamines (tripelennamine) three times a day. In 1982, Larsen et al. reported that mast cells had a potential role in the pathogeneses of IC. [59] Kastrup et al. suggested using mast cell count; in particular, in the detrusor muscle of the bladder as a diagnostic criterion. [60] They reported mast cell count significantly higher in detrusor muscle of IC patients compared to control subjects.

In a more intensive study, Holm-Bentzen and his colleagues attempted to relate symptoms and findings of cystoscopy and cystometry in 115 IC patients with or without mast cell count in the detrusor muscle (detrusor mastocytosis). [61] They divided patients into two main groups; those with mast cell count greater than 28, and those with less than 28 mast cells/mm^2. Patients with mast cell count greater than 28 had hematuria, more damaged bladder, redness, scarring, increased visualization of bladder mucosa at cystoscopy before hydrodistension and reduction in bladder capacity compared to those with mast cell count less than 28 per square millimeter. On the other hand, petechial bleeding was found to be similar in both groups, and the patients with a mast cell count less than 28 had a vulnerable mucosa after bladder distension. Because the two groups largely overlapped, the investigators of this study suggested that mast cell count alone cannot be considered as the only factor which induces the symptoms in IC patients.

Hanno et al. agreed with Holm-Bentzen et al. that mast cell count in the detrusor muscle cannot be used to confirm IC diagnosis. They evaluated the mast cell count in 55 patients with IC

and 21 patients who had voiding dysfunction due to a cause other than IC. [1] The mean detrusor mast cell count was not statistically different between the two groups. Thus, although detrusor mast cells could be an important mediator of the disease, it cannot be used alone as an exhaustive diagnostic criterion.

As was mentioned previously, hormones have been implicated as triggers to mast cells activations. Spanos et al. in their animal study reported that estradiol was responsible for the activation of the mast cells in the bladder. [62] This could be an explanation of the higher prevalence of the disease among females. In fact, human mast cells contain estrogen receptors, which may also explain why IC symptoms get worse during ovulation. [63]

There is an association between the existence of mast cells in IC patients and the occurrence of neurogenic inflammation. Some studies have reported that many mast cells degranulated near sensory nerve fibers. [64-67] This suggests that IC could be a neurogenic inflammation that starts when sensory nerves are stimulated and release neuropathies (Substance P) which promote inflammation by several mechanisms including the activation of mast cells. [64] Once the mast cells are activated, they release their mediators which induce pain, and stimulate the sensory nerve fibers again, creating a vicious cycle.

Overall, it is not known whether mast cells play a causative or a secondary role. If they are causative agents, then they will produce the symptoms of IC by degranulation. Another possibility is that they are activated by other factors such as epithelial leak, in which case mast cells can be considered playing a secondary role. Thus, we can tell that they play an important role in IC, but we cannot say for sure that they are the only causative factor. [36]

2.2.3.3 Autoimmune Theory

Since the 1970s, researchers have been suggesting that autoimmune reactions might explain many facets of IC. Silk compared the sera of 20 IC patients and those of other groups: 10 normal volunteers, 15 patients with acute and chronic bacterial cystitis and 10 patients with known thyroid, adrenal and gastric antibodies. [68] He found bladder antibodies in IC patients, but not in any other group in the study. Oravisto et al. agreed with Silk, and reported the presence of antinuclear antibodies in 85% of their IC patients. [69]

There are two different kinds of autoimmune diseases: organ-specific and non-organ-specific. According to several autoimmune studies, it seems that IC is a non-organ specific autoimmune condition. Although the researchers found bladder antibodies, they failed to report bladder-specific auto-antibodies. Jokinen et al. studied the sera of 33 IC patients and found that 28 out of them had antinuclear antibodies, [70] but could not detect any bladder-specific auto-antibody among IC patients. Furthermore, Anderson and his colleagues in their study where IC patients were examined in comparison with controls who matched on age, sex, but with different urological problem, reported the presence of non-organ-specific antibodies in 65% of the IC patients and 22% of the controls. [71] They also found that 40% of the patients and 22% of the controls had antinuclear antibodies while 75% of the patients and 40% of the controls had bladder-specific antibodies. Finding bladder-specific antibodies among the controls indicates that these antibodies are not specific to IC patients. As a result, Anderson and his colleagues concluded that the immunological characteristics of IC are most likely to be secondary to inflammation rather than causative factors.

In fact, there are more studies which support this theory. Evidences show the presence of autoimmune components can be summarized as follows: [72]

- IC has been reported in association with other autoimmune diseases such as Sjögren's, rheumatoid arthritis, lupus, and Hashimoto's thyroiditis.
- Plasma cells and antibody deposits are found in the bladder.
- Using cortisone treatment led to remission of some symptoms of IC which are similar to those in the systemic autoimmune diseases, lupus and scleroderma.
- Mouse immunization with autologous bladder antigens results in IC-like bladder changes.

In conclusion, the exact role of autoimmunity in IC remains nebulous. For a clearer understanding of its function, more detailed animal studies are to be conducted.

2.2.3.4 Inflammation Theory

There is an argument that IC is an inflammatory disease, because several inflammatory mediators e.g., interleukin-6 (IL-6), IL-2, kallikrein, and neutophil chemotactic factors, are increased in IC patient's urine. [73-77] Still, the primary causative agent that starts the sequence of the inflammation process is not yet known. Different possible causative factors have been suggested such as; neurogenic inflammation, dysfunction of the bladder epithelium that leads to the diffusion of different irritating materials, allergy or hypersensitivity to urine components, microbial agent and autoimmune infection. [78] However, there are no specific studies that show which is the real causative factor. This theory needs more research to clarify it.

2.2.3.5 Microbiological Theory

The earlier literature attempts to incriminate microbiological agents such as bacteria, virus, and fungi as possible causes of IC with no success. [48] Hunner was among the first researchers who suggested that IC might be caused by a bacterial agent. [79]

In 1945, Powell argued that lymphatic obstruction might have an important role; however he could not present any strong evidence to support the idea. [47] In 1970, Hanash and Pool examined the urine of 30 IC patients in order to detect the presence of any bacteria or fungi, but failed to find anything. [80]

In contrast, Wilkins et al. were able to isolate Fastidious bacteria, Gardnerella vaginales and Lactobacillus species from catheter specimens and/or bladder biopsies of IC patients. [81] They stated that the presence of these organisms might lead to acute cystitis if no treatment was provided.

Unfortunately, however, the use of more developed, highly sensitive and faster technique like: ribosomal RNA gene sequence and polymerase chain reaction (PCR) could not yet offer any reliable evidence that can allow researchers to confirm the theory. [82, 83]

Later, though, unlike the prior studies that could not prove the validity of the theory, a recent pilot double blind, placebo-control trial found it helpful to use antibiotics to treat IC. [84] The results could however, be biased by the fact that antibiotics have anti-inflammatory effects (it has been proposed that IC is an inflammatory disease). Therefore the improvement that was observed could be due to the anti-inflammatory effect of antibiotics, not because of IC caused by microbes. [85]

Although the general direction of research in this area does not support the microbiological theory, researchers are still interested in pursuing and conducting more studies to understand the role of microbes in this complex disease.

2.2.3.6 Toxic Urine Component Theory

Another suggested etiological factor for IC is the presence of toxic substances in the urine. Several studies have investigated the urine of IC patients for toxicity. Some investigators exposed rabbit bladder to the urine of IC patients or controls and they were able to report the development of IC signs in the rabbit bladder that was exposed to the urine of IC patients, but not to the controls' urine. [86] Another study showed that the urine of IC patients were able to inhibit the proliferation of human epithelial cells in primary culture. [87]

2.2.3.7 Psychological Theory

A psychological etiology of IC has been mentioned. IC often is misdiagnosed as a psychiatric disorder, and its treatment with psychotropic medication is not uncommon.[19]

The major psychological factor, stress, has been considered to play a role in autoimmune and neuroinflammatory syndromes in which the nervous system interacts with the immune system. [88, 89] Stress is also known to worsen syndromes involving mast cells such as interstitial cystitis. [57] The possible role of stress as an etiological factor of IC is thought to be related to its ability to activate mast cells. In vivo animal studies have shown that immobilization stress activates over 70% of bladder mast cells within a short period. [90, 91] It has been suggested that the activation of bladder nerve endings under stress may lead to release of Substance P (SP) and neuropeptide (neurotensin) which then activate local mast cells to secrete vasoactive, proinflammatory and nociceptive mediators. [90, 92] The effect of these, in turn, could explain most of the clinical symptoms of IC.

On the other hand, the chronic pain, frequency, urgency and sleep deprivation associated with interstitial cystitis may contribute to psychological stress and secondary depression. Suicidal ideation is three to four times more common in patients with interstitial cystitis than in

the general population. [93] More than one half of symptomatic patients with interstitial cystitis have depression. [94] Thus, it is not clear if psychological factors play a primary, a secondary, or both primary and secondary roles in the initiation of IC. More research is needed in this area.

2.2.4 Diagnosis

There is no single definitive test that can confirm the diagnosis of IC. One of the difficulties in the diagnosis of IC has been the multitude of symptoms and the lack of a clear etiology and pathogenesis of the disease. In fact, patients may see as many as 8 physicians and suffer from symptoms for 5 to 7 years before an accurate diagnosis of IC is made. [44] Thus, the current diagnosis usually depends on patient symptomatology, urologic evaluation including cystoscopy, and the exclusion of other recognizable bladder diseases.

2.2.4.1 The National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) Diagnostic Criteria

In 1987, the National Institute of Diabetes, Digestive, and Kidney diseases (NIDDK) developed a set of criteria for accrual of patients in IC studies sponsored by NIH. Thus, homogeneity and similarity between one site and another can be ensured. A list of NIDDK guidelines is shown in **Table 2-1**. An IC case can be confirmed if it meets the following inclusion criteria: painful bladder or urinary urgency, and glomerulations (glumerulus is a small tuft or cluster, as of food vessels or nerve fibers) or Hunner's ulcer on cystoscopic examination. [45]

Table 2-1: The Original NIDDK Criteria for Inclusion in IC Studies-1987*

THE ORIGINAL NIDDK CRITERIA FOR INCLUSION IN IC STUDIES
Automatic Exclusion: • Age <18 years • Benign or malignant bladder tumors • Radiation cystitis • Bacterial cystitis • Vaginitis • Cyclophosphamide cystitis • Symptomatic urethral diverticulum • Uterine, cervical, vaginal, or urethral cancer • Active herpes • Bladder or lower urethral calculi • Waking frequency less than five times in 12 hr • Nocturia less than two times • Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics • Duration less than 12 months • Involuntary bladder contractions (urodynamics) • Capacity greater than 400 cc, absence of sensory urgency
Automatic Inclusions: • Hunner's ulcer
Positive Factors: [A] • Pain on bladder filling, relieving by emptying • Pain (suprapubic, pelvic, urethral, vaginal, or perineal) • Glomerulations on endoscopy • Decreased compliance on cystometrogram

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[A] Two required for inclusion in study population

Several felt that these criteria were too restrictive in clinical setting. Thus, later in 1988, the NIDDK criteria were revised. A list of the revised NIDDK guidelines is shown in **Table 2-2**. Current research studies must follow these guidelines in identifying IC cases to be included in the study. Although these criteria help a lot in establishing the homogeneity and similarity in the study population among study centers, some IC cases may be excluded from studies on IC, as these criteria do not represent less common symptoms and signs. [95] Interestingly, strict

application of the NIDDK criteria would have misdiagnosed more than 60 percent of patients who were diagnosed by researchers as definitely having or likely to have interstitial cystitis. [96]

Table 2-2: The Revised NIDDK Criteria for Inclusion in IC Studies-1988 *

THE REVISED NIDDK CRITERIA FOR INCLUSION IN IC STUDIES
The presence of any one of the following criteria will exclude the diagnosis of IC for study purpose: • Bladder capacity > 350 ml on awake cystometry using either gas or liquid as a filling medium • Absence of an intense urge to void with the bladder filled to 100 ml of gas or 150 ml of water during cystometry using a fill rate of 30-100 ml/min • The demonstration of phasic involuntary bladder contractions on cystometry using the filling rate described above • Duration of symptoms less than 9 months • Absence of nocturia • Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics • A frequency of urination , while awake, less than 8 times per day • A diagnosis of bacterial cystitis or prostatitis within 3 month period • Bladder or lower urethral calculi • Active genital herpes • Uterine, cervical, vaginal, or urethral cancer • Urethral diverticulum • Cyclophosphamide or any type of chemical cystitis • Tuberculosis cystitis • Radiation cystitis • Benign or malignant bladder tumors • Vaginitis • Age less than 18 years
To be diagnosed as having IC, patients must have either glomerulations in cystoscopic examination or classic Hunner's ulcer, and either pain associated with the bladder or urinary urgency. An examination for glomerulations should be undertaken after distension of the bladder under anesthesia to 80 to 100 cm water pressure for 1 to 2 min. The bladder may be distended up to two times before evaluation. The glomerulations must be diffused (present in at least three quadrants of the bladder) and there must be at least ten glomerulations per quadrant. The glomerulations must not be located along the path of the cystoscope (to avoid artifact from instrumentation contact).

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2.2.4.2 Traditional Diagnostic Criteria

Currently, IC diagnosis is still based on presenting signs and symptoms after a differential diagnosis. Bladder or urinary tract infection, bladder cancer, sexually transmitted diseases, urethral diverticula, and uterovaginal prolapse should be excluded to confirm that the diagnosis is IC. A strong history of urinary urgency, frequency and pelvic pain, a physical examination to detect suprapubic tenderness, anterior vaginal wall tenderness, Levator muscle spasm, and possible rectal spasm also must be documented. The urine analysis should be normal with a sterile urine culture and negative cytology. Because IC patients may void more than 60 times a day, each patient should be asked to perform a voiding log to show the number of voids per day as a part of the overall method of IC diagnosis. **Table 2-3** summarizes the current traditional diagnostic criteria. [44]

Table 2-3: Current Traditional Diagnostic Criteria*

CURRENT TRADITIONAL DIAGNOSTIC CRITERIA
Differential diagnosis of IC • Bladder or urinary tract infection • Bladder cancer • Sexually transmitted diseases • Urethral diverticula • Uterovaginal prolapse
Patient history • Urinary urgency, and frequency • Pelvic pain
Physical examination • Possible suprapubic tenderness • Possible anterior vaginal wall/ bladder base tenderness

Table 2-3 Cont'd

• Levator muscle spasm • Possible rectal spasm
Clean urine analysis Sterile urine culture Negative cytology
Voiding log more than 8 voids in 24 hours

* Reprinted with permission from J Reprod Med., 2004; 49 (3 Suppl): 235-42, Parsons CL. Diagnosing chronic pelvic pain of bladder origin. Copyright©2004 J Reprod Med, Inc.

2.2.4.3 Additional Diagnostic Tools

2.2.4.3.1 Cystoscopy With Hydrodistension

The purpose of using cystoscopy with hydrodistension is to detect glomerulations and/or Hunner's ulcer in some patients with IC. The main procedure is to fill the bladder under anesthesia with water to a relatively high pressure. This will be followed by emptying the bladder and finally inspecting it. [44] Although using cystoscopy after hydrodistension is one of the recommendations of NIDDK as an important procedure to diagnose IC, it cannot be used alone as only, 11.3% of IC patients will have Hunner's ulcers. [9] Moreover, most patients have no visible lesions upon routine inspection of the bladder. Furthermore, glomerulations are not specific to IC. They can be seen in various types of inflammatory bladder disease (such as after treatment with intravesical chemotherapy and radiation), also with infectious (tuberculosis, fungus), toxic (Cyclophosphamide, formalin) and neoplastic disorders of the bladder. They may also simply be a result of stretching the bladder several hundred cubic centimeters beyond its usual capacity. [97] Cystoscopy with hydrodistension can be used to assess the capacity of the bladder. Small capacity supports IC diagnosis and is inversely proportionate to the presence of Hunner's ulcer. [44]

2.2.4.3.2 Urodynamic Testing

Urodynamic is the study of how the body stores and releases urine. It shows how the bladder and sphincter muscles work and thus helps in explaining symptoms like frequent urination, sudden and strong urge, and painful urination. Most urodynamic tests focus on the bladder's ability to empty steadily and completely. Through these tests a physician can determine if a patient has any difficulty starting the urine stream, if the stream is interrupted, and if any urine remains in the bladder after micturation.[98]

Several urodynamic tests are currently available. In the following section, we will describe those used in the present study to evaluate the change due to the intervention therapy.

Uroflowmetry

Uroflowmetry is the simplest urodynamic test because it is noninvasive and performed through very simple and non-expensive equipment, the uroflowmeter, which creates a graph that provides several important measures as follows: [99]

- Flow rate defined as the volume of the fluid expelled via the urethra per unit time and expressed in milliliters per second (ml/s).
- Maximum flow rate defined as the maximum measured value of the flow rate.
- Average flow rate defined as the voided volume divided by flow time.
- Time to maximum flow defined as the elapsed time from onset of flow to maximum flow.
- Flow time defined as the total time of measurable flow.
- Voided volume defined as the total volume expelled via urethra.

Using this test, the physician is able to keep track of changes in the flow rate from second to second; the peak flow rate and how many seconds it took to get there. Because urine flow is highly dependent on the volume voided (flow rates are highest and most predictable in the

volume range between 200ml and 400ml), it is not easy to specify fixed norms. One way to overcome this is to define the lowest acceptable maximum urine flow rates for minimum voided volumes. For example, the lowest acceptable maximum urine flow rate for a female aged between 46 and 65 with a minimum voiding volume 200 ml is 15 ml/s, and for female aged 66-80 is 10 ml/s when the same voided volume is used. [99] If the results are abnormal this will indicate that bladder muscle (detrusor) is weak or the urine flow is obstructed. [98]

Simple Cystometry (Measurement of Bladder Pressure)

Importantly, uroflowmetry provides limited information about the storage phase of micturation, and thus it cannot show if the abnormal flow is related to weakness in bladder muscle or to an obstruction. On the other hand, cystometry overcomes this limitation. [99] The cystometrogram (CMG) measures how much the bladder can hold, how much pressure builds up inside the bladder as it stores urine, and how full it is when a patient feels the urge to urinate. [98] The principal aim of CMG is to define detrusor function and urethral function during both filling and voiding processes. In this way, a physician will be able to provide a possible diagnosis during cystometry. For instance, during the filling process, if the detrusor function is normal while the urethra is incompetent, the possible diagnosis is incontinence. On the other hand, during voiding, if detrusor is underactive while the urethra is normal, a low flow rate will be observed, and the patient strained to void. [99]

Normal cystometry is defined as the ability to fill the bladder (using distending medium such as sterile water, saline, carbon dioxide, or urine) to a normal maximum cystometric capacity in the absence of any involuntary detrusor contractions or voluntary uninhibited contractions. The normal maximum cystometric capacities will differ depending on the medium used to

distend the bladder. For example, if the distending medium is carbon dioxide, detrusor instability may occur. [100]

The first step in CMG is to empty the patient bladder. This will be followed by filling the bladder with the distending medium using a smaller pressure-measuring catheter called cystometer with a desired filling rate. There are three categories of filling rate: slow-fill cystometry (up to 10 ml/min), medium-fill cystometry (between 10 ml/min and 100 ml/min) and fast-fill cystometry (greater than 100 ml/min). The rate of bladder filling has considerable effect on the results of the test. The faster the bladder is filled, the lower the bladder compliance is (bladder compliance: a relation between bladder volume and bladder pressure). As the patient's bladder is filled, he or she will state when he or she feels the first need to urinate. This is recorded and the process continues. The physician normally asks the patient to wait until he or she feels so full as to want to get off the freeway and use the restroom at a gas station rather than endure until he or she gets back home. This will also be recorded. The filling process will continue until the patient can stand no more due to pain or extreme discomfort. This will be the maximum cystometric capacity. During cystometry the patient may be asked to cough so that involuntary bladder contractions can be identified. [98, 100]

Post Void Residual (PVR)

PVR is defined as the volume of urine left in the bladder at the end of micturation. [99] It is usually measured by either a thin catheter that is gently glided into the urethra or by ultrasound equipment that creates a picture of the bladder and determines the amount of PVR.

Many define normal residuals as less than 30 ml, whereas others choose a cutoff of 50 ml. It is important to mention that residuals must be evaluated in relation to the volume voided.

For example, the residual of 30 ml after the void of 45 ml is not normal. However, the same residual might be reasonable after a patient voids 500 ml of urine. [101]

2.2.4.3.3 O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI)

This index is designed to identify the most prominent voiding and pain symptoms in patients with IC and the extent of the perceived problem **(Appendix B)**. It has been validated by examining 45 newly diagnosed IC patients and 67 women recruited from healthy volunteers at a gynecology clinic. [23] The results showed high internal consistency for both symptom and problem indices (Cronbach's alpha >0.85) as well as high reliability (test-retest reliabilities exceeded 0.9). The validity, reliability and responsiveness of the scores have been reported again more recently. [102] The results were consistent with the previous study.

2.2.4.3.4 Pelvic Pain and Urgency/ Frequency Patient Symptom Scale (PUF)

The PUF includes 8 questions that measure the presence and the severity of IC symptoms and the degree to which patients are bothered by the symptoms **(Appendix C)**. The questions assess the urgency and the frequency of voiding during waking and sleeping hours, the presence of pain or urinary urgency during or after sexual intercourse, the presence of pain in the pelvic area, and the degree to which these symptoms are bothersome.

The maximum total score is 35 while the minimum recorded score among healthy participants is < 2. A total score of 10+ points clearly indicates a very high probability that the patient has IC. [44] A total score of 10 to 14 indicates a 74% chance to have IC, 15 to 19 indicates a 76% chance to have IC, and 20 or higher indicates a 91% chance to have IC. [24]

2.2.4.3.5 Potassium Sensitivity Test (PST)

The PST was developed to identify patients who respond with pain following the instillation of potassium chloride into the bladder. In fact, this test is based on leaky bladder theory. The abnormal permeability of the bladder surface's barrier (GAG) allows potassium to leak and to be absorbed into the bladder wall. This in turn will stimulate nerves, and cause pain and inflammation in the bladder wall. A positive PST (pain following the instillation of potassium chloride into the bladder) indicates that a patient with chronic pelvic pain has a bladder component, and could be an IC case. However, because PST has been shown to give positive results in other bladder diseases such as radiation cystitis or acute bacterial cystitis, these diseases must be ruled out. Furthermore, a negative result of PST does not indicate that IC diagnosis is ruled out. This false negative result can occur when a patient was recently treated with intravesical dimethyl sulfoxide or heparin therapy or hydrodistension. [24]

The main procedure includes a very slow instillation of 40 ml of room temperature sterile water into the bladder through a thin catheter over 2-3 minutes to establish the baseline of pain perception and urgency using 0-5 point scale (5 indicates severe pain and severe urgency). Water retained in the bladder for 5 minutes and then emptied through the catheter. About 40 ml of potassium chloride then is to be instilled, whereby re-evaluation of pain and urgency will be achieved. Potassium chloride can be retained in the bladder for 5 minutes if there is no severe response. A positive PST is indicated for any pain score greater than or equal to 2. If no response takes place, then the catheter is removed and the patient is asked to urinate and re-evaluate the level of pain and urgency. PST validity was tested previously. Of 1500 PSTs performed on individuals with IC, approximately 80% were positive. [24]

2.2.4.3.6 Urinary Biomarkers

There is no single and specific diagnosis of IC. Moreover, the currently used criteria have been developed for clinical research and may be too restrictive. It is important, therefore, to find an objective marker for IC to facilitate the diagnosis. It has been indicated that certain objective biomarkers could be more specific than either symptomatic or cystoscopic criteria for IC. [103-106] Besides, some of these biomarkers give rise to new theories of possible etiologies for IC. [107]

Several biomarkers have been discovered in urine, serum, or tissue from IC patients. [105] Anti-proliferative factor (APF), heparin binding epidermal growth factor (HB-EGF), epidermal growth factor (EGF), and interleukin 6 (IL-6) were found to be highly significantly different between patients and asymptomatic matched controls. [106]

It is important to note that IL-6 is significantly elevated not only in urine specimens from IC patients, but also in specimens from patients with other urinary tract disorders. [108] This makes IL-6 an ineffective biomarker for diagnosis. The remaining three biomarkers have been linked to each other in studies showing APF regulation of HB-EGF and EGF production in the bladder urothelial cells. [109, 110] APF has been found to decrease levels of HB-EGF and increase levels of EGF in IC patients compared to asymptomatic controls and patients with bacterial cystitis. [103] These findings indicate that APF play an important role in the process of bladder urothelial cell proliferation through its regulation of HB-EGF and EGF production.

To summarize, since 1915, the diagnosis of IC has been one of exclusions and remains so today. Finding a specific diagnostic tool for IC diagnosis is not a rapid process; it requires much intensive efforts, research, and highly committed patients who are willing to help and participate in researches.

2.2.5 Treatment Options

Because the etiology of IC is poorly understood, treating IC is one of the greatest challenges for health care providers. In fact, there are currently no universally effective therapies available. Interestingly, in comparison to all the other common symptoms of IC, pain remains the hallmark of this disease. Pain can be classified to nociceptive, visceral, or naturopathic. IC pain often includes all the three types and this makes the treatment very complex and extremely difficult. [111]

According to the several etiological theories presented previously, treatment options should be based on three general principles; first, restoring epithelial function by using heparinoids (compounds with a structure similar to that of GAG), second, modulating neuronal activity by using antidepressant, and third, controlling allergies by using antihistamines. [36] In fact, there are several treatment options. Currently the most frequently used treatment is either an oral one or an invasive one which could be intravesical and/or surgical. The following sections will provide a summary of these options.

2.2.5.1 Oral Treatment for Interstitial Cystitis

2.2.5.1.1 Nonsteriodal Anti-inflammatory Drugs (NSAIDs), Narcotics and Antihistamines

NSAIDs are the first oral treatment options prescribed to IC patients. The anti-inflammatory effect reduces inflammation, if exists, through inhibiting the production of prostaglandin. Unfortunately, however, NSAIDs have been ineffective in many IC patients. [111]

Several types of narcotics are used; Nalmefene is one of them. It is a long acting opiate antagonist that has been used to treat IC pain with only limited success. Nalmefene can decrease

mast cell degranulation and it showed a 50% reduction in suprapubic bladder pain in clinical study. [111] Further studies still need to be conducted on this treatment.

The main aim of using antihistamines in first line treatment is to decrease mast cell activity and thus reduce the development of pain caused by the degranulation of these cells. The efficacy of antihistamine varies and the most commonly used antihistamine for IC treatment has been Hydroxyzine. Its mechanism of action includes blocking both mast cells secretion and H_1-receptors. [111] Interestingly, animal studies showed that Hydroxyzine can inhibit the release of substance P as well. [112] Inhibiting substance P and histamine are thought to reduce hyperemia and fibrosis respectively.

2.2.5.1.2 Tricyclic Antidepressants (Amitriptyline)

Amitriptyline is one of the most prescribed tricyclic antidepressants. It differs from all the previous oral treatments in its ability to treat the neuropathic pain in IC patients. [111] Although the use of Amitriptyline has been started since 1987, its efficacy was proven only in 2004 in a randomized clinical trial. [113] The investigators in that trial showed that 63% of IC patients were satisfied with Amitriptyline compared to 4% in the placebo group. How Amitriptyline relieves pain is still to be further clarified. Its effects on urinary frequency symptoms and bladder capacity, however, are more readily explained by its concomitant anticholinergic properties. Furthermore, Amitriptyline has antihistaminic properties, thus it is able to block H_1-receptors on the mast cell as well. [111]

2.2.5.1.3 Immunosuppressive Agents

Immunosuppressive agents (such as prednisone and cyclosporine) are thought to reduce the inflammatory response in the bladder, and to treat empirically the autoimmune processes related to IC. Recently, in a small study in Canada of 14 patients with the ulcerative type of IC who

were treated daily with 25 mg of prednisone, the investigators reported a 69% decrease in pain symptoms among the IC patients. [114] This study was very restrictive because of the small sample size; it also only included ulcerative IC patients. Nevertheless, this new study opens a new option of treatment for IC pain.

Like prednisone, cyclosporine has shown some early promise. A recent study in Finland assessed the effects of long term treatment (more than 1 year) with cyclosporine (started at 3 mg/kg/day, gradually decreasing to as low as 1 mg/kg/day) on 23 IC patients. [115] The investigators reported that 20 out of the 23 IC patients were completely relieved of pain. Despite this impressive result, there is still a need for larger randomized clinical trials to clearly demonstrate the therapeutic benefits of both prednisone and cyclosporine before they are used as a new treatment option.

2.2.5.1.4 Pentosan Polysulfate Sodium (PPS) (Elmiron®)

Because this study tests the efficacy of PPS (Elmiron®) as a new intravesical therapy for IC, more details about this treatment option is to be presented here. PPS is indicated for the initial and maintenance treatment of interstitial cystitis. It is one of the most frequently used oral treatment options. It is actually the only oral agent that is approved by the Food and Drug Administration (FDA) for the treatment of IC (the approval date was 9/26/1996). [116]

General Description

Pentosan polysulfate sodium is a semi-synthetic sulfate polysaccharide similar to heparin-like macromolecular carbohydrate derivative which chemically and structurally resembles glycosaminoglycans. **Figure 2-1** shows the chemical structure of PPS.

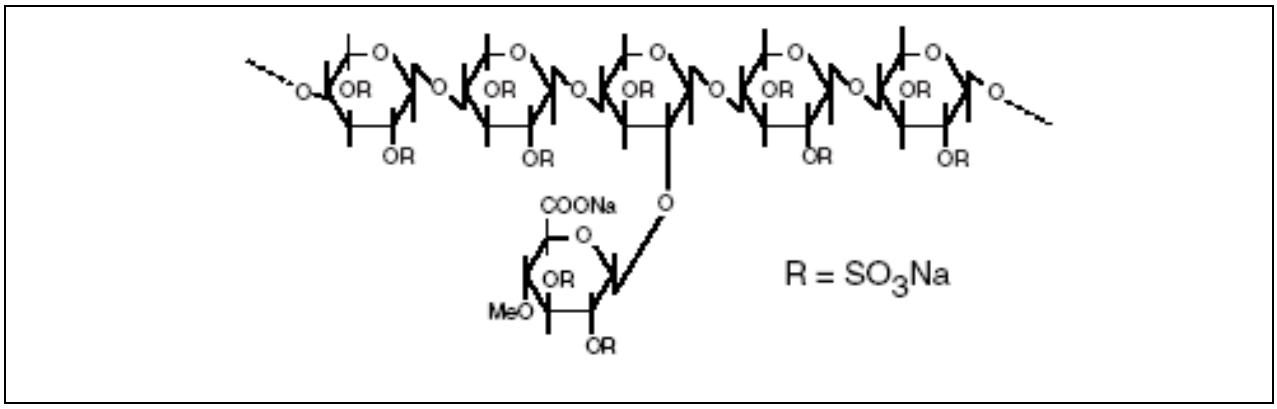


Figure 2-1: Chemical Structure of Pentosan Polysulfate Sodium

It is a white odorless powder, slightly hygroscopic, and soluble in water to 50% at pH 6. It has a molecular weight of 4,000 to 6,000 Dalton. [117] PPS brand name is Elmiron® that is formulated for oral use. Elmiron® is supplied in white opaque hard gelatin capsules containing 100 mg of PPS.

Pharmacological Properties

PPS is a weak anticoagulant (1/15 the activity of heparin) and has been used to prevent thrombotic disease. [117] Several theories have been suggested to explain the PPS mechanism of action. Yet, its exact mechanism still unknown. The use of PPS was on the basis of GAG theory; PPS can augment and repair the GAG layer of the bladder, and consequently relieve IC symptoms. [111] Intravesical pretreatment with PPS was shown to reduce the damage done by the cytotoxic substance acrolein in transitional cells in the bladder of female rats. [118] More specifically, the treatment worked through enhancing the GAG layer. In human, PPS has been reported to reduce bladder permeability based on the potassium sensitivity test. [119] IC patients who were treated with PPS and showed clinical improvement in their symptoms were more

likely to have reduction in potassium sensitivity in their bladder at the end of the study compared to IC patients who did not show any improvement.

Another suggested mechanism is that PPS may have anti-adherence properties. Animal studies showed that PPS reduced the adherence of agents like calcium and protein to the urinary bladder of rabbit. [120] Furthermore, bacterial adherence to acid treated rabbit bladders was brought back to control levels by treatment of the bladder with PPS. These studies showed that pretreated bacteria with PPS had no effect on the bacteria's ability to adhere to acid treated bladder which supports the general hypothesis that the effect of PPS lies on what PPS does on injured bladder wall rather than what it does to bacteria.

PPS also may have a cytoprotective effect that leads to reduction of the inflammation of bladder mucosa accompanying IC. In vitro studies showed that PPS inhibits the stimulation of connective tissue mast cell and mucosal mast cells, which, in turn, results in a significant reduction in histamine secretion. [121, 122]

Pharmacokinetic Properties

Administration, Absorption, and Distribution

PPS is given orally, usually 100 mg t.i.d., on an empty stomach. Pharmacokinetic studies showed that the absorption of the administered dose is ≈ 3% (dosage not reported) [120] or less than 1% for an oral, single 1500 mg dose.[123] Animal studies showed that PPS is distributed by lymphatic system and blood, possibly through macrophages, to different parts of the body. [124] PPS is distributed to the uroepithelium of the genitourinary tract. Lesser amounts can be found in bone marrow, lung, liver, periosteum, skin, and spleen. Animal studies showed that erythrocyte penetration is very low. [117] It should be noted that, since no studies were conducted to show the

effect of food on PPS, for safety PPS must be administered either one hour before or two hours after meals.

Metabolism

It is metabolized through both partial desulfation (occurs in the liver), and partial depolymerisation (occurs in the kidney). Both desulfation and depolymerisation can be saturated with the continued administration of PPS.[117] Simon et al. reported that most of the administered dose of radiolabeled PPS (200μCi less than 15 mg) (84%) was excreted in feces as intact PPS, while a smaller percentage (6%) was excreted in urine as low molecular weight and desulfated PPS. [125]

Excretion

After orally administered radiolabeled PPS, the elimination half-life in urine was determined to be 4.8 hours for unchanged drug. [117] Importantly, a single dose of PPS can completely eliminated from the body in 144 hours. [120]

In human excretion studies (included 3 healthy male volunteers), approximately 3.5% of the administered PPS (radiolabeled) excreted in the urine. [117] Interestingly, after multiple doses of PPS, the urine excretion of radioactivity was found to be approximately 11% of the administered dose. [117, 120] This indicates that very small dose of PPS reaches the site of action (bladder) after oral administration.

Side Effects and Drawbacks

PPS is usually well tolerated. The main documented side effects can be divided into two main classes according to frequency: [117]

- Side effects with frequency between 1% and 4% include: alopecia, diarrhea, nausea, headache, rash, dyspepsia, abdominal pain, liver function abnormalities and dizziness.

- Side effects with frequency less than 1% include: digestive (vomiting, mouth ulcer, colitis, esophagitis, gastritis, flatulence, constipation, anorexia, gum hemorrhage), hematological (anemia, ecchymosis, increased prothrombin time, increased partial thromboplastin time, leucopenia, thrombocytopenia), hypersensitive reactions (allergic reactions, photosensitivity), skin (pruritus, urticaria) and special senses (conjunctivitis, tinnitus, optic neuritis, amblyopia, retinal hemorrhage).

There are two main drawbacks of oral PPS; first, it is expensive (approximately US$100-150/month) and second, it may take 3 to 6 months of PPS therapy before improvement can be felt. [78]

2.2.5.2 Invasive Treatment for Interstitial Cystitis

When oral treatment does not help the patient in relieving the pain, the option of invasive treatment is the one to use. Intravesical therapy (the direct instillation of medication into the bladder using catheter through the urethra) is one of the mainstays in the treatment of IC. It targets the bladder mucosal lining and /or bladder wall inflammation, resulting in relief of pain, frequency and urgency symptoms. Although several intravesical agents are used to treat IC patients, the FDA has approved only one of them for IC Intravesical therapy; named Rimso-50® (dimethyl sulfoxide: DMSO). [126] There are two main types of intravesical therapy; either single or multiple drug therapy. Multiple drug therapy is developed to add another therapeutic effect to the pharmacological effect of DMSO. For example, steroid or heparin may be added to DMSO because of their anti-inflammatory effects. [127]

2.2.5.2.1 Intravesical Therapy

Several factors can affect the efficacy of any treatment among which the route of administration is the major one. The variability of success of oral medications can be relayed to the pharmacokinetic of these medications which includes absorption, metabolism and renal excretion. The fact that only small amount of active ingredient reaches the bladder leads to the reduction in the effectiveness of the oral therapies, besides the need of higher doses for longer duration, which, in turn, increases the possibility of side effects.

Intravesical therapy overcomes many of these disadvantages. By applying intravesical therapy, high dose will reach the bladder easily without being affected by metabolism process, drug interaction, liver or gastrointestinal functions. Furthermore, very few side effects can occur because of the poor absorption through the bladder itself. On the other hand, intravesical therapy has certain disadvantages such as the possibility of urinary tract infection due to catheterization, patient discomfort in addition to the costs related to visits, waiting time and the need for anesthesia. [35]

Until now, double blind studies of intravesical therapies have not been performed because of limitations of study design. For instant, DMSO produces a garlic breath, while sodium oxychlorosene lavage (Clorpactin®) is painful and needs general or regional anesthesia before instillation. Thus, it is very difficult to keep these drugs from being recognized. [35]

The present study examined the efficacy of Elmiron® (Pentosan Polysulfate Sodium) as a new intravesical drug. Two examples of Intravesical therapy are presented here.

2.2.5.2.2 Hydrodistension

Although cystoscopy with hydrodistension is a method used to diagnose IC, it is also a therapeutic procedure. The efficacy of hydrodistension has proven to be variable. [128] Hydrodistension must be done under general anesthesia followed by distending the bladder at 80 cm water pressure for 2-8 minutes. [27] The response rate can range from 12% to 70%. The mechanism by which this method help in reducing the pain among IC patients is believed to be a mechanical stretch of the bladder mucosa and damage to the submucosal neuronal plexus. By this way, the transmission of pain through the afferent fibers will be decreased. [111] Another possible mechanism is that hydrodistension may cause all the bladder mast cells to degranulate at once, thus the symptoms remain quiescent until another mast cells migrate. It has been suggested that distension lead to sloughing the defective epithelium, and this let the new epithelium to grow back with a normal function. [27] The therapeutic effect of hydrodistension is last for approximately 3-6 months. After that period, patients may repeat the hydrodistension to obtain another period of prolonged improvement.

2.2.5.2.3 Dimethyl Sulfoxide (DMSO)

DMSO is the only intravesical FDA-approved drug for the treatment of IC. It has many pharmacologic properties: anti-inflammatory, analgesic, muscle relaxant, mast cell stimulation, and collagen dissolution. It is a widely-used drug for IC because of its affordability, ease of office administration, and proven safety. [35] Studies that assessed the efficacy of DMSO are still ongoing and the results show moderate improvement, however, with high relapse rate. The mechanism of action is believed to happen due to the ability of DMSO to deplete substance P and to stimulate mast cell degranulation. [111] Perez-Marrero et al. reported an improvement in IC pain in 93% of patients compared to 35% in the saline placebo group. But they also indicated

that 59% of the patients relapsed in the following month. [129] In another recent study in Europe which included 28 IC patients, a modest response to DMSO instillation was reported. [130]

2.3 EFFICACY OF PENTOSAN POLYSULFATE SODIUM (PPS)

2.3.1 Studies that Assessed the Efficacy of Oral PPS

Several studies have evaluated the efficacy of PPS as an oral treatment for IC. [27-33] Although the results were not consistent, the general trend in these studies is acknowledging the significant efficacy of oral PPS for IC patients with a response rate between 27-42%; [36] the details about each of these studies are presented in the following paragraphs. Importantly, one recent meta-analysis included only prospective randomized double blind clinical trials that compared oral PPS with placebo, confirmed that oral PPS is more efficacious than placebo in the treatment of pain, urgency, and frequency symptoms of IC. The results of this study showed that oral PPS is not significantly different from placebo in the treatment of nocturia in particular. [131]

Till now, approximately seven studies have assessed the efficacy of oral PPS, with the clinical trial design as the most widely used one. [27-33] Most of these studies compared the efficacy of oral PPS to placebo. The sample sizes of these studies ranged from 62 to 380 participants per study. Most of the study populations were females, white, and with average age ranged from 42.5 to 45.5 years. **Table 2-4** provides a summary of each of these studies. More details can be found in the following paragraphs.

Parsons is one of the earliest researchers who studied the efficacy of PPS. In 1987, Parsons et al. conducted a randomized double blind study that included 62 IC patients from two

different medical centers. [29] Patients were randomized to either drug or placebo with a dose of either 100 mg three times daily or 200 mg twice daily based on the medical center they attend. After 3 months, if patients failed to respond to treatment, cross over to placebo was begun (from drug to placebo or vise versa). If the patient responded to the drug, he or she returned in 3 more months, and if there still was a positive response, cross over to placebo was instituted. To complete the study, a patient has to fail drug arm and placebo arm, or to have 2 successive visits (6 months) with positive results. The primary outcome was improvement in symptoms. A 3 day, voiding volume records were obtained from each patient in each visit as well. The results showed that PPS did significantly better than placebo in improving all symptoms (pain has the best improvement). Moreover, objective improvement in average voided volumes was greater with PPS than with placebo.

In the same year, Holm-Bentzen et al. conducted another double blind clinical controlled multicenter trial, and showed opposite results to that of Parsons et al. [27] A total of 115 patients with painful bladder disease (according to clinical and /or cystoscopic records) were recruited from 7 different centers and divided into two different protocols with two different inclusion criteria. In both protocols, patients were randomized to receive either 200 mg of PPS or placebo capsules twice daily for 4 months. Every month patients have to fill a symptom score scale. The study showed that for both protocols there were no significant differences between the pre- and post-trial symptom values in either PPS or placebo group. Furthermore, the study failed to show any difference in the symptom urgency between the two groups in both protocols. A significant increase in the bladder capacity (determined by cystoscopy) in the PPS group was found. Importantly, dividing the patients into two protocols may affect the statistical power of the study which in turn may be responsible for the negative results of this trial.

In 1993, Parsons et al. conducted another randomized double blind clinical trial that included a larger number of IC patients (148 patients) from 7 different centers. [30] Patients were randomly assigned to receive 100 mg of PPS or placebo 3 times a day for three months. Data about the efficacy of PPS was collected through a follow-up questionnaire completed by the patients at the end of the treatment period. A global assessment form was completed by patients to evaluate any change in their condition as either "worse", "no better", or "improved". The improvement levels were: "slight (25%)", "moderate (50%)", "great (75%)", and "no symptoms (100%)". Successful therapy was defined when a patient reports at least 50% overall improvement in his/her symptoms. The investigators provided an evaluation for overall improvement after examining the patient and reviewing the data provided on the symptom scales. The volumes and numbers of void were collected for 3 consecutive days before and after 3 months of treatment. Data about pain and urgency were also collected before and after 3 months of treatment. About 32% of patients on PPS showed significant improvement compared to 16% of those in placebo. Moreover, patients on PPS showed a significant decrease in pain and urgency and a significant increase in the void volume in comparison to placebo group.

Mulholland et al. showed the same results in their double blind placebo controlled trial that included 110 well-documented IC cases from 5 different centers, and continued for 3 months. [28] In this study, patients were randomly assigned to receive either 100 mg of PPS or placebo 3 times a day. Data about symptoms and laboratory values were collected at baseline and 12 weeks after the start of treatment. Similar to the trial described above, Mulholland et al. used patient global assessment and investigator assessment forms plus pain and urgency scales to assess the efficacy of the trial treatment. The volumes and numbers of void were also collected.

The study showed a significant overall improvement among patients on PPS compared to those on placebo.

In 2000, Waters et al. conducted a retrospective analysis and follow-up survey to determine the efficacy and safety of oral PPS. [31] A total of 27 cases and 27 controls were enrolled into the study. Both cases and controls should be diagnosed as interstitial cystitis at least 1 year before the study. Cases had to be on PPS therapy at least 8 weeks, while controls had to be taking at least one oral medication as a treatment for IC. Data about disease-related symptoms and overall changes over time were collected. Cases provided information about IC symptoms before the beginning of therapy and up to current use, or at the point of cessation of therapy. On the other hand, controls reported changes in symptoms during the 12 months before the interview. Like most of the above mentioned clinical trials, this study showed that symptoms in both groups improved over time; however, the improvement was significantly greater among IC cases. Interestingly, no change occurred in the rate of nocturia in the PPS group compared to the control group.

Compared to all the above described trials, Sant et al. were the first to test the efficacy of oral PPS compared to another drug, and for a longer follow-up period (24 weeks). [32] Although their trial was a pilot one, they were the first to consider the level of symptoms' severity as one of the main inclusion criteria. In this way, they eliminated the bias that could be resulted from the level of response to treatment due to the severity of symptoms. The target sample size was 136 IC patients, however only 121 were randomized in a 2 X 2 factorial study design that included 4 arms (PPS (100 mg/3 times a day), Hydroxyzine (50 mg/ at bedtime), placebo, and a combination of hydroxyzine and PPS). The primary endpoint was a participant reported global response assessment at 24 weeks compared to the baseline. Other endpoints were the O'Leary-

Sant IC Symptom and Problem Index, the University of Wisconsin Symptom Score, patient reported symptoms of pain/discomfort and urgency, and a result of 24 hours voiding log. All the outcomes were evaluated at baseline, and after 3, 7, 10, 17, and 24 weeks of randomization. The results of this trial showed no significant difference in the response rate for hydroxyzine compared to placebo. Furthermore, a non-significant trend was seen in PPS group compared to placebo. In general there were no treatment differences in any of the secondary endpoints.

Recently in 2005, Nickel et al. were the first to test both the onset of effect and dose-response effect for PPS in a randomized double blind, parallel-group, multicenters study. [33] A total of 380 patients were enrolled from 30 different sites and randomized to 100, 200, or 300 mg of PPS 3 times daily. About 230 subjects completed the 32 week study. The primary endpoint was O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI); a four-item questionnaire validated as an outcome parameter in IC. Score 15 and above was considered as severe symptoms. The secondary endpoint was the patient's overall global assessment. Data were collected at baseline, and after 4, 8, 12, 16, 24, and 32 weeks of the beginning of the study. Although significant improvements in the ICSI scores from baseline to endpoint were observed in the three different groups, the responses to the three different dosages were not statistically different. Moreover, the percentages of responders to any of the three doses (showed 50 to 100% improvement) increased steadily over time. This demonstrates that the duration of therapy is more important than the dosage itself. The main limitations in this trial included the lack of comparable placebo group, of sufficient power due to the low completion rate of 60%, and of generalizability, as this trial only included patients with moderate to severe symptoms. This makes it not applicable to extend the results on early diagnosed patients.

Table 2-4: Summary of Studies that Assessed the Efficacy of Oral Pentosan Polysulfate Sodium (1987-2005)

AUTHOR YEAR JOURNAL	TYPE OF STUDY DOSE DURATION	SAMPLE SIZE CHARACTERISTICS	DIAGNOSTIC CRITERIA	OUTCOMES	RESULTS AND NOTES
Parsons et al., 1987 J Urol.	RDBPCT* Two centers cross over design 100mg PPS t.i.d or 200mg PPS d.i.d or placebo 6 months	62 IC patients 90% female, 10% male	▪ Had at least 1 year symptoms ▪ Negative urine culture and cytology ▪ Hunner's ulcer or glomerulations after cystoscopy with hydrodistension ▪ Biopsy proved inflammation	Improvement was defined from patient global assessment as reporting at least 50% improvement	▪ Improvement was observed in all symptoms ▪ Remission were observed in 40-60% of subjects versus 18-39 % for placebo ▪ Pain was the most sensitive symptom to show good response followed by urgency and nocturia The cross over mainly to increase sample size in each arm
Holm-Bentzen et al., 1987 J Urol.	RDBPCT * Multi centers (7centers) with two different protocols 200mg PPS d.i.d or placebo 4 months	115 IC patients 43 Protocol A 100% female 72 Protocol B 85% female, 15% male	All patients must have: ▪ At least 1 year symptoms or cystoscopic evidence ▪ Negative urine cultures Protocol A: >28 mast cell/mm2 in detrusor muscle in bladder biopsy Protocol B: ▪ All patient had mast cell < 28/mm2 ▪ 3 or more voiding /night ▪ >10 total points on a define symptom scales of pain, frequency, nocturia, dysuria	Clinically improvement was defined as a decrease of at least 1 point in the mean total symptom score values	▪ No difference between pre and post trial in regards to symptoms, urodynamics, cystoscopic appearance and mast cell counts ▪ Significant increase in the cystoscopically determined bladder capacity in the sodium ▪ pentosan polysulfate group in protocol A was found

Table 2-4 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY DOSE DURATION	SAMPLE SIZE CHARACTERISTICS	DIAGNOSTIC CRITERIA	OUTCOMES	RESULTS AND NOTES
Mulholland et al., 1990 Urology.	RDBPCT* Multi centers (5 centers) 100mg PPS t.i.d or placebo 3 months	110 IC patients 89%female, 11% male	To be included patients must have: ▪ Moderate urgency in 5 point scale ▪ Frequency of at least 10 voids/day ▪ Nocturia at least 2/night ▪ Pain as recorded on a 5 point analog scale ▪ Had at least 1 year symptoms ▪ Failed previous therapy e.g. RMSO, Cloropactin® ▪ Average voided volume 200ml or less ▪ Negative urine culture and cytology ▪ Cystoscopy with hydrodistension showed glomerulations or ulceration with capacity of 800ml or less Main exclusions: ▪ <18 years old ▪ Pregnant or lactating ▪ Use of anticoagulant therapy ▪ Chronic use of narcotic ▪ Allergy to PPS ▪ Use of artificial sweeteners ▪ History of treatment with PPS within 6 weeks of the study	Improvement was defined from patient global assessment as reporting at least 25% improvement Treatment was considered to be successful if there was: ▪ A decrease in pain of 1 point or more ▪ A decrease in urgency of 1 point or more ▪ A decrease of 3 or more per day in frequency of urination ▪ An increase in urine volume of 20ml or more / void	▪ Of patients on treatment 28% showed significant improvement (>25%) compared to 13% of those on placebo ▪ For pain and urgency, the improvements due to PPS compared with placebo were statistically significant or approached significance. ▪ Voided volume, favored the treatment over placebo but not significant ▪ No differences in frequency were observed between the two groups
Parsons et al., 1993 J Urol.	RDBPCT* Multi centers (7 centers) 100mg PPS t.i.d or placebo 3 months	148 IC patients 100% female	Patients must have: ▪ Anesthetic bladder capacity (350-1000ml) ▪ >8 void / day ▪ Average voided volume :50 to 200cc ▪ Nocturia 1 to 2 times/ night Patients lack 1 or 2 of the above criteria entered if they have: ▪ pain and or moderate urgency ▪ Negative cytology and cultures	Improvement was defined from patient global assessment as reporting at least 50% improvement ▪ Treatment was considered to be	▪ Of patients on treatment 32% showed significant improvement compared to 16% of those on placebo ▪ Patient on drug showed significant decrease in pain and urgency ▪ An average increase of more than 20ml in voided volume was reported among patients

Table 2-4 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY DOSE DURATION	SAMPLE SIZE CHARACTERISTICS	DIAGNOSTIC CRITERIA	OUTCOMES	RESULTS AND NOTES
Parsons et al., 1993 J Urol. **Cont'd**			▪ Cystoscopic finding of glomerulations Main exclusions: ▪ <18 years old ▪ Pregnant or lactating ▪ Use of anticoagulant therapy ▪ Chronic use of narcotic ▪ Allergy to PPS ▪ Use of artificial sweeteners ▪ History of treatment with PPS within 4 weeks of the study	successful if there were: ▪ A decrease in pain of 1 point or more ▪ A decrease in urgency of 1 point or more	on treatment
Waters et al., 2000 J Am Osteopath Assoc.	Retrospective case control study	27 Cases 27 Controls Gender NI**	All participants ▪ Had IC diagnosis at least 1 year ▪ Had persistent symptoms ▪ Undergone at least 1 cystoscopy with hydrodistension ▪ Negative urine culture Cases: ▪ Had to be on PPS for at least 8 weeks Controls ▪ Had to be taking at least one oral medication	For cases: changes in symptoms since they start using PPS. For controls: changes in symptoms during the 12 months before the interview.	Changes in frequency, urgency, and pain were significantly greater among cases. No change in nocturia was observed. Study population used concomitant medications
Sant et al., 2003 J Urol.	2X2 Factorial study design double blind Two treatment effects and 4 different groups: ▪ 100mg PPS t.i.d ▪ 50mg/at bed time hydroxyzine ▪ Combination of PPS and hydroxyzine	136 IC patients (121 Respondents) 89% female	To be included patients: ▪ Had to be >18 years old ▪ Had IC diagnosis at least 1 year ▪ Had performed cystoscopy with hydrodistension followed the NIDDK All patients had moderate symptoms of frequency (at least 11 daily), pain (at least 4 in 0-9 scale) for at least 24 weeks before to study entery	Responders were those who either moderately or markedly improved inpatient global assessment (a 7 point centered scale that assess the overall change)	▪ No significant difference in global response between hydroxyzine and no hydroxyzine groups. There was a trend for higher response in PPS arm compared to no PPS arm ▪ The combined therapies demonstrated the highest response rate followed by PPS alone and

Table 2-4 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY DOSE DURATION	SAMPLE SIZE CHARACTERISTICS	DIAGNOSTIC CRITERIA	OUTCOMES	RESULTS AND NOTES
Sant et al., 2003 J Urol. **Cont'd**	▪ Placebo 24 weeks				hydroxyzine alone ▪ No statistically significant differences between the main treatments in symptom changes over time for any secondary outcomes
Nickel et al., 2005 Urology.	Randomized double blind ranging dose trial Multi centers (30 centers) 100mg PPS t.i.d 200mg PPS t.i.d 300mg PPS t.i.d 32 weeks	380 IC patients (230 Completed the study) 90% female 10% male	Diagnoses with IC confirmed by : ▪ Symptomology history for 6 months or longer ▪ Positive cystoscopy with hydrodistension (glomerulations or Hunner ulcers) conducted at least 6 weeks before the trial and combined with urgency and pain ▪ Negative urine analysis Patients were excluded if: ▪ They would be using other therapies for IC ▪ Pregnant or lactating ▪ Had liver problems ▪ Use Coumadin, anticoagulants, heparin ▪ (For complete information return to the paper)	Responders were defined as those who reported moderately greatly improved or no symptoms in the patient global assessment	▪ For the three dosage of the PPS. A clinically response rate was observed ▪ No significant differences in efficacy among the three doses were reported ▪ The response appear to increase with increasing the duration but not the dose <u>Main limitation is lack of comparable group</u> <u>60% completion rate</u> <u>Patients could continue using antidepressant and antihistamine but not start to use during the trial</u>

* RDBPCT : Randomized double blind placebo-controlled clinical trial
** NI: Not identified

2.3.2 Major Problems in Studies Conducted to Assess the Efficacy of PPS

Several clinical trials were conducted to test the efficacy of PPS; however it is generally not appropriate to compare the results between these trials for several reasons. First of all, the fact that IC is such a debilitating syndrome with unknown pathogenesis and no clear diagnostic criteria makes it difficult to know if the study population of each of these trials were similar in disease severity or not. For example, each trial used different criteria to identify IC cases. Second, very few studies considered the level of symptoms' severity and its effect on response to the tested treatment. In fact, most of the previously described trials did not differentiate the study population in the terms of severe, moderate, or early diagnosed cases which may have affected the degree of response to the tested treatment, and thus biased the results. Moreover, although the previous trials mentioned both their primary and secondary endpoints, very few of them described, in detail, the instruments used to collect the data, or the criteria used to determine the responders clearly. This limitation disables the ability of other researchers to utilize these studies or work on refinement of the methods that were used before.

2.3.3 Pentosan Polysulfate Sodium as a New Intravesical Therapy

Using PPS as an intravesical therapy is a new hope for IC patients. Most of the studies that assessed its efficacy as an intravesical therapy were not published, conducted as pilot studies, or performed outside USA.

To the best of our knowledge, the only published clinical trial that assessed the efficacy of PPS as an intravesical therapy was done by Bade et al in the Netherlands in 1997. [37] It was a very small clinical trial that included only 20 IC patients all of whom were females, and followed

them for 3 months. This trial was based on a very small pilot study in which 6 IC patients received intravesical instillation of PPS (300 mg in 50 ml of 0.9% sodium chloride), and 4 of them showed long-term symptomatic, objective remissions, and excellent tolerance to the treatment. [132] As a result, Bade et al. accomplished the first clinical trial to assess the efficacy of intravesical instillation of PPS among IC patients. Participants were randomized to receive either intravesical PPS (300 mg in 50 ml of 0.9% sodium chloride) or a placebo applied twice a week for 3 months. Data about symptoms, bladder capacity, voiding volumes and urinary frequency were assessed after the 3 months. Furthermore, the long term outcome of those who decided to continue the treatment was obtained. Significant symptomatic relief was reported in 4 of those who received the intravesical PPS compared to 2 with placebo. Moreover, a significant increase in bladder capacity was reported among patients who were treated with PPS compared to placebo group. Interestingly, 18 months after the beginning of the study, symptom relief was reported by eight patients of those who were still receiving PPS and in 4 on placebo. Importantly, the instillations of PPS were done by participants at home during the whole study except for the first visit, when it was done by a professional nurse. This may have introduced bias to the results, as there was no way to know if PPS instillations were valid and reliable, or if the participants performed all the required instillations.

In USA, the only study that has been conducted so far to evaluate the effect of direct bladder application of PPS on the symptoms of IC among 31 females IC patients was the one by Davis et al. [38] They used O'Leary-Sant's IC Symptom Problem Questionnaire, Parsons' Patient Symptom Scale (PUF), and the pain index to assess the efficacy. After receiving 5 instillations of PPS over 21 months, participants reported 39.43% of reduction in average pain score and 15% or more of reduction in the other three assessment scale scores.

The present study is the first clinical trial in USA that was conducted to assess the efficacy of intravesical instillation of PPS in the bladder.

2.4 EPIDEMIOLOGY OF IC

2.4.1 IC Prevalence

Although there have been several attempts to estimate the prevalence of IC, most of these attempts have not been based upon representative populations. Furthermore, among a few studies which can be classified as population-based, discrepancies exist in the estimated prevalence rates. The main reasons for the discrepancies could be related to the use of different diagnostic criteria, geographical variation, and the statistical methods which the investigators used to calculate the prevalence rates. **Table 2-5** provides a summary of the main studies that attempted to estimate the prevalence rate of IC. More details can be found in the following paragraphs.

In 1975, Oravisto was the first investigator to conduct a population-based study to provide an accurate estimate of both prevalence and incidence of IC in Helsinki, Finland and the surrounding area. [7] There were approximately 974,305 inhabitants (523,794 female and 450,511 male) in the study area. The total number of IC patients at the time of the diagnosis was 103 (95 female and 8 male) based on review of hospital records, history of chronic voiding symptoms, sterile urine, and bladder biopsy showing fibrosis, edema, and /or lymphatic infiltration. Oravisto reported the joint prevalence rate to be 10.6 cases per 100,000 inhabitants for the total population and the prevalence rate among females to be 18.1 cases per 100,000 women. Because the number of men was too small, the investigator did not calculate the prevalence rate for males.

In the Netherlands, Bade et al. conducted a cross-sectional study to determine the prevalence rate of IC. [133] An urologist-based questionnaire was used to assess prevalence. The questionnaire had 3 parts: 1) epidemiological section: included questions about the average number of patients seen per year with chronic micturation disorders, and the number, average age and gender of interstitial cystitis patients, as well as additional information about the disease history and present symptoms, 2) diagnostic section: included questions regarding diagnostic investigations and diagnostic criteria for interstitial cystitis patients, and 3) therapy section: included questions about the most common therapy modalities, and what are the first, second and third choices. The questionnaire was sent to 235 urologists; however, only 153 participated in the study. About 122 responses were found to be completed and used in estimating the prevalence rate. The prevalence rate was reported to be 8 to 16 cases per 100,000 female patients. This was in line with the prevalence rate calculated by Oravisto. [7]

In Japan, Ito et al. estimated the prevalence rate of IC through sending a questionnaire to 300 chief urologists at major hospitals to determine the number of patients with interstitial cystitis. [134] The questionnaire included questions similar to those were in the previous study by Bade et al. [133] Responses were received from 262 urologists (response rate 87.3%) out of the 300, and were used in the analysis. Most Japanese urologists used two or more diagnostic criteria with bladder biopsy, the most common diagnostic procedure. Based on the result of the survey, the prevalence rates were estimated to be 1.2 per 100,000 patients and 4.5 per 100,000 female patients, with the female to male ratio of 5.8:1. Interestingly, this low prevalence rate may be explained by the presence of racial effect and/or the lack of awareness among Japanese urologists and patients about interstitial cystitis.

Held et al. were the first to estimate the prevalence rate of IC in USA. [2] Data from a random survey of 127 board-certified urologists were utilized. Three different ways were used to calculate the prevalence rate using information reported by the urologists on the percentage of female IC patients, the total number of visits for cystitis, and the total number of diagnosed IC patients in their practice. The three estimated values of the prevalence rate were 16.3 per 100,000, 25.1 per 100,000, and 76.3 per 100,000 with an average rate of 36.6 per 100,000.

In 1994, Jones et al. conducted another study to estimate the prevalence rate of IC in USA. [11] They relied on participants' self-reports of previous diagnosis of IC in 1989 National Household Interview Survey. Approximately 20,561 adults were asked if they ever had symptoms of urinary tract infection that lasted 3 months or longer, and if they were told that they had painful bladder syndrome or IC. About 118 participants in the total sample were classified as having IC (110 female and 8 male). The study reported that 0.5% of the civilian non-institutionalized population stated having IC and that the female/male ratio was 9:1. Interestingly, the data which were used in this study were based on self-reports with no verifiable medical record. This may have introduced misclassification bias to the results.

Curhan et al. conducted another study in 1999 to determine IC prevalence among women in the US. [3] Data from the Nurse Health Study (NHS) I and II were used for that purpose. Although the data about IC diagnosis were self-reported like that in Jones et al.'s study, Curhan et al. evaluated the accuracy of self-reports using medical records and the diagnostic criteria of the National Institute of Health for enrollment in research studies of IC. Surprisingly, the prevalence of IC was 67 per 100,000 women in NHS II and 52 per 100,000 women in NHS I. This study showed that the prevalence rate of IC in the US is more than 50% greater than previously reported ones and 3 fold greater than one reported in Europe.

Most recently, Clemens et al. used a comprehensive managed care patient's database in Pacific Northwest (Kaiser Permanente Northwest database) to estimate the prevalence of IC in both men and women. [12] Kaiser Permanente is the largest non-profit health maintenance organization in the United States, serving 8.2 millions in 9 states and the District of Columbia. After applying a specific exclusion criteria there were 136,400 women and 120,553 men in the study population. The investigators used 4 definitions of IC to calculate the prevalence rate as follows: 1) patients assigned a diagnosis of IC (International classification of Disease [ICD]-9 595.1) , 2) patients assigned a diagnosis of IC without any of specific exclusion criteria (used in most epidemiological studies) , 3) patients assigned a diagnosis of IC who had undergone cystoscopy during the study period, and 4) patients assigned a diagnosis of IC who had undergone cystoscopy with hydrodistension for IC during the study. The prevalence rate of IC was 197 per 100,000 women and 41 per 100,000 men (definition 1), 158 per 100,000 women and 28 per 100,000 men (definition 2), 99 per 100,000 women and 19 per 100,000 men (definition 3), and 45 per 100,000 women and 8 per 100,000 men (definition 4). Based on any of the above definitions the female to male ratio for each estimate was 5:1, which was close to the ratio reported by Ito et al. in 2000 in Japan. This recent study is very important because it shows that the IC prevalence rates in USA are significantly higher for women and men than previously published estimates. Furthermore, the men now account for higher proportion of patients than previously reported.

Interestingly, several researchers argued about the validity of the previously estimated prevalence rates. [4, 5, 6] They stated that all the previous studies were based on formerly diagnosed cases rather than evaluate the prevalence of symptoms accompanied IC. Early cases start with only one symptom while advanced cases experience multiple severe symptoms, thus using

classic criteria to diagnose IC would underestimate the prevalence. In fact, when traditional diagnostic criteria are strictly applied, up to two thirds of IC cases may be missed. [96] As a result, three recent studies (one in Finland, one in Vienna and the other one in USA) were conducted to estimate the prevalence rate of IC using criteria that based on evaluating IC according to the symptoms.

In Finland, Leppilahti et al. evaluated IC prevalence using O'Leary–Sant IC Symptom and Problem Index questionnaire in a population based study. [5] Approximately 2,000 women were randomly selected from Finland and enrolled in the study. Women with a high symptoms and problem score (each ≥12) including nocturia ≥ 2 and pain ≥ 2, excluding urinary tract infection and pregnancy, were assumed most likely to have IC. According to this definition, Leppilahti et al. indicated that IC is more common in Finland than previously estimated with a prevalence of 300 per 100, 000 (clinically confirmed probable cases) to 680 per 100,000 women (probable and possible cases).

In Vienna 2006, Temml el al determined the prevalence of IC using O'Leary–Sant IC Symptom and Problem Index questionnaire. [6] The investigators used the same definition of IC case that was used by Leppilahti et al. [5] The overall prevalence rate of IC was estimated to be 306 per 100,000 women.

Rosenberg et al. repeated the study by Leppilahti et al, [4] however in USA. They used two validated surveys that were developed to help in evaluating IC based on symptoms (O'Leary-Sant (OLS) IC Symptom and Problem Index, and the Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale), thus the mild cases will not be under estimated. According to their study, which was conducted in primary care office and included 1,218 women, the prevalence rate of IC in women based on the result from OLS survey was 575 per 100,000. This result was close to

Leppilahti et al. population based study. [5] On the other hand, the prevalence rate which was based on PUF was much higher (12,600 per 100,000 women). The results from this study suggests that the prevalence rate among US women somewhat between the above two estimated numbers. It is worthy of note that OLS was not design as a screening test, however to evaluate the development of established IC, while PUF was validated as a screening tool for IC. [23, 24]

Interestingly, previous use of the PUF by Parsons et al., [24] in a random sample of 317 women attending IC lectures suggested that nearly 22% of women in the general population may have IC (1 in 4.5 women). This was based on computing the expected number of women who would have positive potassium sensitivity test as a function of observed PUF scores and the prior probability of being normal versus not normal, using reduced logistic regression model. To test that hypothesis, Parsons et al. conducted another study in 2004 among all female members of the University of California, San Diego third-year medical students. [135] They used PUF and intravesical potassium sensitivity test (PST) to determine IC cases. Females with score 7 or greater were asked to undergo clinical evaluation including PST. Interestingly, Parsons et al. identified probable IC (PUF score 7 or greater) in 30.6% and documented IC (PUF score 7 or greater with positive PST) in a minimum of 10% of study population. This study supports the previous two studies and indicates that IC may be a chronic disease with higher prevalence rate than previously estimated. According to this study, the estimated prevalence of IC in US should be increased from approximately 1.5 million to perhaps 25 to 30 million women.

In summary, the literature about the prevalence rate of IC still insufficient and poor. Most of the studies have been conducted among females and very few included males. Moreover, all the interests were directed to the adult population, and provided no information about IC in children. Also, all the estimates until now were based on white population at most. It

is interesting to speculate that there may be racial differences in the frequency of IC, because the rate among Japanese women has been reported to be less than that of the US women. [134] Despite all the previous limitations, one can cautiously conclude that there might be an increase in the estimated prevalence rate of IC since 1975 among both women and men and that the increase seems to be faster among men and may be responsible for decreasing the ratio between female and male from 9:1 to 5:1.

Importantly, in order to be able to determine the exact prevalence rate of IC we need diagnostic criteria with high specificity to be applied in all the studies. It is worthy of note that most of the previous studies used different methods to identify IC cases. Some of these studies relied on self-reported symptoms. Other studies were procedures based to confirm the diagnosis of IC. This has the potential to introduce misclassification bias in some studies and underestimation in other studies. Thus, we still need well-designed epidemiological studies that base on strong accurate diagnostic criteria and include different races, ethnic, and ages groups to determine the exact prevalence rate of IC.

Table 2-5: Summary of the Studies that Estimated the Prevalence Rate of Interstitial Cystitis Worldwide (1975-2006)

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE	DIAGNOSIS OF IC BASED ON	RESULTS	NOTES
Outside USA					
Oravisto, 1975 Ann Chir Gynaecol Fenn.	Cross-sectional Finland	974,305 Males and females	▪ Hospital records review ▪ History of IC Chronic voiding symptoms, sterile urine, bladder biopsy showing fibrosis, edema, and/or lymphatic infiltration	103 IC cases (95 female, 8 male) were identified out of 974,305 Joint prevalence rate 10.6/100,000 inhabitant Females prevalence rate 18.1/100,000 women	
Bade et al., 1995 J Urol.	Cross-sectional The Netherlands	235 Urologists (122 responded)	Urologist based questionnaire Included 3 parts: ▪ Epidemiological section The average number of patients seen per year with chronic micturation disorders, the number, average age and gender of interstitial cystitis patients treated, the disease history and presenting symptoms ▪ Diagnostic section ▪ Diagnostic investigations and diagnostic criteria for IC) ▪ Therapy section: ▪ Common therapy , first, second and third choices of therapy	Female prevalence rate 8-16 cases/100,000 female patients	The most common diagnostic procedure based on counts of mast cells Only 48 percent of the responders reported interstitial cystitis in male patients, with a male-to-female ratio of less than 1:10
Ito et al., 2000 Br J Urol.	Cross-sectional Japan	300Chief urologists (262 responded)	Urologist based questionnaire Collected the following information: ▪ The total number of patients with IC per year, the patient's age and sex, their chief complaints and disease	Joint prevalence rate 1.2/100,000 patients Female prevalence rate 4.5/100,000 female	The most common diagnostic procedure based

Table 2-5 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE	DIAGNOSIS OF IC BASED ON	RESULTS	NOTES
Outside USA					
Ito et al., 2000 Br J Urol. **Cont'd**			history, the total number of all patients and their sex distribution, the criteria used by each urologist, and the first, second and third choice of therapy	patients	on biopsy result
Leppilahti et al., 2005* J Urol.	Cross-sectional Finland	2000 Females (1331 Responded) selected randomly from Finnish population register	▪ Patients who had classified as either moderate or severe cases by O'Leary Sant and who had no urinary tract infection were invited for clinical examination ▪ If IC was suspected base on these examinations a cystoscopy with hydrodistension was performed ▪ Probable IC was based on NIDDK ▪ Possible IC was assigned if other bladder diseases were excluded but the severity of all NIDDK criteria were not strictly achieved	32 had moderate or severe IC out of 1331 21 of 32 underwent clinical evaluation 3 had probable IC and 4 had possible IC After correction: The estimated prevalence rate: possible cases: 300/100,000 women Probable and possible cases: 680/100,000 women	Total O'Leary score: 0-3 no symptoms 4-6 mild 7-11 moderate 12+ severe No diagnosis confirmation or excluding IC could be made among 8 patients with moderate or severe symptoms
Temml et al., 2006* Eur Urol.	Cross-sectional Vienna	981 Women Attending voluntary health survey in Vienna	Women who got ≥12 in each of the ICSI and ICPI and had ≥2 nocturia, and ≥2 score in pain assessment scale after excluding urinary tract infection and pregnancy were considered as most likely to have IC	3 had a high risk for IC symptoms based on OLS out of 981 women The overall prevalence rate: 306/100,000	Total O'Leary score: 0-3 no symptoms 4-6 mild 7-11 moderate 12+ severe These scores grouped to: 0-6 no risk of IC 7-13 minimal risk 14-23 moderate risk 24-36 high risk

Table 2-5 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE	DIAGNOSIS OF IC BASED ON	RESULTS	NOTES
Inside USA					
Held et al., 1990 Interstitial Cystitis. New York: Springher-Verlag	Cross-sectional USA	127 Chief urologists	Three different ways were used to calculate the prevalence rate: ▪ Information reported by the urologists on the percentage of female IC patients ▪ The total number of visits for cystitis ▪ The total number of diagnosed IC patients in their practice	Estimated prevalence rates: 16.3/100,000 25.1/100,000 76.3/100,000 Average rate of 36.6/100,000	Because this study was only published in book, it was not easy to gather complete information about the method of calculating the prevalence rate
Jones et al., 1994 J Urol.	Cross-sectional USA	20,561 Adults males and females (participated in the National Household Survey)	Based on Self-report, participants were asked: ▪ If they ever had symptoms of a urinary tract infection that persist for 3 months or longer ▪ If they were told that they had IC	118 IC cases were identified out of 20,561 adults 0.5% of the civilian non-institutionalized population would state having IC. 573/100,000 civilian non-institutionalized population	Male to female is 1:9
Curhan et al., 1999 J Urol.	Cross-sectional USA	184,583 Females (participants in the nurse health study I n= 91,155, and II n= 93,428)	All participants were asked in a questionnaire: ▪ Whether IC had ever been diagnosed by cystoscopy ▪ All participants who answered yes were sent a supplementary questionnaire to gather more information ▪ Self-reported IC was confirmed from medical records ▪ NIDDK were used but were not applied completely Based on that IC cases were classified into:	110 IC cases were identified out of 184,583 (participants in the nurse health study I = 47 out of 91,155, II = 63 out of 93,428) The estimated prevalence rates: In Nurse II :67/100,000	The study population is much healthy and more educated Nurse II younger than Nurse I showed higher prevalence

Table 2-5 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE	DIAGNOSIS OF IC BASED ON	RESULTS	NOTES
Inside USA					
Curhan et al., 1999 J Urol. **Cont'd**			Definite: ▪ Report of positive cystoscopy with hydrodistension ▪ Biopsy demonstrated chronic cystitis ▪ Negative urine cytology Probable: ▪ Report of positive cystoscopy Possible: ▪ Letter stated that patient underwent cystoscopy with or without distension with diagnostic impression of IC	In Nurse I: 52/100,000	The inclusion of probable and possible may overestimate the prevalence rate Only 6.4% of self-reported were correctly confirmed. If we apply this to the study by Jones the prevalence rate will reduce to 56/100,000
Parsons et al., 2004 Urology	Cross-sectional USA	52 Females (all female members of the third year medical student class at the university of California	▪ Patients who had PUF score of 7 or greater and positive PST	5 IC out of 52 females 10% had IC (5/52) This indicates that the prevalence of IC is not 1.5 million but 25 to 30 million women	This study combined a screening tool with clinical diagnostic tool The result could be more than 10% as those 5 only who accept to perform the PST
Clemens et al., 2005 J Urol.	Cross-sectional USA	136,400 Females 120,553 Males Kaiser Permanente Northwest Comprehensive	▪ From medical record identify cases with primary or secondary diagnosis as IC ▪ Applied exclusion criteria that was used in most epidemiological studies	269 Women with IC were identified out of 136,400 Female 49 men with IC were identified out of 120,553 Male	Male to female is 1:5 in all the 4 definitions Cannot be generalized like all

Table 2-5 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE	DIAGNOSIS OF IC BASED ON	RESULTS	NOTES
Inside USA					
Clemens et al., 2005 J Urol. **Cont'd**		managed care patient data base	**4 Definition of IC were used:** ▪ Patients assigned a diagnosis of IC (international classification) ▪ Patients assigned a diagnosis of IC without any of the exclusion criteria used in most Epi studies ▪ Patients assigned a diagnosis of IC without any of the exclusion criteria used in most Epi studies but undergone cystoscopy ▪ Patients assigned a diagnosis of IC without any of the exclusion criteria used in most Epi studies but undergone cystoscopy with hydrodistension	Definition1: 197/100,000 female 41/100,000 men Definition2: 158/100,000 female 28/100,000 men Definition3: 99/100,000 female 19/100,000 men Definition4: 45/100,000 female 8/100,000 men	previous studies as most of the population were whites
Rosenberg et al., 2005* J Urol.	Cross-sectional USA	1218 Women from Primary care office	▪ Using 2 validated surveys, namely the O'Leary-Sant (OLS) IC symptom and problem index, and the Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale. ▪ Probable IC was defined by an OLS composite score of 24 or greater (12 or greater on both the symptom and problem indices including symptomatic pain and nocturia scores of 2 or greater as used in the Finnish study). ▪ Probable IC based on PUF score was determined by estimating the likelihood of a positive potassium sensitivity test.	161 IC (7 probable cases based on OLS, 154 based on PUF) were identified out of 1218 women from primary care office The estimated prevalence rate: 575/100,000 Based on O'Leary-Sant instrument 12,600/100,000 Based on PUF instrument	

* IC prevalence was based on the prevalence of IC symptoms

2.4.2 IC Incidence

Very few studies conducted to estimate the incidence rate of IC. During the period between 1962 and 1971, Oravisto reported a minimal annual incidence rate of 0.66 cases per 100,000 inhabitants in the city of Helsinki and the surrounding area. [7] The annual incidence rate among females during the same period has been reported to be 1.2 cases per 100,000 women. Latter in 1987, Held et al. estimated the incidence rate of IC in the US to be 2.6 per 100,000, which is four times higher than that reported in Finland by Oravisto. [2] Suggestions provided to explain the difference in estimating IC incidence rate in the two studies included; using different diagnostic criteria and the low response rate (26%) in Held et al. study.

In 2003, Roberts et al., estimated the incidence rate of IC in Olmsted County, MN, USA. [136] The findings were consistent with the general idea that IC is a rare disease. Residents of Olmsted County who had received a physician-assigned diagnosis of IC during the period 1976 to 1996 were included in the study. 20 Patients were identified during the study period (16 females and 4 males). The overall age- and sex adjusted incidence rate was 1.1 per 100,000 population. The age-adjusted incidence rates were 1.6 per 100,000 in females and 0.6 per 100,000 in males.

Recently in 2005, Clemens et al. estimated IC incidence rate using Kaiser Permanente Northwest database during the period 2002 to 2003 to be 21 per 100,000 women and 4 per 100,000 men. [12] Although this study indicated that the incidence rate of IC significantly increased since 1975, great care should be applied when drawing a conclusion. It is worthy of note that the same limitations found in studies that estimated prevalence can be also found here.

The diagnostic criteria which were not consistent in incidence studies plus geographical variation between study populations adds to the confused state of multiple reported incidence rates of IC.

2.4.3 Possible Risk Factors

Several possible risk factors have been identified from reviewing the literature of the epidemiology of IC. Surprisingly, very few epidemiological studies were conducted to identify these risk factors among one single population. The following sections summarize the possible risk factors of IC based on the results of different epidemiological and clinical studies.

2.4.3.1 Gender & Age at Onset

Women are more frequently diagnosed with IC than men. They make up 90% of patients with IC. [137] Recent studies reported female to male ratio to be approximately 5:1 [12, 134] instead of 9:1. [11] Because the correct diagnosis is often made several years after the actual onset of the disease, the onset age has moved to older age. In women, the duration of symptoms before the diagnosis is reported to be around 5 to 7 years [3] compared to 4 years in men. [138] The onset of IC usually occurs between 30 and 70 years of age, [139] with a median age of 43. [140] The prevalence of the disease appears to be increasing among young and middle aged women. [96] In women, the diagnosis generally peaks in the third to sixth decades of life. [18] On the other hand, the mean age at diagnosis among men has been reported to be 67 years old, which is older than that in women. [138] There is a strong belief that IC in men is misdiagnosed by nonbacterial prostatitis and benign prostatic hypertrophy.

Although, the NIDDK mandates that patient with age younger than 18 years is an automatic exclusion criterion for IC, there is increasing evidence that the syndrome can affect

children as well. Epidemiological survey on adults with IC indicates that symptoms sometimes begin in childhood. [20] A history of childhood bladder symptoms is reported by 10% to 28% of IC patients. [2, 18] Close et al. retrospectively reviewed the chart of 20 children referred for chronic sensory urgency, frequency and bladder pain who underwent cystoscopy with hydrodistension. According to their small study, the onset age among children ranged from 2 to 11 years with a median age of 4.5. [141] Definitely, prospective studies are needed to study the association between childhood disease and the development of IC later in life.

2.4.3.2 Race

Most of the studies that were conducted to describe the epidemiology of IC included mainly whites (more than 90%). Thus, the data about the distribution of IC among different races are very limited. According to Held et al., IC has been more common among Jewish women (14%) compared to the general population (3%). [2] In 1993, Sant retrospectively reviewed the patients database at the IC Center, New England Medical Center and reported IC among 8.5% of study population, with 3% being African American, 3.5% Hispanic American, and 2% Asian American. [142] Although the clinical and the endoscopic findings as well as response to treatment were similar in both minority and the rest study population, the average duration of symptoms before diagnosis was 2.9 years in minority compared to 13 months in the rest of the study population. This could be due to low economic status that decreases the access to health care. Recently, Forrest et al. characterized IC in men in a study included 92 IC cases. Approximately 83% of the study populations were white and 17% were American Indians of Cherokee descent. [143] More effort is needed to encourage minority population to participate in IC health research in order to delineate how race play a role in IC.

2.4.3.3 Genetics

Evidence increases that the syndrome may have a genetic component. Case reports of strikingly high prevalence of IC within first-degree relatives are substantiated by various studies that suggested a genetic susceptibility to the disorder. [144] In a pilot study, Warren et al. reported that adult female first degree relatives of IC patients may have a prevalence of IC 17 times that found in the general population. [145] Another evidence of the genetic component of IC came through Parsons et al. [146] Urgency/frequency problems in female relatives were reported by 35% of 466 patients with IC and by 33% of 166 patients with urethral syndrome.

2.4.3.4 Hormones

Several evidences support the importance of considering hormonal effect when studying IC. Given that the majority of IC patients are females and the clinical literature suggests a flare in IC symptoms during premenstrual period, [64, 147, 148] a direct influence of gonadal hormones and estrogen may be considered. Theoharides et al. showed that estradiol may influence pathophysiological responses via bladder mast cells expressing high affinity estrogen receptors. [147] Estrogen may modulate neurogenic inflammation by interacting with substances that participate in the pathogenesis of neurogenic inflammation such as substances P. [149] The clarification of the importance of hormones in the understanding and treatment of IC may produce applications of selective modulation of pain control.

2.4.3.5 Dietary Factors

It has been reported that several food could initiate an attack of urgency and frequency and cause a flare-up of IC symptoms. [13, 150, 151] These food can be divided into two main categories; those stimulate histamine and serotonin release from the stomach and those with high levels of

biogenic amines (tryptophan, phenylalanine, tyrosine, and tyramine). The selective metabolites of these biogenic amines have the ability to bind to the sulfate groups of polysaccharides in the GAG layer and inactivate their hydrophilic properties. As a result of that a break in the mucous layer will develop. [150]

Attention was drawn to the possible association between food and IC symptoms during clinical studies, when IC patients reported relief of pelvic pain when they were on specific dietary programs and deleted certain food. IC patients who consumed less amount of coffee compared to the general experienced less exacerbating IC symptoms. [151] Furthermore, acidic, alcoholic, and carbonated beverages are reported as drinks that increased IC pain in more than 50% of the patients. [18]

2.4.3.6 Co-morbid Conditions

Different conditions have been documented among IC patients. Approximately half IC patients have allergies where the mast cell activation may contribute to the pathogenesis of both allergies and IC. Irritable bowel syndrome, generalized pain disorder, autoimmune diseases such as lupus erythematosis and Sjögren's (SHOW-grins) syndrome also have been observed in conjunction with IC. Furthermore, higher incidence of chronic fatigue, multiple sclerosis, fibromyalgia and migraine have been reported among IC patients. [13]

2.4.4 Factors Associated With the Severity of IC symptoms

Very limited literature was found about factors that may be associated with the severity of IC symptoms. [6, 17, 152] Moreover, several limitations can be addressed in these studies and called for further investigations. Temml et al. identified correlations for IC symptoms among women

attending a voluntary health survey project in Vienna. [6] The investigators used O'Leary-Sant IC Symptom and Problem Index mainly to identify IC cases. Women with high (≥12) symptom and problem scores including nocturia (>2) and pain were considered most likely to have IC. The researchers reported psychological stress and bowel disorders as important factors associated with symptom severity after adjusting for age and BMI. It is important to mention that Temml et al.'s study was a questionnaire-based analysis and no individual underwent a thorough urologic evaluation. This put a question mark on the validity of the diagnosis of IC in the study.

Simon et al. studied the characteristics of 424 IC patients participated in the Interstitial Cystitis Data Base (ICDB) study by symptom severity. [17] Interestingly, the investigators reported that as severity of symptoms increases, there appears to be a slight, non-significant trend toward greater age. Moreover, patients with severe symptoms tend to be less educated, less likely to be employed, and reported a smaller household income. The study also showed that bladder volumes at first sensation and at maximal capacity were inversely associated with symptom severity. Importantly, all the analyses were univariate; therefore the reader cannot tell if all these factors independently explain the increase in the severity of symptoms. Furthermore, the investigators did not use a validated standardized instrument to measure the dependent variable (symptom severity).

Clemens et al. investigated 174 men with chronic prostatitis and 111 women with IC to quantify symptom severity and identify demographic, medical and psychosocial characteristics. [152] Focusing on women with IC, symptom severity was assessed using the O'Leary-Sant IC Symptom and Problem Index. Interestingly, self-reported urinary frequency and urgency, worse depression scores, lower educational level and postmenopausal status were independent predictors of increased symptom severity among women with IC. Importantly, Clemens et al.

used the total O'Leary-Sant score (symptom index and problem index) as a measure of symptom severity, which makes their dependent outcome not specifically symptom severity. Moreover, certain covariates in the multivariate models were similar to some questions that make up the total O'Leary-Sant score, therefore collinearity can be a problem, although, the investigators indicated that no collinearity was found. Regression coefficients biased by collinearity might cause variables that demonstrate no significant relationship with the outcome when considered in isolation to become highly significant in conjunction with collinear variables, yielding an elevated risk of false-positive results (Type I error). Alternatively, multiple regression coefficients might show no statistical significance due to incorrectly estimated wide confidence intervals, yielding an elevated risk of false-negative results (Type II error). [153]

The current study assessed comprehensively to what extent several factors included; socio-demographic, lifestyle, reproductive, clinical and sexual functioning factors affect the severity of IC symptoms.

2.5 HEALTH RELATED QUALITY OF LIFE (HRQL)

2.5.1 The Importance of Measuring HRQL

The World Health Organization (WHO) defined Health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". [154] Early, researchers were more interested in measuring the impact of diseases and injury when evaluating human health through either using morbidity or mortality statistics. In fact, there are other important faces of health that this definition includes and also needed to be assessed. Measuring HRQL helps the researchers to determine how a specific event can affect other indicators of human health such as mental and social well-being. In order to be able to have a complete picture about the impact of specific outcome on human health, it is important to determine how this outcome affects all the different aspects of health that the WHO specified in its definition.

2.5.2 Evolution of HRQL Research

HRQL assessment provides valuable information to all members of health care system. Interest in HRQL assessment has continued to increase in recent years. This can be illustrated from both national and international activities. [155-157] Since 1985, The United States Food and Drug Administration have been using HRQL measurements in the process of approving any new anti-cancer drug. [158] In addition to clinical trials, HRQL assessment has evolved into a primary outcome measure in health services, acute care, and chronic diseases. [159,160]

Interest in HRQL is also seen in international professional societies. The International Society for Quality of Life Research (ISQOL) was founded in 1994 to promote research in HRQL, the scientific study of HRQL and health care throughout the world. It promotes the HRQL measurements from conceptualization to practice and application. Another organization, the International Society for Quality of Life Studies (ISQOLS) which promotes the research, discussion contributions to the research literature and the teaching in HRQL studies throughout the world. [161]

Another proof of increasing the interest in HRQL research is the large number of related publications. The term "quality of life" appeared in Index Medicus in 1972 with 15 citations in comparison to 52134 citations as in May 2006. Moreover, the first journal focusing on HRQL, Quality of Life Research was published in 1992. [161]

2.5.3 Definition of HRQL

In order to conduct valid HRQL studies or to adequately describe, assess, or discuss HRQL, a clear definition of HRQL is required. There is no single definition of the term HRQL. Hunt and McKenna pointed out that there was no agreed definition, no theoretical base, inappropriate use of measures, lack of the recognition of the social basis of definition and measurements and confusion between HRQL and quality of care. [162] Several definitions can be found and most of these definitions showed that HRQL is a multidimensional concept. Many experts agreed on the subjectivity and dynamism of the concept. [163]

The multidimensional aspect of the HRQL is demonstrated in the several domains that have been used to identify HRQL (physical, social, psychological, somatic, and spiritual). Most of the studies that assessed HRQL rely on subjective, self-reported measures rather than

objective measures. The use of self-report HRQL became more dominant after several studies reported a lack of agreement between the HRQL rating given by the patients, family members, and health care providers. [164] The dynamism of the concept reflects the importance of assessing the HRQL along a continuum, as HRQL standards for each person may change over time. Values and self-evaluations of life may change over time in response to life and health events and experience.

In 1990, Spilker described HRQL assessment through three interrelated levels: a) Overall assessment of well-being, b) broad domains such as physical, psychological, economic, and social, and c) the components of each domain. [165] On the other hand, the WHO defined HRQL as "individuals' perceptions of their position in life in the context of the culture and value system in which they live and in relation to their goals, standards, and concerns". [157] The WHO definition includes six different domains as follows: physical health, psychological state, level of independence, social relationship, environmental features and spiritual concerns.

Like both of the two previous definitions, the workshop on HRQL Research in Cancer Clinical Trials cosponsored by the National Cancer Institute, and the Office of Medical Applications of Research National Institute of Health, defined HRQL as a multidimensional concept "Health Related Quality of Life is the value assigned to duration of life as modified by impairments, functional states, perceptions, and social opportunities as influenced by disease, injury, treatment, or policy". [156] Studies by Grant, Padilla and Ferrell demonstrated the need of multidimensional definition of the HRQL by identifying four consistent domains: physical well-being, psychological well-being, social well-being and spiritual well-being. This model has been validated through different studies on cancer patients. [166]

2.5.4 HRQL Dimensions

Many researchers agreed that there are four to five basic dimensions of HRQL: 1) physical, 2) psychological, 3) social, 4) somatic /disease and treatment related symptoms, and 5) spiritual. [167] The most used traditional dimension is the physical one. The main questions that assess this dimension are about strength, energy, ability to perform activity of daily living and self-care. Interestingly, the response of this dimension correlates with the physicians' estimate of the patients' well-being and functional status. [166] The psychological dimension is unlike the physical dimension in that the health care providers poorly estimate the psychology of their patients. The main questions that assess this dimension are about anxiety, depression and fear. [168] The third dimension reflects the quality of an individual's relationship with family, friends, and general community. The somatic dimension reflects the treatment side effect and the disease symptoms, while the spiritual dimension reflects the perception that life has meaning and purpose. [166] Some researchers consider the later as part of the psychological dimension.

2.5.5 Measuring HRQL

There is no one right way to measure health related quality of life, however, the measure needs to be tailored to the aim of the assessment. Consistent with the multidimensional nature of health related quality of life, investigators have identified a wide range of measures to tap quality of life. These include measures of emotional well-being (for example, measured with indicators of life satisfaction and self-esteem), psychological well-being (for example, measured with indicators for anxiety, depression, and a wide range of cognitive indicators), social well-being and roles (for example, measured with indicators of social support and activities), and physical

health and functioning (for example, measured with scales of self-rated health, disability or ability to perform activities of daily living). [169]

Health related quality of life measures can be divided into either generic or specific measures. Generic measures assess global relevant concepts such as the ability to function in everyday life and emotional well-being. [170] They are not specific to certain disease, age, or treatment. For that reason, generic questionnaires are very useful measures that allow for comparisons between different conditions. [171] They permit comparison of the HRQL in patients with certain disease, like IC, to that of patients without that disease.

Many generic measures have been developed and their psychometric properties have been comprehensively evaluated. [169] Examples of generic quality of life measures include Nottingham Health Profile (NHP), Medical Outcome Study (MOS) Short Form-36 Health Survey (SF-36), European Quality of Life Index (EuroQOL), and the World Health Organization Quality of Life measure (WHOQOL-100). [172] Interestingly, the common health concepts represented by the generic instruments include physical, social, and role functioning. Sleep, sexual and cognitive functions are represented less frequently.

On the other hand, specific measures are designed to assess the impact of specific condition and its treatment on certain concepts and domains. [173] Examples of disease specific measures include the Rheumatoid Arthritis Quality of Life scale (RAQoL) and the European Organization for Research and Treatment of Cancer QLQ-C30. [174, 175]

2.5.6 Medical Outcome Study (MOS) Short Form-36 (SF-36) Health Survey

The SF-36 is a multipurpose, short-form health survey that composed of only 36 questions. It yields eight-scale profile of scores as well as physical and mental health summary measures.[176] It

is referred to as a generic measure because it assesses health concepts that represent basic human values that are relevant to everyone's functional status and well-being. [177] For that reason, the SF-36 has been useful in comparing general and specific population, the relative burden of diseases, determining the health benefits produced by a wide range of different treatments, and screening individual patients. [176]

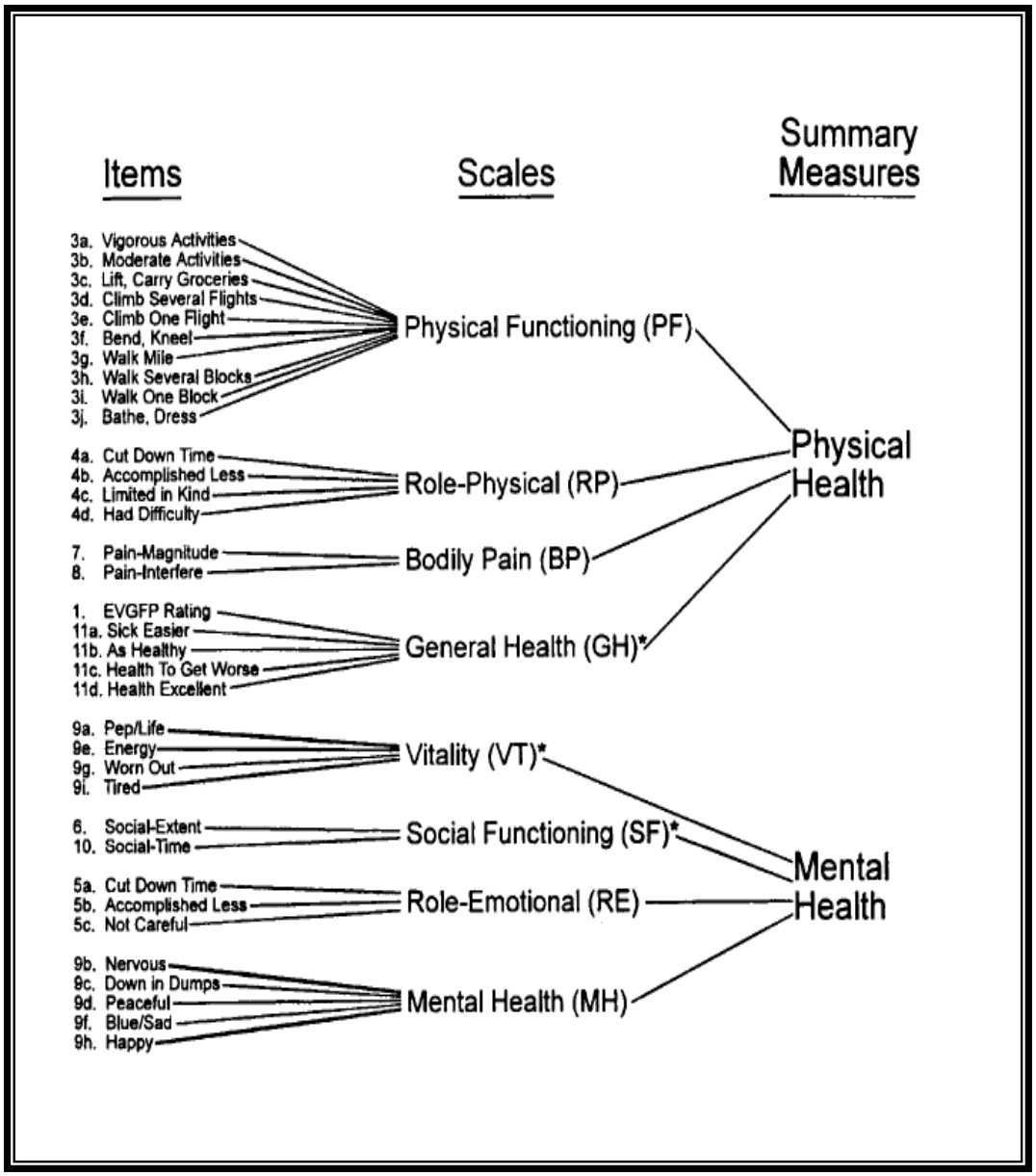
Importantly, SF-36 has been documented in more than 1000 publications. [176] The number of studies that either used or cited SF-36 is increasing significantly. If you made a quick search using PubMed, more than 5000 publications will be retrieved.

The SF-36 was constructed through the Medical Outcomes Study (MOS), which was a four-year observational study that investigated the changes in physician practice styles and patient outcomes under different healthcare settings such as health maintenance organizations, large physician groups, or individual physician fee-for-service practices. [178] One of the aims of the MOS was to construct reliable and valid tools for measuring and monitoring patient-reported functioning and well-being.[179] Forty different physical and mental health concepts were used in the MOS to assess its aims. The eight health scales of the SF-36 were selected out of these 40 concepts to represent the most frequently measured concepts in widely used health surveys, and those most affected by disease and treatment. [176] The selection process was the most difficult stage in developing the SF-36. Health distress, sexual functioning, family functioning, and sleep adequacy were among the concepts which seriously considered in the selection process, but not chosen. [177]

The eight different domains of the SF-36 include ; physical functioning, role limitations related to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. SF-36 includes a single

item that measures change in health over time. [177] All scale scores range from 0 (indicates worst health), to 100 (indicates best health). The SF-36 has high construct validity, [177, 180] high internal consistency, [177, 181] and high test-retest reliability. [182]

The eight domains of the SF-36 can be grouped into scales that either assess physical health (physical functioning, role limitations due to physical, and pain scales) or mental or emotional health (the mental health, role limitation due to emotional problems, and social functioning scales). [176] Related to physical health, the physical functioning scale assesses limitations in performing normal physical activity, such as walking, carrying groceries; the role limitations due to physical problems measures disability that is related to any physical problem; while the pain scale measures the severity and limitations due to the pain. On the other hand, scales that measured mental health and emotional health assess that through mental functioning and role limitations due to emotional problems such as disability to mental problem. Interestingly, vitality, general health perceptions, and social functioning scales have been found to measure both physical and mental domains simultaneously. [183] Two summary scores can be presented according to factor analysis; Physical Component Summary **(PCS)** or Mental Component Summary **(MCS)**. [184] **Figure 2-1** shows how the 36 items in the SF-36 can be summarized in just two component summary scales.



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* Significant correlation with Other Summary Measures

Figure 2-2: SF-36 Measurement Model §

Table 2-6 gives the reader more details about how these two summary scales correlated with the eight SF-36 domains, in addition to the interpretation of extreme scores in each of the SF-36 domains, and the two summary scales.

Table 2-6: Summary Information About SF-36 Domains (Scales) and Physical and Mental Component Summary Measures *

CORRELATIONS			NUMBER OF				DEFINITION (% OBSERVED)[E]	
Domains (Scales)	**PCS[A]**	**MCS[A]**	**Items**	**Levels**	**Mean±SD[C]**	**R[D]**	**Lowest Possible Score**	**Highest Possible Score**
Physical Functioning (PF)	.85	.12	10	21	84.5±23.3	.93	Very limited in performing all physical activities, including bathing or dressing (0.8%)	Performs all types of physical activities including the most vigorous without limitations (38.8%)
Role-Physical (RP)	.81	.27	4	5	80.9±34.0	.89	Problems with work or other daily activities as a result of physical health (10.3%)	No problems with work or other daily activities (70.9%)
Bodily Pain (BP)	.76	.28	2	11	75.2±23.7	.90	Very severe and extremely limiting pain (0.6%)	No pain or limitations due to pain (31.9%)
General Health (GH)	.69	.37	5	21	71.9±20.3	.81	Evaluates personal health as poor and believes it is likely to get worse (0.0%)	Evaluates personal health as excellent (7.4%)
Vitality (VT)	.47	.65	4	1	60.9±20.9	.86	Feels tired and worn out all of the time (0.5%)	Feels full of pep and energy all of the time (1.5%)
Social Functioning (SF)	.42	.67	2	9	83.3 ± 22.7	.68	Extreme and frequent interference with normal social activities due to physical and emotional problem (0.6%)	Performs normal social activities without interference due to physical or emotional problems (52.3%)
Role-Emotional (RE)	.16	.78	3	4	81.3 ±33.0	.82	Problems with work or other daily activities as a result of emotional problems (9.6%)	No problems with work or other daily activities (71.0%)
Mental Health (MH)	.17	.87	5	6	74.7 ±18.1	.84	Feeling s of nervousness and depressions all of the time (0.0%)	Feels peaceful, happy, and calm all of the time (0.2%)
PCS[A]			5	67[B]	50.0 ±10	.92	Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness health rated "poor" (0.0%)	No physical limitations, disabilities, or decrements in well-being, high energy level, health rated "excellent" (0.0%)
MCS[A]			5	93[B]	50.0 ±10	.88	Frequent psychological distress, social and role disability due to emotional problems, health rated "poor" (0.0%)	Frequent positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "poor" (0.0%)

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A PCS: Physical Component Summary, MCS: Mental Component Summary.

B Number of levels observed at baseline; scores rounded to the first decimal place (n= 2474).

C Score for eight domains are the percentage of the total possible score achieved for each domain. Score for PCS and MCS are T-scores.

D R: Reliability.

E Percentage observed come from general US population sample.

2.5.7 Factors Associated With Poor Quality of Life in IC Patients

Identifying factors that are independently associated with decrements in HRQL in IC patients is of great interest when it comes to study the impact of IC symptoms on HRQL. Up to now, only one recent study investigated these factors among IC patients.[185] Nickel et al. studied 217 women with moderate/severe IC who were enrolled in a clinical trial of intravesical bacillus Calmette-Guerin. Both PCS and MCS from SF-36 were used as dependent variables. Data from O'Leary-Sant IC Symptom and Problem Index, University of Wisconsin Interstitial Cystitis Inventory (WICI) and Medical Outcomes Study sexual functioning scale were also collected. Moreover, the investigators constructed three composite indexes from O'Leary-Sant IC Symptom and Problem Index, pain/urgency Likert scales and 24-hour voiding dairy to document the severity, frequency and bother of pain, urinary urgency and frequency. The final multivariate models showed that employment status, pain composite index score and Medical Outcomes Study sexual functioning scale predicted PCS, while only Medical Outcomes Study sexual functioning scale remained strong predictor of MCS. It is important to mention that the investigators in this study assessed several IC clinical measures that are expected to be highly correlated with each other. Moreover, it was not clear in the article if the authors included all these measures in the multivariate analysis or if they picked the highly significant variables. Furthermore, the above described study focused mainly on socio-demographic, IC clinical factors and sexual functioning that impair the two main composite summary scales. We still need to know in more details the effect of all these factors add to other lifestyle and reproductive factors on each domain of HRQL as well.

2.5.8 Impact of IC on Health Related Quality of Life

Interstitial Cystitis is a devastating urinary tract disorder. Until now, we do not know the exact causes of it, the best way to diagnose it or the effective method to treat it. People who are diagnosed with IC suffer from severe painful symptoms and experience several difficulties that can greatly affect their health related quality of life. When IC remains unrecognized and the symptoms continue to be untreated for years, the impact of IC on patient's life cannot be overstated. The burden of IC extends far beyond symptoms of pelvic pain, and urgency into the physical, social, role limitation, and emotional functioning and well-being of patients. IC leads to social isolation, severe disability, unemployment, depression and even suicide. [14, 15] In fact, approximately 50% of IC patients are unable to work full time, and more than 60% of IC patients experience dyspareunia. [16]

Real examples from letters that have been sent to Interstitial Cystitis Association (ICA) are listed here to show the severe impact of IC on the life of the patients. One woman wrote describing her suffering "years of non stop pain, 40 to 60 bathroom trips a day, little sleep, lots of tests, 12 doctors, hundreds of allergy shots, diets, antibiotics, and six unnecessary operations". Another woman wrote "if I had cancer, I would know sooner or later that I would be either in remission or dead, but with IC, I only suffer day after day, without hope of getting better. So many times I have thought of killing myself to get out of the pain and mental suffering caused by this disease." [16]

Studies that assessed the impact of IC on the health related quality of life can be divided into two main types; studies used general questions to collect data about HRQL, and that which used standardized instruments. In the following section we will review both types.

2.5.9 Studies that Used General Questions to Assess HRQL in IC Patients

In 1987, Held et al. assessed health related HRQL for 3 series of patients with IC, including 64 cases enrolled by random sample of urologists, 902 females with IC who are member of the Interstitial Cystitis Association, and a matched sample (119 participants) of the general US population. [2] Held et al. did not use a validated instrument to assess the health related quality of life; however they had specific questions about quality of life. Their study showed that IC patients were 3 to 4 times as likely to report thoughts of suicide and 5 times as likely to have been treated for emotional problems as the general population.

Koziol et al. in their survey to determine the natural history of IC reported that 94.3% of IC patients find travel to be difficult or impossible, 89.9% reported that leisure activities adversely affected, while 88.2% indicated that sleep is difficult. [18] In another study that included 565 IC patients, Koziol assessed the effect of IC on HRQL using questions about psychological factors such as feelings of fatigue, impact of disease on employment and anxiety. [20] The results showed that a large proportion of IC patients experienced excessive fatigue and adverse effects on employment due to their illness.

More recently in 2006, Temml et al. studied the HRQL and sexuality of IC patients. They included 981 women of those attending a voluntary health survey project in Vienna in their study. [6] Data about IC symptoms were collected using the O'Leary-Sant (OLS) IC Symptom and Problem Index. Furthermore, 16 questions were used to assess HRQL and 5 questions to assess sexuality. IC symptoms were found to have a significant impact on HRQL and sexuality. More than half of the women with a moderate or high risk for IC (identify using the O'Leary-Sant (OLS) IC Symptom and Problem Index) had an impaired HRQL due to burning in the urethra, pain in the lower abdomen, and pain in the bladder. Temml et al. indicated that women with

moderate to high risk of IC had 5 fold higher prevalence pain during orgasm, and 3 fold increased risk of pain in the vagina after sexual activity.

2.5.10 Studies that Used Standardized Questionnaires to Assess HRQL in IC Patients

Although clinical case series suggest that the impact of IC on health related quality of life is severe and debilitating, very few epidemiological studies that used standardized instruments can be found. Furthermore, comparison between these studies is limited because each study used different methods to present HRQL data (some used HRQL domains, other used items from HRQL domains), different diagnostic criteria, different comparison group to measure the impact of IC on HRQL. In general all the studies support the potential impact of IC on HRQL. **Table 2-7** provides summary of these studies. More details can be found in the following paragraphs.

The Interstitial Cystitis Data Base Study (ICDB Study) is an important study that was conducted to determine the treated history of IC and to identify common patients' characteristics. [17] It is a longitudinal, multicenter, observational study sponsored by the National Institute of Diabetes, Digestive, and Kidney diseases (NIDDK). Data about the health related quality of life in IC patients were collected as part of this study using the SF-36 validated instrument. In 1997, Simon et al. published preliminary baseline descriptive statistics from this study. [17] Approximately 424 patients (388 females, 36 males) completed the SF-36 HRQL questionnaire. The study showed that overall symptom score correlated inversely with health related quality of life. Patients with severe symptoms significantly report having greater limitations in basic daily functions. Overall, 7.8% of IC patients reported poor general health, 54% reported that they had limitations in work or other activities, 38.5% reported limitations in lifting groceries, 8.3% in bathing and dressing, and 71.7 % had interference in social activities. Although the study used

SF-36 to assess health related quality of life, this paper did not provide specific details about which domain is the most affected and how the HRQL can be changed with time.

In 2000, Michael et al. conducted a study to determine the HRQL among women with IC participated in the Nurses' Health Study I and II. [21] The SF-36 was used to collect data about HRQL from all the participants in the Nurses' Health Study I and II. Only data collected from IC self-reported patients confirmed with medical records (99 patients) were used for comparison. After adjusting for age and co-morbid conditions, women with IC had significantly lower scores in 5 of the 7 health related quality of life dimensions (including role/physical, bodily pain, vitality, social function, and mental health) compared to women without IC. Although, this study showed that there is considerable variability in the 7 dimensions of health related HRQL among IC patients compared to the previous study by Simon, [17] several limitations can be defined. First, because the study population was nurses, selection bias may have been introduced to the study. As a result, healthier group of women with IC were included in this study. This might underestimate the effect of IC on HRQL. Second, the investigators excluded confirmed IC cases (11 cases) if they did not answer the SF-36 from the analysis. This may bias their results especially if those women were severely ill. Finally, Michael et al. included women who reported initiation of IC symptoms after completing the HRQL instrument (9 cases), thus we do not know if the worsening in HRQL scores was a result of these symptoms or of other conditions among those cases.

In 2002, Rothrock et al. focused on the impact of IC on mental health. They conducted a case control study that included clinical sample of 65 females with previous diagnosed IC and 40 age matched controls. [22] They used SF-36 to assess HRQL, Beck Depression Inventory (BDI) and (Hamilton Rating Scale for Depression (HRSD)) to assess depression symptoms. IC patients

reported significantly poor health related quality of life than controls in all the 7 domains of the SF-36 (physical function, role/physical, bodily pain, vitality, social function, role/emotional, mental health). Interestingly, time since diagnosis was not associated with depressive symptoms or any aspect of HRQL except for role limitations due to emotional problems. Regarding the depression symptoms, IC patients reported greater depressive symptomatology on the BDI compared to controls as well as on the HRSD. This study also showed that patients with severe disease (measured using 3 symptom severity questions developed for the National Institutes of Health Interstitial Cystitis Database (ICDB) Study [17]) reported significantly greater limitations in physical, social functioning, and mental health than patients with mild diseases. However, patients with severe disease did not have more depressive symptoms. The main limitation in this study was related to the use of non-standardized tool to classify IC cases into mild, moderate and severe, which may have introduced misclassification bias to the results. Furthermore, the authors did not adjust for important confounders like age and co-morbid conditions or even assessed if these covariates had significant effects on their results.

Table 2-7: Summary of the Studies that Assessed the Impact of IC on HRQL Using SF-36 (Generic Standardized HRQL Instrument) (1997-2002)

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE CHARACTERISTICS OF STUDY POPULATION	DIAGNOSIS OF IC	RESULTS	NOTES
Simon et al., 1997 Urology	Cohort study USA The ICDB Study	424 IC patients 388 Females 36 Males 91% White	Used the NIDDK criteria. with some changes In specific: The ICDB forgoes the NIDDK requirement that patients undergo a baseline cystoscopy to determine the presence of glomerulations or classic Hunner's ulcer <u>Definition of symptom severity:</u> Based on self-reported frequency, urgency and pain ▪ Frequency was actual average daily frequency from 3 day voiding log ▪ Urgency was based on the following question: over the past four weeks how often have you had the urge to urinate on a scale of 3 response ▪ Pain was based on the following question: how much bodily pain you had during the previous 4 weeks on a scale of 3 response ▪ The total score of the three questions was used to divide cases into three categories mild (3-5), moderate (6-7) severe (8-9)	Patients in the ICDB study possessed a less than desirable QOL Patients with severe symptoms reported greater limitations in basic daily functions	▪ The results based on the baseline data ▪ The severity of symptoms was based on self-reported as answers for three questions. No previous validations or standardization done for these questions. ▪ The categories did not have equal width ▪ Association between severity and QOL was presented for selected items not domains ▪ So this study did not show which domain would associated with symptom severity
Michael et al., 2000 J Urol.	Cross-sectional study USA The Nurse Health Study I, II	15419 Participants 99 IC Cases	All participants were asked in a questionnaire: ▪ Whether IC had ever been diagnosed by cystoscopy ▪ All participants who answered yes were sent a supplementary questionnaire to gather more information ▪ Self-reported IC was confirmed from medical records ▪ NIDDK were used but were not applied completely Based on the above criteria, IC cases were classified into:	There was an impairment in all domains except for role /emotional and physical functioning after adjusting for age and co-morbid conditions compared to healthy women	▪ Study population healthier than normal IC patients as they were nurses ▪ Including probable and possible cases may over estimate IC and lead to misclassification

Table 2-7 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE CHARACTERISTICS OF STUDY POPULATION	DIAGNOSIS OF IC	RESULTS	NOTES
Michael et al., 2000 J Urol. **(Cont'd)**			Definite: ▪ Report of positive cystoscopy with hydrodistension ▪ Biopsy demonstrated chronic cystitis ▪ Negative urine cytology Probable: ▪ Report of positive cystoscopy Possible ▪ Letter stated that patient underwent cystoscopy with or without distension with diagnostic impression of IC	IC women experience less decrement in physical functioning compared to arthritis patients but not hypertension patients IC women showed greater differences in vitality and mental healthy compared to rheumatoid arthritis or hypertensive patients	▪ No relation between severity of symptoms and HRQL or which domain is most likely to be affected by severity of symptoms.
Rothrock et al., 2002 J Urol.	Case control study USA	65 Case 40 Controls 100% Females	Cases: ▪ Selected from department of urology patients ▪ Diagnosed with IC based on NIDDK Controls: ▪ Two controls for each 3 cases ▪ Matched on age, use of OC and HRT **Definition of symptom severity:** Based on self-reported frequency, urgency and pain ▪ Frequency was actual average daily frequency from 3 day voiding log ▪ Urgency was based on the following question: over the past four weeks how often have you had the urge to urinate on a scale of 3 response ▪ Pain was based on the following question: how much bodily pain due have you had during the previous 4 weeks on a scale of 3 response	Patients showed significant poorer quality of life than controls in all domains of the SF-36 Symptom severity and HRQL: Greater symptom severity was related to poor physical and social functioning and mental health Correlations between symptoms and QOL domains:	▪ Controls were selected from general population not from clinic thus they may healthier than cases ▪ Although it is matched study non-conditional analysis was used ▪ No information about the distribution of cases by severity of symptoms was provided ▪ Non of the symptom self-measured was standardized ▪ Correlation between self-reported symptom severity and the physician rating was low 0.42 but significant

Table 2-7 Cont'd

AUTHOR YEAR JOURNAL	TYPE OF STUDY SETTING	SAMPLE SIZE CHARACTERISTICS OF STUDY POPULATION	DIAGNOSIS OF IC	RESULTS	NOTES
Rothrock et al., 2002 J Urol. **(Cont'd)**			▪ The total score of the three questions was used to divide cases into three categories mild (3-5), moderate (6-7) severe (8-9)	Greater pain correlated significantly with vitality, social functioning, role limitation due to physical, mental health Frequency was correlated with physical functioning only Urgency was correlated with pain and social functioning	▪ No adjusting for Co-morbidity or age (20-81) ▪ Poor presentation of the results without any p values or correlations parameter

2.5.11 Health Related Quality of Life as an Outcome in IC Clinical Trials

Although all the previous studies that assessed the impact of IC on HRQL reported that IC patients had significant impaired quality of life compared to healthy population, [2, 6, 17, 18, 20-22] only two IC clinical trials considered using HRQL as an outcome. [186, 187] Furthermore, both of these trials assessed the improvement in HRQL as a result of therapies other than PPS.

Peters et al. were one of those who used HRQL as one of their outcomes when they assessed the efficacy of intravesical Tice strain Sacillus Calmette-Guerin as a new therapy for IC in a double blind placebo randomized clinical trial.[186] The trial included 30 IC patients who randomized into two balanced arms (either treatment or placebo). Peters et al. used Rand-36 questionnaire to assess the impact of the trial treatment on HRQL. In general, the study showed that treatment group improved more than the placebo group in all the eight domains of the Rand-36 questionnaire (physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions). However, statistically significant improvements were reported in only two domains; social functioning and fatigue domains.

The second trial was conducted in 2004 by Oyama et al. The researchers used the SF-12 questionnaire to assess the impact of transvaginal manual therapy of the pelvic floor musculature (Thiele massage) among females with IC on HRQL Physical and Mental Summary Components. [187] The study included 21 IC patients who underwent transvaginal massage using the Thiele technique twice a week for 5 weeks. HRQL were evaluated before massage, at protocol conclusion and at a mean of 4.5 months after therapy completion (long-term follow-up). Statistically significant improvements were reported in both Physical and Mental Summary

Components after 5 weeks of the study. Interestingly, after 4.5 months of the completion of the protocol the improvements in the Physical Component Summary and Mental Component Summary of the SF-12 Quality-of-Life Scale were no longer statistically significant.

In summary, there is a limitation in considering HRQL as one of the main outcomes in IC clinical trials despite the impairment effect of IC on patient's HRQL.

2.6 GENERAL SUMMARY

Interstitial cystitis is a chronic idiopathic inflammatory bladder syndrome of unknown causes and pathogenesis. Despite the ongoing efforts to understand this debilitating syndrome, research is still required. After reviewing the literature from different aspects of IC, several gaps could be identified. There is a lack of well-designed epidemiological studies to determine the exact prevalence and incidence as well as the potential risk factors of IC. These important epidemiological concepts will not be determined unless highly specific diagnostic criteria are developed. These criteria should be able to identify all possible IC cases and not only the moderate and/or the severe cases. In order to be able to develop these criteria more efforts should be directed toward the etiology and the pathogenesis of IC. More animal, laboratory and clinical studies are needed to aid in constructing an etiological model of IC.

The present study was developed to answer questions in two main aspects of the IC literature as follows; the health related quality of life in IC patients and the efficacy of a new intravesical therapy (PPS) for IC. Assessing both aspects are very important to improve the quality of life in IC patients.

Focusing on the literatures of HRQL as an important standard, of the evaluation of IC patients' life experience, several unanswered questions arise. Although we know that IC patients experience substantial impairment in different dimensions of their health related quality of life, [2, 6, 17, 18, 20-22] limited efforts have been directed to understand that comprehensively. We need to know if the severity of IC symptoms impairs each domain of HRQL to the same level or not with the use of validated, standardized tools and adjusting for possible covariates. Another question involves: which symptom of IC (pelvic pain, urinary frequency, urinary urgency and/ or nocturia) brings the greatest impairment to HRQL?

Answering these two important questions may help to modify the treatment of IC toward the symptom that is most likely to impair quality of life in IC patients. Furthermore, we may be able to direct our efforts to improve the specific domain of HRQL that is most likely to be impaired according to the severity of the IC condition.

The efficacy of PPS as a new intravesical therapy needs to be investigated. The use of PPS as an oral therapy has been shown to provide a substantial improvement effect on IC symptoms; the flaw in the use of oral PPS is that progress in symptom reduction has been well documented to take 3 to 6 months. [27-33] Because intravesical therapy has several advantages over the oral therapy that are related to increase the concentration of the treatment in the site of action and to decrease the effect of metabolism on the active ingredient, [35] it is important to test the efficacy of PPS as an intravesical therapy. Particularly, after it showed substantial improvement effects on IC symptoms as an oral therapy. Only one trial, before ours, was conducted to assess that with promising results. [37] Because that trial was very small and based on self-catheterization of the medication at home without any monitoring from the investigators of the study, another clinical trial was needed to overcome these limitations and to assess the efficacy of PPS

extensively. It is crucial to determine how PPS improves IC symptoms, and which of these symptoms is most likely to respond to this medication.

Although we know that the quality of life in IC patients is impaired, none of the clinical trials that assessed the efficacy of PPS as an oral therapy used HRQL as a major outcome. This trial assessed if intravesical PPS improved the quality of life in IC patients. Moreover, it also examined which domain was most likely to be improved. The following chapter presents details about the protocol of the study and the statistical analysis plan that we used to assess each aim of our study.

3.0 METHODS

3.1 STUDY DESIGN

The randomized clinical trial is considered the gold standard with regard to test the efficacy of a new treatment. It enables the researchers to evaluate the efficacy of therapeutic, preventive and other measures in both clinical medicine and public health. Randomization makes the trials extremely powerful in comparison to prospective cohort studies; since it provides comparable groups at the beginning of the trial, which assures that the difference in the outcome can only be attributed to the new intervention. [188] Furthermore, randomization prevents the investigators from consciously or unconsciously assigning better prognosis patients to a treatment that they hope will be superior, thus it reduces selection bias. One more benefit of randomization is that it prevents confounding, as it is the only technique which can control for known and unknown risk factors or confounding variables; if the process of subject allocation is performed correctly, randomization is resistant to external manipulation. Thus, it is expected that known and unknown prognostic variables are randomly distributed between study groups, and that randomization will create study groups having similar incidence of the disease or outcome when the treatment under evaluation has no effect. Using the clinical trial design is better than the cohort design as we will have more control over the exposure, something very important for causality and the validity of any association. [188]

As we mentioned previously, it was not applicable to conduct blinded studies to test the efficacy of the well-defined intravesical therapies because of study design limitations. The fact that dimethyl sulfoxide (DMSO), the only intravesical approved therapy by the FDA, produces garlic breath made testing its efficacy impossible by using a double blind randomized clinical trial design. Moreover, other commonly used intravesical therapy named sodium oxychlorosene lavage (Clorpactin®) is very painful and needs general or regional anesthesia when administered, which makes it not suitable to be tested in a blind clinical trial without being recognized.

The intravesical instillation of Elmiron® , Pentosan Polysulfate Sodium (PPS), avoids all the previous limitations in both DMSO and sodium oxychlorosene lavage. Furthermore, its use as oral therapy proved a greater efficacy over placebo in several blind randomized placebo trials.[27-30, 32, 33] Intravesical instillation of PPS is still very recent. Until now, only one small clinical trial was conducted in the Netherlands to test the efficacy and safely of intravesical PPS. [37]

The present study is the first, randomized, double blind, placebo-controlled trial in the US that tested the effect of intravesical PPS on the severity of IC symptoms and the health related quality of life (HRQL) in IC patients. It also examined the factors that may associate with both symptom severity and impairment in HRQL in IC patients, and assessed the correlations between symptom severity and impairment in the different domains of HRQL ***at baseline in a cross-sectional design.***

Most of the results of the clinical trial part of this dissertation were recently published in The Journal of Urology. [189] We represented these results in more details (with permission from Elsevier) in the next chapter.

Forty females diagnosed with IC within one year were recruited and randomized (after obtaining signed informed consent) to receive either intravesical PPS plus oral PPS (treatment group) or intravesical placebo plus oral PPS (placebo group). Twenty subjects received intravesical PPS and 20 subjects received intravesical placebo, twice weekly for six weeks. Both clinical arms received 200 mg oral PPS two times daily during the entire study period (18 weeks).

The blinding process of this study was monitored, assessed and recorded by an independent pharmacist who was aware of each subject designation (treatment or placebo) should the need for un-blinding occur.

3.2 STUDY POPULATION

Because all the prevalence studies up to now showed females as the most likely gender to be diagnosed with IC, only females with IC were recruited. Females who were older than 18 years old, diagnosed with IC within one year and previously untreated with PPS were recruited to participate in the trial. The National Institute of Diabetes, Digestive, and Kidney diseases (NIDDK) exclusion and inclusion criteria were used to determine who should be enrolled. Lists of exclusion and inclusion criteria are following.

3.2.1 Exclusion Criteria

Female was excluded from the study if:

- She had a bladder capacity of greater than 350 ml on awake cystometrogram using water filling medium.
- She showed absence of intense urge to void with the bladder filled to 150 ml with water filling medium on cystometrogram using a fill rate of 30 ml to 100 ml per minute.
- She demonstrated biphasic involuntary bladder contractions on cystometrogram using filling rate of 30 ml to 100 ml per minute.
- She demonstrated an absence of nocturia.
- She had frequency of urination of less than eight times per day in a twenty four (24) hours period.
- Her symptoms are relieved by antimicrobials, urinary antiseptics, anitcholinergics, or antispasmodics.
- She had a diagnosis of bacterial cystitis within a three month period, documented by a positive culture.
- She had recurrent bladder or lower urethral calculi.
- She had active genital herpes with a three month period.
- She had uterine, cervical, vaginal or urethral cancer.
- She has been administered cyclophosphamide or any agent that causes chemical cystitis.
- She had tubercular cystitis.
- She had radiation cystitis.
- She had benign or malignant bladder tumor.

- She had symptoms of vaginitis.
- She had evidence of vesicle urethral reflux or urethral diverticula.
- She had neurogenic bladder dysfunction.
- She had a prior urinary diversion.
- She was receiving investigational drug(s) at the time of enrollment.
- She was receiving or having had prior therapy with oral PPS at the time of enrollment.
- She was pregnant or lactating at the time of enrollment.

3.2.2 Inclusion Criteria

Female was enrolled if she met the following criteria:

- She was eighteen years of age or older and capable of giving consent.
- She was diagnosed with IC within one year of entering the study.
- A cystoscopic examination under anesthesia with hydrodistension and photo documentation was done within one year of entry into the study, and bladder biopsies were performed only if carcinoma was suspected.
- She demonstrated a documented sterile bacterial urine culture.
- She had a score of at least four on the pain scale, five on the O'Leary-Sant Symptom Index and four on the O'Leary-Sant Problem Index at baseline.
- Female of child-bearing potential must test negative for pregnancy prior to treatment or provide documentation for having undergone the following: hysterectomy or tubal ligation. Females who were physiologically capable of becoming pregnant must voluntarily sign a pregnancy waiver included within the informed consent. If a subject became pregnant

during the course of this study, the subject must inform the principal investigator within one working day of learning of the pregnancy.

3.2.3 Subject Consent

All participants signed an informed consent that contained California Experimental Subject's Bill of Rights, and described clearly the protocol of the trial, which includes the purpose of the study, expected risks, benefits, durations, inconveniences and invasive procedure. A complete copy of study informed consent can be found in **Appendix A**.

Two copies were obtained; one for the patient and the other one for the investigator record. All subjects were informed that there are no obligations to participate and subjects may withdraw at any time without prejudice to future medical care. No financial compensation was given to the study participants.

3.2.4 Recruitment

The target was to recruit 40 IC female patients based on the sample size justification that is presented in the power calculation section of this chapter. The recruitment process started on April 2004 and end on August 2006. Because two subjects dropped out after randomization; one subject dropped out directly before receiving any treatment while the second one dropped out after 4 weeks of the trial, another 2 subjects were recruited to replace them. More details about sample size flow chart can be found in the first section of chapter 4.

All trial participants were recruited from the clinical patients of Citrus Valley Medical Research, Inc. Glendora, CA. Female candidates, who were older than 18 years, and were

diagnosed with IC within one year, were invited to participate in the trial. Informed consents were obtained from those who agreed to participate. Only candidates who met the previously specified exclusion and inclusion criteria, and signed an informed consent were enrolled and randomized into two arms.

3.3 RANDOMIZATION

A randomization scheme was generated through SAS statistical software. Restricted (Blocked) randomization with a size of 4 per block was used to allocate participants into two balanced groups (treatment and placebo). The randomization scheme was created by Ortho-McNeil Pharmaceutical, Inc., The drug company, which funded the trial and supplied the intervention medications. The randomization code was kept by an independent pharmacist until the end of the trial, and was given to the statistician after all the required information has been collected.

3.4 PROCEDURE FOR ALLOCATING TRIAL MEDICATIONS

All participants received oral PPS 200 mg (2 capsules) twice a day for a total daily dose of 400 mg during the study period (18 weeks). Oral PPS capsules were administered either one hour prior to meals or two hours after meals.

The 40 participants were allocated into two balanced groups (treatment or placebo) according to the randomization scheme which was created by Ortho-McNeil Pharmaceutical, Inc. The treatment arm, which included 20 participants administered intravesical PPS 200 mg (2

capsules) mixed with 30 ml sterile normal buffered saline twice per week for the first six weeks of the study. The placebo arm, which included the remaining 20 participants administered intravesical placebo of 30 ml sterile buffered normal saline twice per week for the same period. **Figure 3-1** shows a flowchart of the study design.

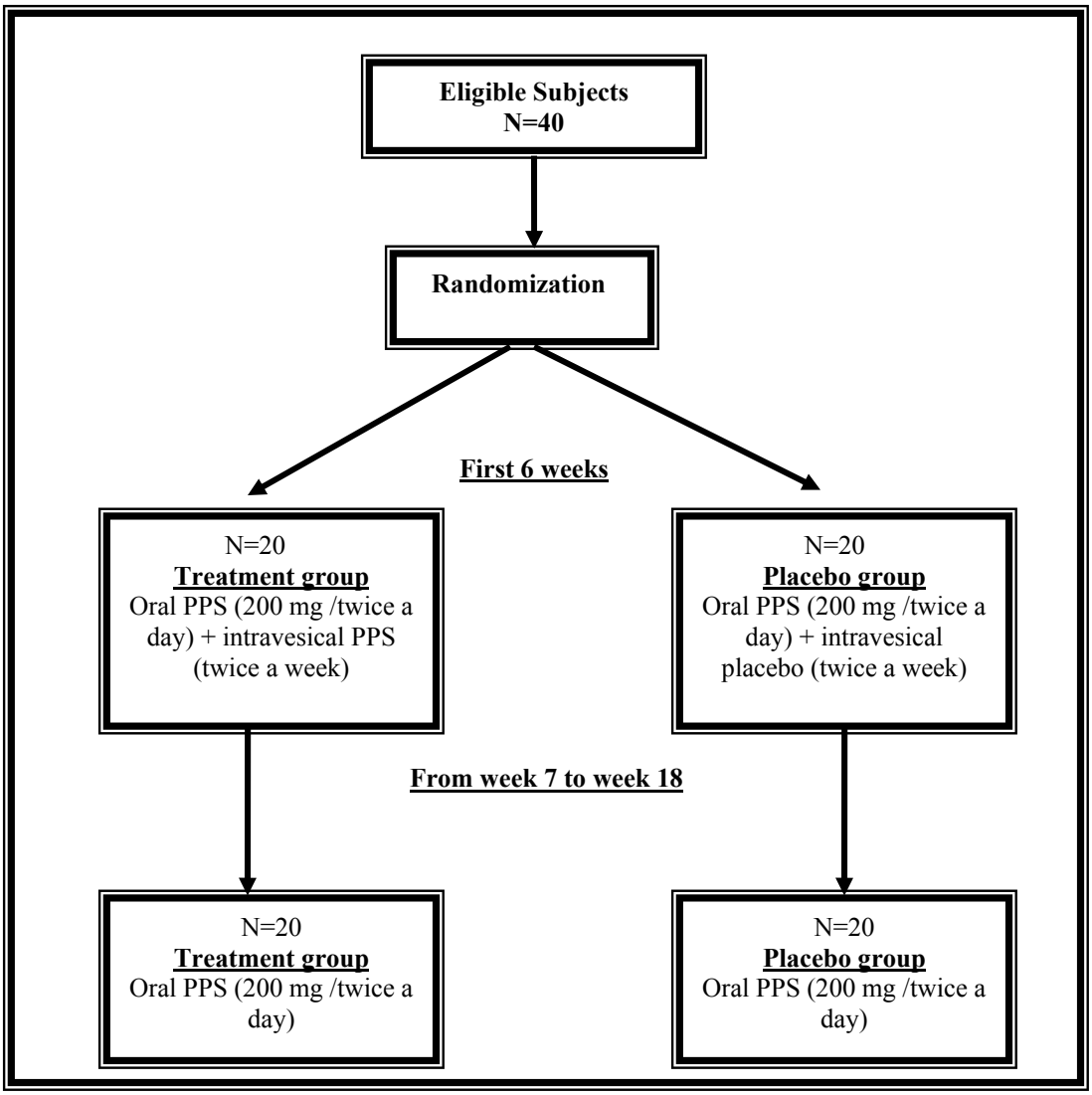


Figure 3-1: Flowchart of the Study Design

3.5 STUDY MAIN OUTCOMES

The present study had several aims that were assessed using two different study designs. The cross-sectional design was used to determine the main socio-demographic, lifestyle and clinical factors that were associated with either the severity of IC symptoms or the impairment in HRQL in IC patients. The same design was also used to assess the correlations between the severity of IC symptoms and the impairment in the different domains of HRQL. Because of the limitation of the cross-sectional design, we cannot tell which of the studied variables are the outcomes, and which are the exposures. [190]

On the other hand, a randomized clinical trial design was used to assess the efficacy of the combination of oral PPS and intravesical PPS compared to oral PPS and intravesical placebo. Using this design, we can easily determine which variables are the outcomes and which are the exposures. The main outcomes to measure the efficacy of the combination of oral PPS and intravesical PPS were changes in: symptom severity, response to trial intervention (defined as any improvement in any of the following: overall IC condition, urgency and urinary frequency as reported by patient), health related quality of life and sexual activity. Different measurement tools were used to collect data about each of the above listed outcomes. **Table 3-1** provides a summary of the current study main outcomes, measurement tools and the corresponding evaluation endpoints.

Table 3-1: Evaluation Endpoints of Clinical Trial Efficacy Outcomes

EFFICACY OUTCOMES		
Outcomes	**Measurement Tools**	**Evaluation Endpoints**
IC symptoms: **Since enrollment:** • Change in the severity of IC symptoms	• O'Leary-Sant ICSI & ICPI (score 0-36) • PUF instrument (score 1-35) • Pain assessment scale (score 1-9) • Urgency scale (score 1-5) • Urinary frequency (voiding log) • Nocturia (voiding log)	All tools: • At week 6 (when patients completed all required instillations) • At week 12 and week 18
Response to trial intervention: **Since enrollment:** • Overall change in IC condition • Change in urinary frequency • Change in urgency	• Patient global assessment	• At week 18
HRQL and Sexual functions: **Since enrollment:** • Change in HRQL • Change in sexual desire • Change in sexual arousal	• SF-36 • Sexual function assessment VAS • Sexual function assessment VAS	All tools: • At week 4, week 18

3.5.1 Instruments that Measure Change in Symptom Severity

These instruments can be divided into two main types; the first measures the overall level of symptom severity through providing a total score e.g. O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and the Problem Index (ICPI) and Pelvic Pain and Urgency/Frequency (PUF) Questionnaire. The second one measures the level of severity in each IC symptom separately e.g. pain assessment scale, urgency scale and voiding log.

The following sections describe each of these instruments in more detail.

3.5.1.1 O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI)

The interstitial cystitis symptom index and problem index were designed to capture the most important voiding and pain symptoms, and to assess how problematic patients find them in the clearest and most concise manner possible. [23] Each index contains 4 items that measure either the frequency of certain IC symptoms (including urinary urgency and frequency, night-time urination, and pain or burning) or how much has each of these symptoms been a problem for IC patient. [23] The maximum score of ICSI is 20, while for the ICPI is 16. ICSI can be categorized to indicate the level of severity of IC symptoms as follows: (0-6) indicating mild symptoms, (7-14) moderate, and (15-20) severe symptoms. Thus, a score of 15 or greater in the ICSI indicates severe symptoms. [33] The initial validation of this instrument was conducted among 45 newly diagnosed patients with IC from three urology practices in the United States. The control group was 67 women from the routine gynecological care with no voiding symptoms. [23] Interestingly, in the validation of the indices for measuring urinary symptoms and their impact, very few interstitial cystitis patients scored lower than six on either index, whereas very few controls scored as high as six. [23] An ICSI score of greater than or equal to five was found to be 94% sensitive and 50% specific for interstitial cystitis/painful bladder. [191] O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) was also validated in prospective treatment studies and the results showed that it is a valid, reliable, and responsive measure of change in IC symptoms. [102]

Finally, it is important to mention that both indices are not intended as screening tests, even though they appear to discriminate between patients with and without IC. However, those indices should be used as an adjunct in the diagnosis and should be useful in the evaluation and

management of patients with IC. [23] A copy of the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and the Problem Index (ICPI) can be found in **Appendix B**.

3.5.1.2 Pelvic Pain and Urgency/Frequency (PUF) Questionnaire

The Pelvic Pain and Urgency/Frequency (PUF) questionnaire was published most recently and studied in a large population of both urologic and gynecologic pelvic pain patients. [24] It was designed by Parsons CL. to include questions that directly reflect a wide variety of symptoms experienced by IC patients. The questionnaire included 8-question symptom scales that were designed to measure the presence and severity of IC symptoms, and how much the patients are affected by those symptoms. One third of these questions assesses urinary frequency issues, second third of the questions assesses urgency, and the last third assesses pelvic pain (pain anywhere in the pelvis: vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum), and pain associated with sexual intercourse.

The PUF is very easy to administer and can be completed within 5 minutes. Two separate scores are obtained: one reflects symptom level, while the other reflects the bother level. Both scores can be added to provide a total symptom and bother score. The maximum total score is 35 while the minimum recorded score among healthy participant is < 2. A total score of 10 points or more clearly indicates a very high probability that the patient has IC. [44] The intravesical potassium sensitivity test (PST) was used to validate the PUF scale, as a new screening test, in a study that included: urologic patients who were suspected to have IC, gynecologic patients with pelvic pain, controls and women attending lectures about IC. [24] Positive potassium sensitivity is known to be associated with a bladder epithelial dysfunction present in most individuals with IC. The results showed that a total score of 10 to 14 indicates 74% chance of having IC, 15 to19

indicates 76% chance of having IC, and 20 or higher indicates 91% chance of having IC. A copy of the Pelvic Pain and Urgency/Frequency (PUF) Questionnaire can be found in **Appendix C**.

3.5.2 Other Instruments that Measure Change in Symptoms Level

3.5.2.1 Pain Assessment

The single most reliable indicator of the existence and intensity of pain is the patient's self-report. [192] Several self-report measurement scales are available. The main three common self-report measurement tools that are used for the assessment of pain intensity and affective distress in adults and children are: 1) numerical rating scale (NRS); 2) visual analog scale (VAS); and 3) adjective rating scale (ARS). Interestingly, each of these tools can be a valid and reliable instrument as long as endpoints and adjective descriptors are carefully selected. [192] In the present study, an adjective rating scale was used to assess the level of pain at baseline and at each visit during the study period. The same scale was also used to determine the level of pain during voiding **(section 3.5.2.2)**. The scale composes of nine different pain levels; as level one indicates no pain and no symptoms, while level nine-ten indicates that the subject suffers from the worst pain, and he or she is in the hospital. This scale can be categorized into three different classes as follows: 1-3 indicates mild pain, 4-6 indicates moderate pain, and 7-9 indicates severe pain. This scale was used successfully in previous studies, [32, 193, 194] and validated in clinical intervention. [195] A copy of the pain assessment instrument can be found in **Appendix D**.

3.5.2.2 Voiding Log

Voiding Log is an important tool to measure several IC symptoms. It can measure urinary frequency, nocturia and urgency. It asks patient to record the time at which he or she urinates for

24 hours. It also requires the patient to place a star next to the times he or she recorded when wake up in the middle of sleep to urinate. Each time the patient records a void, he or she has to assign an urgency number that reflects his or her urgency level at time of urination on an urgency scale (1-5); as 1 indicates no symptom, while 5 indicates severe symptom. Patients also have to assign a pain level at time of void using the pain assessment scale **(section 3.5.2.1).** Several studies used successfully voiding log as a secondary outcome, and some of them collected that for more than one day, while others collected data for only 24 hours. [32, 193, 194] The responsiveness of Voiding Log was recently assessed and showed positive result. [195] In the present study, patients were asked to record each time they urinate during a period of 24 hour each time they have to submit a log. A copy of the Voiding Log instrument can be found in **Appendix E**.

3.5.3 Patient Global Assessment

In order to be able to determine the response rate of the combination of oral PPS and intravesical PPS compared to oral PPS and intravesical placebo, patient global assessment instrument was used.

This instrument is also called the Patient's Overall Rating of Improvement of Symptoms (PORIS), and was previously used as the primary treatment outcome measure in two IC clinical trials. [28, 30] In the original version of this instrument, patient is asked to rate his or her symptoms compared to the baseline as worse, no change (0%), slightly improved (25% improvement), moderately improved (50% improvement), greatly improved (75% improvement), and symptoms gone (100% improvement).

Interestingly, some researchers expressed the opinion that the PORIS should be expanded to contain two or more negative values rather than the single negative value, worse, so it would in theory be more balanced. [196] Although no information was found about validity of this instrument, it was used successfully in previous studies. [28, 30]

The present study used a different version of the patient global assessment questionnaire. [189] This version was used in a previous clinical trial (sponsored by Bioniche Life Sciences Inc., Canada, 2003). The Canadian trial assessed the safety and efficacy of Cystistat® (Sodium Hyaluronate) as a treatment of IC. [197] This version of patient global assessment evaluates the overall change in IC condition since enrollment in the study. It measures the level of change with: worse, no change, and improved as the possible outcomes. It also measures the level of improvement with: moderate, greatly improved, and completely improved as the possible outcomes. The global assessment also allowed the patients to evaluate the changes in urgency and urinary frequency using the same outcomes as overall change in the IC condition. Responders were defined as those who reported improved as a possible outcome. This definition, for responders, was chosen based on the design of this version of the patient global assessment, and it reflects all the corresponding outcomes of improvement (moderately, greatly and completely). A copy of the patient global assessment instrument can be found in **Appendix F**.

3.5.4 Medical Outcome Study (MOS) Short Form-36 (SF-36) Health Survey

The SF-36 survey is a widely used instrument to assess HRQL. It is a multi-purpose, short-form health survey with only 36 questions that assess eight HRQL domains as follows; physical functioning, role-limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems, and general mental

health. The SF-36 includes a single item that measures the change in health over time. The questions are designed to be easy to understand and relevant to most people's lives. The form only takes 5 to 10 minutes to be completed. The original score of each domain ranged from 0 to 100. A zero indicates a worse HRQL while 100 indicates excellent HRQL.

Each domain has a specific number of items scatters within the SF-36 survey, and a specific number of levels reflects the level of the scale and identifies how much the domain or scale is precise. The larger the number of levels the most precise the scale is.

Previous studies showed that the eight domains of HRQL in the SF-36 can be summarized in just two summary scales; the PCS and the MCS. Physical functioning, role-physical, and bodily pain were found to be highly correlated with the physical component and contribute most to the scoring of the PCS measure. [176, 184] On the other hand, the mental component was found to be correlated most highly with the mental health, role-emotional, and social functioning scales, which also contribute most to the scoring of the MCS measure. Interestingly, three of the scales (vitality, general health, and social functioning) have noteworthy correlations with both components.

It is important to mention that the most precise (least coarse) scales are those with 20 or more levels included; physical functioning, general health, vitality, and mental health. They also define the widest range of health status, and, therefore, usually produce the least skewed score distributions. The relatively coarse role disability scales included role-physical and role-emotional, each measure only four or five levels across a restricted range, and, therefore usually have the most problems with ceiling and floor effects. [176] Because each of PCS and MCS measures hundreds of levels of health and extend the range of measurement to higher and/or

lower levels than the eight sub-scales, individuals rarely score at the very top or the very bottom of the PCS or MCS scales; this is a major advantage. [198]

The importance of assessing these two summary scales as valuable outcomes in drugs efficacy studies is related to the ability to determine which aspects of health are most likely to be affected with the tested therapy. In particular, scales that load highest on the physical component are most responsive to treatments that change physical morbidity, whereas scales loading highest on the mental component respond most to drugs and therapies that target mental health. [176]

The SF-36 is a valid instrument. It showed high construct validity, [177, 180] high internal consistency, [177, 181] and high test retest reliability.[182] A copy of the SF-36 Health Survey can be found in **Appendix G**.

3.5.5 Sexual Function Assessment Visual Analog Scale

This instrument was designed to assess sexual function. The sexual function assessment includes two visual analog scales that assess sexual desire and sexual arousal domains, and one numerical scale (0-4) that assesses the frequency of experiencing painful intercourse if happened.

The visual analog scales consist of a line that is 10 cm in length, with “None” at one end and “High” at the other end. Patients are required to make a vertical stroke along the line that best describes the amount of either sexual desire or sexual arousal that he or she felt during the past month.

The numerical scale which assess the frequency of experiencing painful intercourse if exist ranges from 0 to 4; as 0 indicates not at all while 4 indicates always. Sexual function visual Analog Scale was used successfully in previous studies. [199, 200] A copy of the Sexual Function Assessment Visual Analog Scale can be found in **Appendix H**.

3.6 SAFETY MEASURES

Although assessing the safety of intravesical PPS is out of the scope of the present study, we find it is important to let the reader know more about all the safety measures that were collected during the study period to ensure safety of the study subjects.

The use of PPS directly in the bladder is new, for that reason the following safety measures were collected and followed during the study period:

- Within thirty days of the study enrollment, a thorough history and complete physical examination were conducted
- Blood chemistry included; Complete Blood Count (CBC), Blood Urea Nitrogen (BUN) and Creatinine electrolytes were performed within the thirty days prior to the first instillation of PPS and six weeks following the last instillation of PPS (at week 12)
- At baseline, week one through week six, one hour following each intravesical instillation and at week twelve hepatic function panel, Activated Partial Thromboplastin Time (APTT), Prothrombin time, and platelet count were performed
- For women who were able to become pregnant, pregnancy waiver forms were obtained voluntarily and the suitable birth control methods were used. Pregnancy tests were also performed prior to enrollment and by the completion of the study

3.7 PRE-STUDY ENROLLMENT PROTOCOLS

All candidates who signed informed consent underwent cystoscopic examinations with hydrodistension (with bladder biopsy if carcinoma is suspected) to determine the presence of either glomerulations or Hunner's ulcer within one year prior to the beginning of the study. An urodynamic evaluation includes cystometrogram, uroflow, and ultrasound to measure post void residual, was completed within one year prior to the beginning of the trial as well.

30 days prior to the beginning of the trial, physical examinations were conducted by the investigator, and the following laboratory measures were performed as part of the pre-enrollment evaluation:

- CBC, BUN, Creatinine, electrolytes
- Routine urinalysis, urine culture and sensitivity
- Urine and blood sample for biomarkers and hormonal study to be preserved
- Pregnancy test as required
- Hepatic Function Panel
- APTT
- Prothrombin Time
- Platelet count

Information about concomitant medical conditions and current medications were collected prior to the beginning of the study.

Baseline data were collected one week prior to randomization and included demographic and reproductive history, O'Leary-Sant Interstitial Cystitis Symptom and Problem Index, Pelvic

Pain and Urgency/ Frequency Patient Symptom Scale (PUF), pain assessment, voiding log, SF-36 HRQL questionnaire, and sexual function assessment.

3.8 STUDY FLOW CHART

The total duration of the trial was 18 weeks, in which all participants were treated with oral PPS (200 mg twice daily). The intravesical instillation of either PPS or placebo was performed only during the first six weeks of the trial; twice per week (in two visits each week). Participants had to return for follow-up assessments at week 12 and 18 of the study. Different assessments and laboratory testes were completed and performed during the study period according to a well specified study flow chart (a complete flow chart of the trial with all assessment instruments can be found in **Appendix I**). The following section will summarize the protocols and procedures during the study period.

3.8.1 Study Protocol for the First Six Weeks of the Trial

Within thirty days of the pre-study examination, subjects were randomized into two parallel arms based on the randomization scheme that was created by Ortho-McNeil Pharmaceutical, Inc.

Intravesical instillations were given twice a week, in two visits per week, for the first six weeks of the trial. In the first visit of each week, culture and sensitivity of a catheterized urine specimen were performed. A clean-catch urine specimen was collected and tested with a reagent strip, a Multistix® 8SG, for urine analysis, to rule out any urinary infection before each intravesical instillation. If the clean-catch urine (Multistix® test) specimen showed a positive

result for the possibility of infection (a positive Multistix® test shows: leukocytes, nitrites, and blood in any degree) the investigator evaluates the participant and determines if the participant can continue to receive the intravesical instillation or not.

At each visit (visit one and visit two) of each week all the following assessments were performed: hepatic function panel, APTT, Prothrombin time, platelet count, adverse events, concomitant medications, O'Leary-Sant Interstitial Cystitis Symptom and Problem Index, Pelvic Pain and Urgency/ Frequency Patient Symptom Scale (PUF), Pain Assessment, and subject global assessment.

A 24 hour voiding log was dispensed to all participants at visit two of each week and collected back at visit one of the next week prior to instillation. The participant completed the 24 hour voiding log for any 24 hour they selected during the period in which they had the log.

The SF-36, HRQL questionnaire, was completed on week four at visit one, while the sexual assessment function was completed on week four and week six at visit one of each of the previous specified weeks.

3.8.2 Study Protocol for Assessment Visit: Week 12

After the completion of the sixth week of the intravesical instillation, participants returned for follow-up assessments on the 12th and 18th week of the trial.

On the 12th week of the trial different follow-up assessments were performed and included:

- Urodynamic evaluations included: uroflow and ultrasound to measure the post void residual

- Laboratory measures included: CBC, BUN, Creatinine, electrolytes, routine urinalysis, urine culture and sensitivity, hepatic function panel, APTT, Prothrombin time and platelet count
- A 24 hour voiding log was completed within one week of the week 12th visit
- A competition of: O'Leary-Sant Interstitial Cystitis Symptom and Problem Index, Pelvic Pain and Urgency/ Frequency Patient Symptom Scale (PUF), Pain Assessment and Patient Global Assessment
- Reporting of any adverse events
- Reporting of any concomitant medications

3.8.3 Study Protocol for Final Follow-up Visit: Week 18

Participants had to return again at the 18th week of the trial for the final follow-up which included the following:

- A complete physical examination
- An urodynamic evaluation included uroflow and ultrasound to measure post void residual
- Laboratory investigations included: urinalysis, culture and sensitivity, pregnancy test (if applicable)
- A 24 hour voiding log was completed within 1 week, prior to, week 18th visit
- A competition of: O'Leary-Sant Interstitial Cystitis Symptom and Problem Index, Pelvic Pain and Urgency/ Frequency Patient Symptom Scale (PUF), Pain Assessment, Health Related Quality of Life Questionnaire (SF-36), Sexual Function Assessment, and Patient Global Assessment

- Reporting of any adverse events
- Reporting of any concomitant medications
- Self-reported weight and height of the participants

3.9 METHODS OF PREPARING AND DISPENSING CLINICAL TRIAL MEDICATIONS

Trial medications PPS, for both oral administration and intravesical instillation were provided by Ortho-McNeil Pharmaceutical, Inc. in the form of 100 mg capsules.

3.9.1 Oral PPS (Elmiron®)

Oral PPS was provided in a ready pharmaceutical form (100 mg capsule) to be directly dispensed to study participants. A designated staff from Citrus Valley Medical Research, Inc. was responsible for dispensing the oral medication to each participant in the trial. Thirty four PPS 100 mg capsules were provided to each participant in one bottle each week for the first six weeks of the study. This equates to seven days of an oral dose of PPS 200 mg (2 capsules) twice per day, morning and evening doses, which equal to a total dose of 400 mg or 4 capsules per day. Six additional capsules were dispensed because of the possibility of scheduling conflict of one day. Doses for the remaining 12 weeks of the study were dispensed during two visits. In the second visit of the sixth week of the trial, participants were provided 180 capsules divided equally into 6 bottles (30 capsules /bottle) for each of the upcoming six weeks (until their first follow-up assessment visit at week 12 of the trial). Twelve additional capsules (two in each bottle) were

dispensed for the morning dose of the next treatment week, the possibility of scheduling conflict of one day, and/ or any unexpected condition. On their first follow-up visit at week 12 participants were received the last 180 capsules divided equally into 6 bottles (30 capsules /bottle) for each of the last six weeks of the trial with another 12 extra capsules (two in each bottle) for unexpected condition.

3.9.1.1 Drug Accountability

In order to ensure compliance of oral PPS, adequate records on receipts, use, return, loss or other disposition of study medication were maintained. A specific study medication accountability form supplied by Ortho-McNeil Pharmaceutical was used for that purpose. All bottles of oral PPS which were dispensed at each visit were returned at each subsequent visit and were retained for verification.

3.9.2 Intravesical PPS

Treatment arm received intravesical instillation of PPS 200 mg (2 capsules) mixed in 30 ml of sterile normal buffered saline twice a week for the first six weeks.

Preparation of the intravesical PPS was assigned to an independent pharmacist who was un-blinded to the randomization code in order to prepare the appropriate solution for instillations. This person complied with the double blind requirement of the study and charged for preparing the intravesical instillations.

3.9.2.1 Procedures of Intravesical PPS Preparation

Sterile intravesical PPS was prepared using the following procedures:

- The content of two 100 mg Elmiron® capsules is emptied into a 30 ml of sterile buffered normal saline inside the B-D LAMINAR FLOW STERILE HOOD
- The above solution stands for a maximum dissolution for 30 minutes followed by filtration through a particulate matter filter (4.5 microns)
- A re-filtration is performed through another 4.5 microns filter until the solution becomes clear
- A final filtration is done through a 0.22 micron filtered for sterilization
- The final filtrate is placed in a sterile empty vial

The final product must be administered within 4 hours of preparation, for that reason, intravesical instillation was labeled within a four hour expiration time.

3.10 PROCEDURES FOR CATHETERIZATION AND INTRAVESICAL INSTILLATION OF THE STUDY PRODUCT

The following procedures were used in both the intravesical instillation of PPS or placebo and were done by either the principal investigator of the study or a well-trained nurse under the supervision of the principal investigator:

- The participant was asked if she wish to void
- The participant had to drink 8 oz of Arrowhead^{TM} Mountain Spring water
- The principal investigator explained the complete procedure and the needed time to the participant

- Privacy was provided to the participant to prepare herself and lay in the required position
- Principal investigator or the nurse had to wash his or her hand and to wear sterile powder free synthetic surgical gloves
- A 8F LoFric® catheter was used in all intravesical instillation procedures and was prepared according to standard criteria listed on its package (sterile water was used as wetting solution)
- A 4 oz sterile specimen cup was removed from packaging to be used during the process to collect any post void residual (urine sample)
- Antiseptic solution of antimicrobial soap was prepared to be used during catheterization and instillation
- Study product was given by the un-blinded staff member directly before instillation because of the short expiration period
- Study product was drawn from the sterile vial into sterile syringe to be ready for use
- The perineal area was cleaned with the previously prepared antiseptic solution
- A preparatory prophylaxis (Lidocaine Hydrochloride Jelly, USP 2% 100 mg (20 mg/ml)) was applied to the catheter tip first and then to the perineum. The purpose of the prophylaxis was to prevent urethral spasms and the perineal sensitivity
- Under sterile conditions, the LoFric® catheter was introduced into the bladder by either the principal investigator or the nurse under the supervision of the principal investigator
- Any post void residual was emptied into the sterile specimen 4oz cup (sent for urine culture and sensitivity test at visit one from each week)
- The previous procedures were done as part of the prophylaxis part of the instillation process

- Before instilling the study product, an intravesical instillation of 8 ml of 1% Lidocaine and 3 ml of 8.4% sodium bicarbonate was instilled into the bladder
  - ✓ The purpose of instilling the 8 ml of 1% Lidocaine was to provide a topical and short acting anesthetic to the bladder membrane, thus prevent bladder and urethral spasms, and the possible uncontrolled expulsion of the study medication or placebo from the bladder. The effect of the topical anesthetic of the 1% Lidocaine is sixty to ninety minutes
  - ✓ The purpose of instilling the 3 ml of 8.4% sodium bicarbonates was to prepare the bladder membrane for the absorption of the 1% Lidocaine by alkalizing the acids in any urine residual
- Five minutes was given as a waiting period for the full effect of the bladder lining preparation of the prophylactic short acting anesthetic
- After those five minutes, the intravesical instillation of either PPS or placebo was conducted followed by removing the catheter, and asking the participant to retain the solution for a minimum of thirty minutes to a maximum of sixty minutes
- Time at which the instillation completed was recorded
- The participant was asked to drink 8 oz of Arrowhead™ Mountain Spring water
- The participant was asked to clean the perineal area to remove antiseptic solution
- The participant was asked to void to get out the study product, in case she cannot void within one hour of catheterization. 8F LoFric® catheter was used again to remove the study solution
- Time of voiding was recorded as well

3.11 COLLECTING URINE AND BLOOD SPECIMENS

According to the study flow chart, urine specimens were collected for both urine analysis and urine culture and sensitivity as follows:

- At week one through week six (in both visit one and visit two of each week) before each intravesical instillation a clean catch urine specimen was collected for urine analysis (using a reagent strip, a Multistix® 8SG), to rule out a urinary tract infection before the study instillation was performed
- At week one through week six (in visit one of each week) at the time of catheterization and prior to intravesical instillation a sterile catheterized urine specimen was collected for laboratory use for a documented urine culture and sensitivity test
- Blood specimens were drawn one hour post the completion of study drug instillation for the purpose of assessing any effect on hepatic function panel, APTT, prothrombin time, and platelet count

3.12 LABORATORY MEASURES

All laboratory measures included CBC, BUN, Creatinine, electrolytes, routine urinalysis, urine culture and sensitivity, hepatic function panel, APTT, prothrombin time, and platelet count were performed in one single lab to ensure the reliability of these measures.

Quest Diagnosis Inc.; California was responsible for all the laboratory analysis of the present study. It used fixed standard norms during the whole study period.

3.13 ETHICAL CONSIDERATION, DECLARATION OF HELSINKI AND IRB APPROVAL

Ethical approval was obtained for the whole study protocol as well as informed consent. The study was conducted according to the principles of the Declaration of Helsinki and part 50 of the FDA code of Federal Regulations Title 21 **(Appendix J).**

IRB approval was obtained from IRB board of Foothill Presbyterian Hospital, Glendora, CA, and IRB board of the University of Pittsburgh, PA **(Appendix K).** The protocol of the study was also approved by Food and Drug Administration (FDA) and Ortho-McNeil Pharmaceuticals, Inc.

3.14 STATISTICAL ANALYSIS

SPSS version 13.0 (SPSS, Inc., Chicago IL) and Stata version 10 (StataCorp LP., College Station TX) were used to conduct all statistical analyses.

3.14.1 Justification of the Statistical Analysis Approach

In order to be able to use parametric methods in statistical analysis, several assumptions related to the distribution of the data must be hold. If these assumptions about the shape of the distribution are not made, and if the central limit theorem also inapplicable, because the sample size is small, then non-parametric methods, which require fewer assumptions about the shape of the distribution, must be used. [201]

Sample size is an important factor that often limits the applicability of tests based on the assumption that the sampling distribution is normal. We can assume that the sampling distribution is normal even if we are not sure that the distribution of the variable in the population is normal as long as the sample size is large enough (e.g., 100 or more observations). [202] Thus, the inferences of the parametric technique are based on the large sample properties. With our sample size of 40, the properties may not be applied. Therefore, ***the general analytical approach that we used to assess the study aims was the non-parametric one.***

As we mentioned previously in the recruitment section **(3.2.4.)** of this chapter, two subjects dropped out; subject one dropped out directly after randomization and before giving us any chance to collect her baseline data (placebo group) while subject two dropped out after 4 weeks of the study due to clinical reason related to her medical history and not to the trial intervention (treatment group). In order to keep the projected sample size of 40, two additional subjects were recruited; the first of them received the same intervention that was assigned to subject one while the second case received the same intervention that was assigned to subject two. In total, 42 subjects signed an informed consent, of whom 40 subjects received all the required instillations of either PPS or placebo. All the available data at baseline were used to assess the first three aims of the current study (n=41). For the rest of the study's aims which were based on clinical trial design, intention to treat analysis approach with Last Observation Carried Forward method (LOCF), to deal with missing and dropouts, were used (treatment group: n=21, placebo group: n=20).

3.14.2 Power Calculations

This is a single center pilot project in the design of double blind randomized placebo-controlled trial. Preliminary data showed that using intravesical instillation of PPS can reduce the O'Leary-Sant Interstitial Cystitis Symptom Index score from 14.3 to 11.1 (about 3.2 over an average) during a treatment period of 17.59 week. [38] This justifies the use of a sample size of 40 assessable patients (20 per arm) in this trial. This sample size provided 80% power to detect a difference of 2.25 in the mean total O'Leary-Sant Interstitial Cystitis Symptom Index score at endpoint between the treatment group and the placebo group (based on two sample t test with SD of 2.5, and a significant level of alpha =0.05, two sided).

Because we used non-parametric analysis approach to assess the aims of the present study, no power calculation was performed for any of our aims.

3.14.3 General Descriptive Statistical Analysis

As a first step, general descriptive analyses were performed at baseline for the total study population (n=41) as well as by the study groups (treatment group =21, placebo group = 20) to provide a complete and a clear description of the current study population, and to assess if the randomization process produced two comparable groups or not.

3.14.3.1 Descriptive Statistics at Baseline

Descriptive statistics included socio-demographic (age, race, educational level, employment status, marital status), lifestyle (smoking history, BMI), reproductive history (age at menarche, ever pregnant, number of pregnancy, menopausal status, type of menopause, use of hormone

replacement therapy (HRT) and oral contraceptive (OC)), clinical characteristics (cystoscopic findings, severity of IC symptoms, number of co-morbid conditions, concomitant treatments, voided volume), scores of all instruments that were used to assess IC symptoms (O' Leary Sant IC Symptom Index and Problem Index, PUF, pain assessment, urgency assessment, number of voids during waking hours and number of voids during night), scores of HRQL domains (SF-36) and scores of sexual function domains (sexual assessment visual analog scales) were performed at baseline for the total study population and by the study groups. Continuous variables were presented as median (25^{th} and 75^{th} percentiles), while categorical variables were presented as proportions. Fisher's exact test and Chi-square test were used to examine if there were differences between the two groups (treatment and placebo) for categorical variables, while Mann-Whitney U test (the non-parametric version of the two independent samples t test) was used if the variables were continuous.

3.14.3.2 Oral PPS Compliance

Because both groups administered oral PPS during the entire study period and because it is well known that oral PPS has a significant improvement effect on IC symptoms, [27-30, 32, 33] it was very important to assess oral PPS compliance by study groups. We wanted to be sure that both groups achieved similar level of oral PPS compliance during the entire study period and during the first six weeks of the trial in particular (when one group received the intravesical therapy while the other received the placebo). In this way we were able to identify if the compliance was a potential confounder in the current study or not.

The proportion of oral PPS compliance was calculated for each week of the trial by dividing the total number of capsules that was administered (the number of dispensed capsules – the number of returned capsules) during that week by 28 capsules (the total number of capsules

that the participants should administer during each week). Oral PPS compliance during each six weeks period (first six weeks, second six weeks and third six weeks) was the average of the weekly compliance during each six week period (for example, the compliance during the first six weeks was the summation of the compliance in week 1, 2,3,4,5 and 6 divided by 600).

3.14.4 Statistical Analysis for the First Aim

Our first aim was: To determine to what extent socio-demographic, lifestyle, reproductive and clinical factors are associated with symptom severity and impairment in HRQL in women diagnosed with IC.

We **hypothesize** that age, education, smoking history, menopausal status, and co-morbid conditions will be associated with symptom severity, and that the same factors, with the exception of smoking history, will also be associated with impairment in HRQL in women diagnosed with IC.

All available data at baseline (n=41) were used to assess this aim. Two main stages were performed as described below:

3.14.4.1 Data Management and Manipulation

3.14.4.1.1 Preparing HRQL Domain Scores

Data from the SF-36 questionnaire were entered using SPSS statistical software. In order to be able to calculate scores for the different domains of the SF-36, 10 items in the SF-36 were recoded (reversed and/or recalibrate). Those 10 items scattered in 5 different scales: bodily pain, general health, vitality, social functioning, and mental health. The main idea behind that is to

ensure that a higher item value indicates better health on all the SF-36 items and scales. Missing item responses were recorded with mean substitution if a respondent answered at least half of the items in a multi-item scale (or half plus one in the case of scales with an odd number of items). [177] Raw domain scores were calculated by adding the raw scores of the items that form each domain. All domain raw scores were converted into the final scores that range from 0-100 using a specific formula described in the SF-36 health survey manual and interpretation guide. [177] This step is important to enable the researchers from comparing their results with other published results of the SF-36. Score checking (calculating scores for randomly selected cases by hand, testing correlations between items and domain, etc) [177] was performed to ensure that all scores were calculated correctly. Finally, norm-based scores were calculated for each of the eight domains through using the means and the standard deviation of the 1998 general US population score for the corresponding SF-36 scale as described in physical and mental summary scales user manual. [184]

3.14.4.1.2 Preparing IC Symptom Severity Score

Two validated instruments were used to collect data about IC symptoms; The O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), and the Pelvic Pain and Urgency/Frequency (PUF) Questionnaire. The first one was designed to evaluate changes in IC symptoms while the second one was designed to use as a screening test. Therefore, we used the ICSI mainly to classify IC cases into three different classes as follows: ICSI scores from 0 to 6 = mild symptoms, from 7 to 14 = moderate and from 15 to 20 = severe symptoms. An ICSI score of greater than or equal to six was found to be 90% sensitive and 95% specific for interstitial cystitis/painful bladder. [23] Furthermore, these cut of points were used successfully in previous studies. [32]

Because only moderate and/or severe cases were included in the current study, we decided to use the severity of IC symptom score as a continuous variable rather than categorical one.

3.14.4.2 Analysis Plan

The main idea from this step was to determine any important covariate that may confound the tested association between the severity of IC symptoms and the impairment in HRQL domains in the second aim of the current study.

Univariate associations between the severity of IC symptoms (ICSI score) and each of the socio-demographic variables (age, race, marital status, educational levels and employment status), the lifestyle factors (smoking history and BMI), the reproductive factors (ever pregnant, number of pregnancy, menopausal status, use of hormone replacement therapy (HRT) or oral contraceptive (OC)) and the clinical and sexual factors (the number of concomitant chronic conditions, presence of glomerulations, presence of Hunner's ulcers, having sexual intercourse, sexual desire and sexual arousal) were tested using either non-parametric correlation for continuous variables or Mann-Whitney U test and Kruskal-Wallis test for categorical variables. The same analyses were performed to assess the univariate associations between each of the above listed factors and the eight HRQL domains of the SF-36 instrument.

Multivariate median regression were performed to assess if the factors which were found to be associated with either the severity of IC symptoms or each score of the SF-36 domains in the univariate analyses were confounded by age and/ or co-morbidity.

3.14.5 Statistical Analysis for the Second Aim

Our second aim was: To determine if symptom severity is correlated with impairment in all HRQL domains after adjusting for confounders that will be identified from assessing the Specific Aim 1 of this study.

We **hypothesize** that symptom severity will be associated with impairment in physical function, social function and mental health domains of HRQL and that these associations will not be significantly altered after adjusting for lifestyle and socio-demographic factors.

All available data at baseline (n=41) were used to assess this aim. Bivariate non-parametric correlations between each of the eight domain scores of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotion, mental health) and the severity of IC symptoms (ICSI score) were performed. Non-parametric median regression was used to adjust for any possible confounders.

3.14.6 Statistical Analysis for the Third Aim

Our third aim was: To determine which symptom (pain, urinary frequency, nocturia and/or urgency) is most likely to impair IC patients' HRQL represented by Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36 instrument.

We **hypothesize** that there will be variability in the effect of each symptom on PCS and MCS scales, and that pain will be the symptom most likely to impair both summary components.

All available data at baseline (n=41) were used to assess this aim. The statistical analysis to assess this aim consisted of two main stages as follows:

3.14.6.1 Data Management and Manipulation

The main dependent variable was the score for each of the physical and mental summary scales. The main independent variables were baseline pain scores (general pain and pain during urination using pain assessment scale), urinary frequency (from voiding log), nocturia (from voiding log) and urgency score (urgency scale).

The algorithm published in the SF-36 physical and mental health summary scales user manual [184] was applied to the SF-36 SPSS file. Three main steps were performed to calculate the two summary scales PCS and the MCS as follows:

- ✓ The first step was standardizing each of the eight scales of the SF-36 by using a Z-score transformation. A Z-score for each scale was computed by subtracting the mean of the 1998 general US population score from each SF-36 scale and dividing the difference by the corresponding scale standard deviation.
- ✓ The second step involved the computation of the aggregate scores for the physical and mental components using the physical and mental factor score coefficients from the 1990 general US population. For example, to compute the aggregate physical component score, each SF-36 scale, Z score from the first step was multiply by its respective physical factor score coefficient this was followed by summing the eight products.
- ✓ The last step was the transformation of each component score to norm-based scores (mean=50, SD=10). This was done by multiplying each aggregate component scale score by 10 and adding the resulting product to 50.

3.14.6.2 Analysis Plan

Because we expect that the occurrence of each of the IC symptoms is not independent of each other, which mean patient can suffer from all these symptoms together, the first step of the analysis was to perform bivariate non-parametric Spearman correlations between these symptoms to determine the degree of dependency. Possible confounders for the associations between each of the IC symptoms and each of the summary component scales were determined by univariate analyses. Non-parametric Spearman correlations between each of the IC symptoms and each summary scale (PCS and MCS) separately were performed to determine the unadjusted associations. Finally multivariate median regression was used to adjust for the main study covariates as well as all other well known covariates. [21, 203]

3.14.7 Statistical Analysis for the Remaining Aims

Using the clinical trial design, the remaining aims (the fourth, fifth, sixth, seventh, eighth and ninth) were assessed. These aims test the efficacy of the trial treatment on the following four main outcomes:

- IC symptoms through the fourth and fifth aims
- Proportion of responders through the sixth aim
- HRQL domains and the two summary scales (PCS and MCS) through the seventh and the eighth aims
- Sexual function domains through the ninth aim

Table 3-1 provides a summary of all these outcomes and the main measurement tools that were used to collect them as well as the main endpoints. The statistical analyses for the remaining six aims were performed in two main stages as follows:

3.14.7.1 Descriptive Statistical Analysis

As a first step in assessing the remaining six aims of the current study, time plots (stratified by study groups) of the median scores of the following outcome measures were performed; thus we have a complete picture about the change in the main study outcome over time:

- The PUF total score (1-35) as well as its components (symptom score (1-23) and bothering score (0-12))
- The O'Leary-Sant total score (0-36) as well as its components (symptom index score (0-20 and problem index score (0-16))
- The pain assessment score, urgency score, urinary frequency and nocturia
- The median of PCS and MCS
- The median of each of the SF-36 domain
- The median of both the sexual desire and sexual arousal scale

3.14.7.2 Testing the Efficacy of the Trial Intervention

Although the performed statistical analyses for the last six aims were approximately similar, we preferred to present the analysis for each aim separately for the reader convenience.

3.14.7.2.1 Statistical Analysis for the Fourth Aim

Our fourth aim was: To determine if the intravesical instillation of PPS plus the administration of oral PPS will reduce symptom severity more than oral PPS plus intravesical placebo at the following endpoints: week 6, week 12, and/or week 18 of the trial.

We **hypothesize** that the use of both intravesical PPS and oral PPS for the first 6 weeks of the trial will improve IC symptoms significantly more than the use of oral PPS and intravesical placebo.

This study used two validated instruments to collect data about the overall severity of IC symptoms; the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and the Problem Index (ICPI), [23] and the Pelvic Pain and Urgency/Frequency (PUF) Questionnaire.[24]

The O'Leary-Sant composes of two indices. The ICSI includes questions about the main four IC symptoms (urgency, urinary frequency, nocturia, and pain), while the ICPI assess how much each symptom has been a problem for a patient. Thus it gives a complete picture of IC. [23] On the other hand, the PUF includes questions that assessed how sexual activity may affect by IC symptoms, specifically pain and urgency. PUF also includes questions about the four main IC symptoms and how much they bother the patient. [24] Thus each instrument may provide extra information over the other one, for that reason we used both instruments to assess this aim.

To test our fourth aim, changes in the total score of the O'Leary-Sant and the PUF instruments as well as in their components (ICSI & ICPI of O'Leary-Sant, symptom score & bother score of PUF) were calculated by subtracting scores at each of the above specified endpoints from baseline scores. Negative sign was inserted to indicate a reduction in symptom severity (equates improvement). As a first step, it was of great interest for us to test if there were significant change in the scores of the O'Leary-Sant, the PUF instrument and their components

from baseline to each endpoint in each arm separately. Wilcoxon signed-rank test (the non-parametric version of the paired t test) was used for that. On the other hand, Mann-Whitney U test (the non-parametric version of the two independent samples t test) was used to assess if the change in the total score of the O'Leary-Sant and the PUF instruments as well as their components from baseline to each endpoint in the treatment group was greater than that in the placebo group.

3.14.7.2.2 Statistical Analysis for the Fifth Aim

Our fifth aim was: To determine which symptom (pain, urgency, nocturia and/or urinary frequency) is most likely to be improved as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at the following endpoints: week 6, week 12, and/or week 18 of the trial.

We **hypothesize** that pain will be the most improved symptom as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at each endpoint.

To test this aim, changes in pain score (general pain), urgency score, urinary frequency and nocturia were calculated from baseline to each of the above specified endpoint. Negative sign was inserted to indicate a reduction in the severity of each symptom (equates improvement). Wilcoxon signed-rank test was used to determine if these changes at each endpoint were significant in each study arm separately.

It was also of great interest for us to test if the change in each outcome was significantly more among the treatment group in comparison to the placebo group at any of the specified endpoint. Mann-Whitney U test was used for that.

3.14.7.2.3 Statistical Analysis for the Sixth Aim

Our sixth aim was: To determine if the proportion of responders (defined by those who reported any improvement through patient global assessment instrument) is significantly more among those who received both intravesical PPS and oral PPS (treatment group) in comparison to those who received intravesical placebo and oral PPS (placebo group) by the end of the study (at week 18).

We **hypothesize** that the proportion of responders will be significantly more among the treatment group compared to the placebo group at week 18 of the study.

To assess this aim, responders were defined as those who evaluated the changes in their overall IC condition, urinary frequency and/or their urgency since enrollment as improved through the patient global assessment instrument at the end of the study. Chi-square or Fisher's exact test was used to test if the proportion of responders among the treatment group was significantly greater than that among the placebo group. Because the current study included only moderate or severe IC cases, it was also of great importance to determine the level of improvement among responders (moderately improved, greatly improved or completely improved) in each group and to test if the differences were statistically significant using Chi-square or Fisher's exact test as required.

3.14.7.2.4 Statistical Analysis for the Seventh Aim

Our seventh aim was: To test if the intravesical instillation of PPS plus the administration of oral PPS will improve IC patients' HRQL represented by Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36 more than intravesical placebo plus oral PPS at week 4 and/or at the end of the trial (at week 18).

We **hypothesize** that the use of both intravesical PPS and oral PPS will improve HRQL in IC patients significantly more than the use of intravesical placebo plus oral PPS at both endpoints.

To test this aim, changes in PCS and MCS were calculated from baseline to each of the above specified endpoint. Negative sign was inserted to indicate a reduction in the score of the two components of the quality of life (equates impairment). As a first step, Wilcoxon signed-rank test was used to determine if these changes at each endpoint were significant in each study arm separately. Then, Mann-Whitney U test was used to test if the change in each summary component was significantly more among the treatment group in comparison to the placebo group at any of the specified endpoint.

3.14.7.2.5 Statistical Analysis for the Eighth Aim

Our eighth aim was: To determine which domain of HRQL is most likely to be improved as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at week 4 and/or at the end of the trial (at week 18).

We **hypothesize** that the use of either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS will not have the same improvement effect on all HRQL domains at both endpoints, and that administering intravesical PPS plus oral PPS will significantly improve all HRQL domains by the end of the trial.

The results from the seventh aim give a general idea about the effect of the trial treatment on HRQL represented by the summary components. This aim provides more details about the previous aim and determines the exact domains that improved as a result of the trial treatment.

To test the eighth aim, changes in each domain of the SF-36 from baseline to each of the above specified endpoint were calculated. Negative sign was inserted to indicate a decrease in

the score of the domains of the quality of life (equates impairment). Wilcoxon signed-rank test was used to determine if these changes at each endpoint were significant in each study arm separately.

It was also of great interest for us to test if the change in each domain was significantly more among the treatment group in comparison to the placebo group at any of the specified endpoint. Mann-Whitney U test was used for that.

3.14.7.2.6 Statistical Analysis for the Ninth Aim

Our ninth aim was: To determine if the administration of both intravesical PPS and oral PPS will improve sexual function more than intravesical placebo and oral PPS at week 4 and/or at the end of the trial (at week 18).

We **hypothesize** that the use of both intravesical PPS and oral PPS will improve sexual function of IC patients more than the use of intravesical placebo and oral PPS at both endpoints.

Similar to the above described analyses, changes in sexual desire score and sexual arousal score from baseline to each endpoint were calculated. Negative sign was inserted to indicate a reduction in the score of the sexual function domains (equates impairment). This was followed by testing if these changes from baseline to each endpoint were significant in each treatment group using Wilcoxon signed-rank test. Mann-Whitney U test was used to test if these changes were significantly more among the treatment group in comparison to the placebo group at each endpoint.

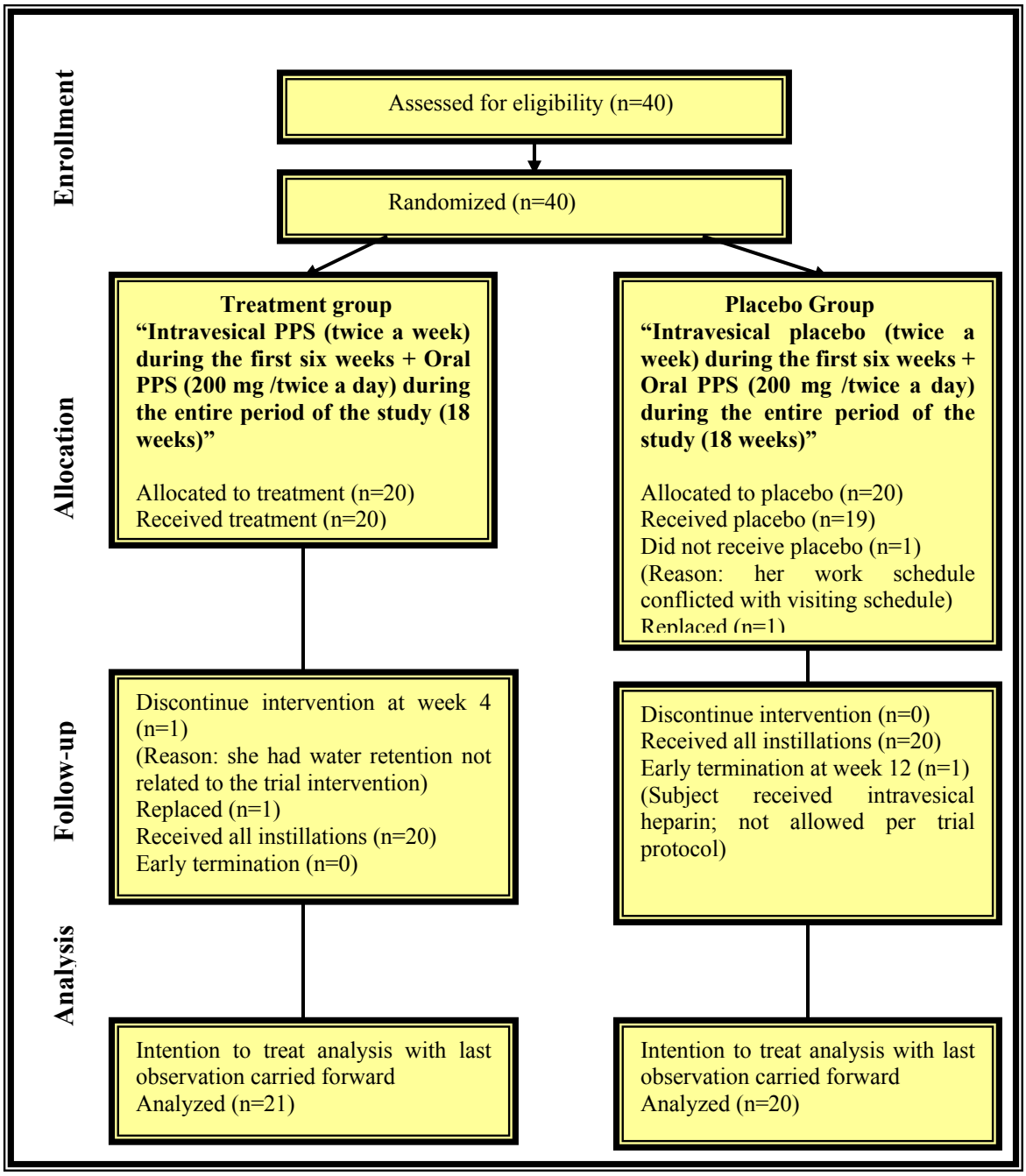
4.0 RESULTS

4.1 RECRUITMENT AND FLOW DIAGRAM OF SUBJECT PROGRESS

All the study subjects were recruited from the patients of the study clinical site (Citrus Valley Medical Research Inc., Glendora, CA) during the period from April 2004 to August 2006. Initially, 40 subjects were assessed for eligibility and participated in the trial. Two subjects dropped out; the first subject (placebo group) did not start the study because of a conflict with her work schedule while the second subject (treatment group) discontinued receiving the trial intervention after 4 weeks of the study because she had water retention which was not related to the trial intervention. Therefore, another two subjects were enrolled; the first of them received the same intervention that was assigned to the first drop out while the second received the same intervention that was assigned to the second drop out. At the end of the trial, 40 subjects completed all the required instillations of either the PPS or the Placebo during the first six weeks of the study. There was one early termination (at week 12) among the placebo group; she received intravesical heparin after week 12 of the trial (a medication that was not allowed per the trial protocol) thus, she became no longer evaluable.

Intention to treat analysis (ITT) approach with last observation carried forward (LOCF) method (to handle missing) was used. This resulted in a total of 41 participants (treatment =21,

placebo =20) available for the final analysis. **Figure 4-1** provides a flow diagram of subjects' progress during each phase of the study.



*Reprinted with permission from *Journal of Urology*, 2008; 179(1): 177-85, Edward L. Davis, Samar R. El Khoudary, Evelyn O. Talbott, Josephine Davis, Lisa J. Safety and Efficacy of the Use of Intravesical and Oral Pentosan Polysulfate Sodium for Interstitial Cystitis: A Randomized Double Blind Clinical Trial. Copyright© 2008 Elsevier.

Figure 4-1: Flow Diagram of Subjects' Progress Through the Phases of the Trial *

4.2 DESCRIPTIVE RESULTS

4.2.1 Descriptive Results for the Total Study Population (n = 41) at Baseline

4.2.1.1 Socio-Demographic Profile

This was a convenience sample of IC patients identified by physicians at Citrus valley Medical Research Inc. Glendora, CA. All study subjects were females diagnosed with IC within one year of the beginning of the study, and previously untreated with either intravesical or oral PPS. The median age was 37.8 years old with a wide range from 20 to 71 years old. In spite of this wide range, subjects were distributed uniformly (~ 25% in each category) into four different age groups as follows: 20-29, 30-39, 40-49 and 50+. The majority of the study participants were Caucasian ~71% (29/41). Moreover, Hispanic constituted ~20% (8/41) while the remainder proportion ~9% (4/41) included Black, Asian and other races. Approximately 56% (23/41) of the study subjects were married, ~24% (10/41) never married, ~12% (5/41) divorced and ~7% (3/41) were classified as either widowed or other status. Interestingly, ~68% (28/41) of our study population had at least post-secondary education (≥13 years of education) while ~29% (12/41) had secondary education (9-12 years of education) and only 1 subject had elementary education (≤ 8 years of education). Therefore, 40 subjects had at least a high school degree. Although our study subjects were moderate to severe IC cases, 78% (32/41) were able to maintain employment. Of those who were employed, about 28% (9/32) classified their job area as professional, ~22% (7/32) as managerial/administration, ~9% (3/32) as clerical, ~9% (3/32) as service and ~31% (10/32) as other. The nine unemployed subjects were classified as homemaker (6/9) or unemployed not disabled (2/9) or unemployed disabled (1/9). **Table 4-1** shows the baseline demographic of the total study population.

Table 4-1: Baseline Demographic Characteristics of the Total Study Population (n=41)

CHARACTERISTICS	N	BASELINE DATA
Age	**41**	
Median		37.8
(25^{th} percentile , 75^{th} percentile)		(28.1, 44.9)
Age Categories %	**41**	
20-29	11	26.8
30-39	12	29.3
40-49	10	24.4
50+	8	19.5
Ethnicity %	**41**	
Caucasian	29	70.7
Black	2	4.9
Hispanic	8	19.6
Asian	1	2.4
Other	1	2.4
Marital Status %	**41**	
Married	23	56.1
Widowed	1	2.4
Divorced	5	12.2
Never Married	10	24.4
Other	2	4.9
Education (years)	**41**	
Median		14
(25^{th} percentile , 75^{th} percentile)		(12, 15)
Education %	**41**	
Elementary	1	2.4
Secondary	12	29.3
Post-Secondary	28	68.3
Employment %	**40**	
Employed	32	78
Not Employed	9	22

4.2.1.2 Reproductive and Lifestyle Profile

Table 4-2 shows the main reproductive and lifestyle factors of the current study participants. The median age at menarche was 13 years old; 75% of the study subjects reached puberty age at 13.5 years old or younger. About 76% (31/41) of the participants were ever pregnant and approximately half of them (17/31) had from 1 to 2 pregnancies while the remainder had either 3-4 pregnancies (9/31) or 5+ pregnancies (5/31). More than half of the subjects ~63% (26/41) were not menopausal (had menstrual period during the previous 12 months of the baseline interview). For those who reached menopause ~37% (15/41), the main type of menopause was surgical ~ 60% (9/15) while natural menopause was reported by 33% (5/15) and menopause as a result of drug therapy by ~7% (1/15). About 88% (36/41) of the current study population ever used oral contraceptive while ~29% (11/38) ever used hormone replacement therapy.

In term of the main lifestyle factors about the current study population: smoking history and Body Mass Index (BMI); more than 50% of the participants were ever smoked (24/41). The median BMI was 24.4 Kg/m^2. Moreover, more than 50% of the current study population fall into the normal and/or underweight category (BMI < 25 Kg/m^2) while ~29% were classified as over weight (BMI: 25 Kg/m^2-29 Kg/m^2) and ~17% were considered as obese (BMI ≥ 30 Kg/m^2) according to the CDC definitions. [204]

Table 4-2: Baseline Reproductive and Lifestyle Characteristics of the Total Study Population (n=41)

CHARACTERISTICS	N	BASELINE DATA
Age at Menarche (Year)	**41**	
Median		13
(25^{th} percentile , 75^{th} percentile)		(12, 13.5)
Ever Pregnant %	**41**	
Yes	31	75.6
No	10	24.4
Number of Pregnancies %	**31**	
1-2	17	54.8
3-4	9	29.0
5+	5	16.2
Menopausal Status %	**41**	
Menopause	15	36.6
Not Menopause	26	63.4
Type of Menopause %	**15**	
Surgical	9	60
Natural	5	33
Drug Therapy	1	7
Ever Used OC %	**41**	
Yes	36	87.8
No	5	12.2
Ever Used HRT [A] %	**38**	
Yes	11	28.9
No	27	71.1
Ever Smoked %	**41**	
Yes	24	58.5
No	17	41.5
BMI [B] (Kg/m^2)	**41**	
Median		24.4
(25^{th} percentile , 75^{th} percentile)		(21.9, 27.5)
BMI [B] %	**41**	
$< 25\ Kg/m^2$	22	53.7
25-29 Kg/m^2	12	29.3
$\geq 30\ Kg/m^2$	7	17.1

[A] Three were missing at baseline

[B] BMI: body mass index. BMI was based on self-reported weight and height at week18

4.2.1.3 Clinical Characteristics Profile

Table 4-3 summarizes the major clinical characteristics of the study participants. According to the O'Leary-Sant IC symptom index score categories, our subjects were classified as either having moderate ~46% (19/41) or severe IC symptoms ~51% (21/41). Only one participant was classified as having mild IC symptoms. According to the results of cystoscopy with hydrodistension, all the study subjects had glomerulations. Furthermore, ~76% (31/41) of them had severe glomerulations while ~15% (6/41) had moderate glomerulations and ~9% (4/41) had mild glomerulations. Hunner's ulceration was found among ~15% (6/41) of the study subjects. Interestingly, the subject who was classified as having mild IC symptoms according to the O'Leary-Sant IC symptom index score categories can be reclassified as severe IC case based on the results of her cystoscopy with hydrodistension. In fact, she had severe glomerulations and two Hunner's ulcerations.

Because of the complexity of IC condition and the multifactorial etiologies, patients often cannot use only one medication to manage their devastating symptoms. As we mentioned previously, IC treatment is currently prescribed on the basis of a patient's symptoms. Therefore, the study participants were allowed to continue using their medications while participating in the study. About 76% (31/41) of the participants used antihistamines during the study period, ~56% (23/41) used narcotics and/ or analgesics, ~ 54% (22/41) used antidepressants and ~34% (14/41) used antispasmodics. Several co-morbid conditions were reported among study population such as endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia…etc. The median number of co-morbid conditions was 3, and 75% of the participants had 5 or less co-morbid conditions. In terms of the voided volume at baseline, both the results from urodynamics and

cystometrogram showed small bladder capacity of the study participants. The median bladder capacity based on urodynamics was 153 ml while it was 131 ml based on cystometrogram.

Table 4-3: Clinical Characteristics of the Total Study Population at Baseline (n=41)

CHARACTERISTICS	N	BASELINE DATA
Severity of IC Symptoms [A] %	**41**	
Mild (0-6)	1	2.4
Moderate (7-13)	19	46.3
Severe (14-20)	21	51.3
Glomerulations %	**41**	
Yes	41	100
No	0	0
Severity of Glomerulations [B] %	**41**	
Mild	4	9.7
Moderate	6	14.6
Severe	31	75.7
Hunner's Ulcers %	**41**	
Yes	6	14.6
No	35	85.4
Types of Concomitant Medications [C] %	**41**	
Narcotics and/or Analgesics (yes)	23	56.1
Antihistamines (yes)	31	75.6
Antispasmodics (yes)	14	34.1
Antidepressants (yes)	22	53.7
Number of Co-morbid Condition [D]	**41**	
Median (25^{th} percentile , 75^{th} percentile)		3 (2, 5)
Uroflow Volume (ml) [E]	**41**	
Median (25^{th} percentile , 75^{th} percentile)		153 (72.5, 231)
Cystometrogram (CMG) (ml) [F]	**33**	
Median (25^{th} percentile , 75^{th} percentile)		131 (72.5, 230)

[A] Severity of IC symptoms was based on the O'Leary-Sant Interstitial Cystitis Symptom Index score, range from 0-20

[B] Severity of glomerulations was based on the following clinical definitions developed by the PI:
Glomerulations: Being a red, ulcerative bladder lesion that looks like a stain "glomerulations that is a collection of capillaries in one area. In the bladder these lesions are not a collection of capillaries but they are areas of local inflammation most likely caused by a collection of mast cells suddenly degranulating and causing an intense local inflammatory reaction, I.E. ulceration and bleeding
Mild glomerulations: Few submucosal glomerulations i.e. 0-2-5 lesions per cystoscopic view, associated with submucosal vascular injection. Vascular injection meaning that the mucosa turns red but there are none to only a few glomerulations
Moderate glomerulations: On hydrodistension, the bladder membrane turns red with vascular injection and there are greater than 10 but less than 15 glomerulations per cystoscopic view

Table 4-3 Cont'd

Severe glomerulations: On hydrodistension, the bladder membrane turns red with vascular injection and there are submucosal glomerulations too numerous to count in nearly all of the bladder cystoscopic views. This can be with or without "Hunner's Ulcers", which are patches of bladder membrane where glomerulations blend into a large greater than 1.0cm, patch of bladder tissue

C The concomitant medications was defined as follows: **Antispasmodics** (Oxytrol, Detrol LA, Ditropan XL, Sanctrua, Vesicare), **Cyclic antidepressants** (Elavil, Zoloft), **Antihistamines** (Allerga, Clarinex,Nyquil, Atarax), **Analgesics and Narcotics** (Ultracet, pyridium, Vicodin, Darvocet, Ambien, Morphine, Lidocaine)

D Co-morbid conditions were conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc.

E Based on Uroflowmetry measures.

F CMG was too painful for 8 of the study participants; treatment (n=15) and placebo (n=18).

4.2.1.4 Severity of IC Symptoms

Table 4-4 shows the severity of IC symptoms in two different ways. The results from either O'Leary-Sant instrument or PUF instrument provide a cumulative score that reflects the severity of all symptoms together. On the other hand, the results from single scale for each symptom show the severity of each symptom independently. The median total score of the O'Leary-Sant instrument (0-36) was 26, which indicates severe IC symptoms. Moreover, 75% of the study participants reported a total score of 30 or less. In terms of the component indices of the O'Leary-Sant instrument, the median score of the symptom index (0-20) was 14 while of the problem index (0-16) was 12. O'Leary et al. reported that almost no IC cases had a score less than 6 on either component indices, while almost no controls had a score as high as 6.[23] The results from PUF instrument were consistent with the results from O'Leary-Sant index; the median total score of the PUF instrument (1-35) was 22. Moreover, 75% of the subjects reported a total score of 25.5 or less. The median score of the PUF symptom component (1-23) was 14 while of the bother component (0-12) was 8. Interestingly, a PUF total score of 15 or more is associated with about 84% chance of having a positive potassium sensitivity test (a strong indication of IC). [24]

With regard to the severity of each IC symptom separately; the median level of pain (1-9) was 4 (equates moderate level of pain). The median level of urgency (1-5) was 3 (equates

moderate level of urgency). About 50% of the study participants reported 12 voids or less during waking hours and 2 voids or less during sleeping hours.

Table 4-4: Baseline IC Symptom Scores of the Total Study Population (n=41)*

STUDY MAIN OUTCOMES	BASELINE SCORES
O'Leary-Sant Total Score (0-36) [A] **O'Leary-Sant ICSI** [B] **Score (0-20)** **O'Leary-Sant ICPI** [B] **Score (0-16)**	26 (19, 30) 14 (10, 16) 12 (9.5, 14)
PUF [B] **Total Score (1-35)** [C] **PUF Symptom Score (1-23)** **PUF Bother Score (0-12)**	22 (18.5, 25.5) 14 (12, 17) 8 (6, 9)
Pain Assessment Score (1-9) [D]	4 (4, 5)
Urgency Scores (1-5) [E, F]	3 (2.6, 3.5)
Number of Voids During Waking Hours	12 (9.5, 17)
Number of Voids During Sleeping Hours	2 (1, 4)

* Data were presented as median (25th percentile, 75th percentile)

A O'Leary et al. reported that almost no IC patients had a score less than 6 on either index (ICSI, or ICPI), while almost no controls had a score as high as 6 [23]

B ICSI: Intestinal Cystitis Symptom Index, ICPI: Intestinal Cystitis Problem Index, PUF: Pain and Urgency/ Frequency Patient Symptom Scale

C A PUF total score of 15 or more was associated with about 84% chance of having a positive PST, a strong indication that IC may be present [24]

D A score of 1 indicates no pain; a score of 9 indicates severe pain

E Mean of urgency scores from voiding log (24 hour period)

F A score of 1 indicates no urgency; a score of 5 indicates severe urgency

4.2.1.5 Quality of Life of Study Participants (HRQL)

Tables 4-5 and **4-6** show HRQL scores in comparison to normative samples of the US females from the 1990 and the 1998 general social surveys respectively. [177, 184] **Table 4-5** shows the scores of the SF-36' eight domains of the current subjects in comparison to a normative sample of the US females (ages: 18-65+) from the general social survey, 1990. [177] All the scores in this table were presented in the original format: (0-100) as 0 indicates poor HRQL while 100 indicates excellent HRQL. Interestingly, the scores of the eight domains were much lower than

those of the normative sample of the US females. The median score of the physical functioning domain among our subjects was 65 compared to 90 among the normative sample; the median score of the role-physical domain was 25 compared to 100; of the bodily pain domain was 32 compared to 74; of the general health domain was 52 compared to 72; of the vitality domain was 25 compared to 60; of the social functioning domain was 50 compared to 87.5; of the role-emotional domain was 33.3 compared to 100 and of the mental health domain was 60 compared to 80 among the normative sample. Therefore, our subjects reported the lowest scores (<34) in vitality, role-physical, bodily pain and role-emotional domains.

Table 4-5: Baseline Scores of SF-36 Domains for the Total Study Population and a Normative Sample of USA Females (Ages 18-65+)/ General Social Survey, 1990

HEALTH RELATED QUALITY OF LIFE DOMAINS [A]	CLINICAL TRIAL POPULATION N=41 SCORES	US FEMALE SAMPLE [177] N=1,412 NORMS
Physical Functioning	61.5±29.4 65 (40, 87)	81.5±24.6 90 (65, 100)
Role-Physical	31.1±36.6 25 (0, 50)	77.6±36.2 100 (50, 100)
Bodily Pain	33.5±19.5 32 (22, 41)	73.6±24.3 74 (52, 100)
General Health	52.7±22.3 52 (32, 72)	70.6±21.5 72 (57, 85)
Vitality	29.4±20.8 25 (12.5, 42.5)	58.4±21.5 60 (45, 75)
Social Functioning	50.0±33.2 50 (25, 75)	81.5±23.7 87.5 (62.5, 100)
Role-Emotional	51.2±40.2 33.3 (0, 100)	79.5±34.4 100 (66.7, 100)
Mental Health	57.3±19.1 60 (40, 72)	73.3±18.7 80 (64, 88)

* Data were presented as mean ± SD, median (25th percentile, 75th percentile)

[A] Score for each domain ranges between 0-100: 0 indicates worse HRQL and 100 indicate excellent HRQL

Table 4-6 provides norm-based scores of the eight domains and the two component summary scales (PCS and MCS) of the SF-36 in comparison to those of a most recent normative sample of the US females (ages: 18-65+) from the general social survey, 1998. Calculating the norm-based scores of both the SF-36 domains and the two summary component scales makes it possible to compare those scores with each others as well as with the norm-based score of the normative sample from the US females. Any score above or below 50 is above or below the average and each one difference in the score is one tenth of a standard deviation. Both the PCS and MCS of the study population were extremely below the average (medians: 37.7, 39.4 respectively). Moreover, the two summary scores were lower than the norm-based scores of the normative sample as well (medians from normative sample: 52.6, 52.3 respectively). Therefore, the reader should expect that all the norm-based scores of the domains that constitute the two summary components will be below the average (<50). In fact, all the norm-based scores of the eight domains were below both the average (<50) and the normative US female sample scores. The median score of the physical functioning domain among the study population was 42.5 compared to that of the normative US female sample (52.9), of the role-physical domain was 35 compared to 56.2, of the bodily pain domain was 33.6 compared to 50.7, of the general health domain was 41.5 compared to 50.9, of the vitality domain was 34.9 compared to 49.1, of the social functioning domain was 35.4 compared to 57.1, of the role-emotional domain was 34.3 compared to 55.3 and of the mental health domain was 41.4 compared to 50.4 among the normative USA female sample, 1998. Thus, the current study subjects reported the lowest norm-based scores (≤35) in bodily pain, role-emotional, vitality and role-physical domains.

Table 4-6: Norm-Based Scores [A] of the 8 Domains, PCS and MCS/ SF-36 for the Total Study Population at Baseline and a Normative Sample of USA Females (Ages 18-65+)/ General Social Survey, 1998

HEALTH RELATED QUALITY OF LIFE DOMAINS	CLINICAL TRIAL POPULATION N=41 NORM-BASED SCORE	US FEMALE SAMPLE [184] N=1,198 NORM-BASED SCORE
Physical Functioning	41±12.3 42.5 (32, 51.7)	48.6±10.7 52.9 (44.6, 57.1)
Role-Physical	36.8±10.3 35 (28, 42.1)	49.2±10.3 56.2 (42.1, 56.2)
Bodily Pain	33.8±8.4 33.6 (29.3, 37.5)	49.4±10.3 50.7 (41.8, 55.9)
General Health	41.9±10.5 41.5 (32.2, 50.9)	49.8±10.2 50.9 (43.9, 57.9)
Vitality	37±9.8 34.9 (28.9, 43.1)	49.4±10.4 49.1 (42, 56.2)
Social Functioning	35.4±14.4 35.4 (24.6, 46.3)	49.3±10.4 57.1 (40.9, 57.1)
Role-Emotional	39.9±12.7 34.3 (23.7, 55.3)	49.7±10.1 55.3 (44.8, 55.3)
Mental Health	39.8±10.8 41.4 (30, 48.2)	49.1±10.4 50.4 (43.6, 57.3)
PCS [B]	38.3±9.5 37.7 (32.1, 47.3)	49.2±10.6 52.6 (43.5, 56.9)
MCS [B]	39.1±12 39.4 (28.6, 49.5)	49.5±10.4 52.3 (44, 57.2)

[A] Norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] PCS: Physical Component Summary, MCS: Mental Component Summary

4.2.1.6 Sexual Function Characteristics

Table 4-7 provides descriptive information about sexual function of the total study population at baseline. Approximately 72.5% (29/40) of our subjects reported that they had sexual intercourse during the previous month of the baseline assessment. Moreover, ~ 38% (11/29) of those who had sexual intercourse stated that they experienced painful intercourse always, 24.1% (7/29) stated that they experienced painful intercourse usually about 75% of the time, 20.7% (6/29) stated that they experienced painful intercourse sometimes less than 25% of the time, 13.8% (4/29) stated that they experienced painful intercourse sometimes about 50% of the time, and only one subject stated that she never experienced painful sexual intercourse. Both the sexual desire and sexual arousal scores were less than 5 cm on the visual analog scale (0-10 cm). About 50% of the study subjects marked their sexual desire as 3.3 cm or less, while their sexual arousal as 2.6 cm or less.

Table 4-7: Baseline Sexual Function Characteristics of the Total Study Population

SEXUAL FUNCTION VARIABLES	N*	BASELINE RESULTS
Had Sexual Intercourse [A] %	**40**	
Yes	29	72.5
No	11	27.5
Experience Painful Intercourse [A] %	**29**	
Not at all	1	3.4
Sometimes, less than 25% of the time	6	20.7
Sometimes, about 50% of the time	4	13.8
Usually, about 75% of the time	7	24.1
Always	11	37.9
Sexual Desire (0-10cm) [A, B]	**40**	
Median (25^{th} percentile, 75^{th} percentile)		3.3 (0.9, 5)
Sexual Arousal (0-10cm) [A, B]	**40**	
Median (25^{th} percentile, 75^{th} percentile)		2.6 (1.2, 5.1)

* N =40, one was missing at baseline

A All sexual assessments were assessed for the previous month to the baseline.

B Both sexual desire and sexual arousal were based on visual analog scale (0-10cm); 0 =none while 10= high.

4.2.2 Descriptive Results by Study Group: Treatment (n=21) and Placebo (n=20) at Baseline

The results in this section describe the study population by study group. The main purposes of that were: to give a complete description about each group and to test if the two groups were comparable in relation to their demographic, lifestyle, reproductive, clinical history and severity of IC symptoms. Therefore, we can determine if there were any other factors that we should take in consideration while assessing the efficacy of the trial intervention.

4.2.2.1 Socio-Demographic Profile

Table 4-8 shows the demographic characteristics of the two study groups. Importantly, the two groups were comparable in terms of age, ethnicity, marital status, education and employment

status. The median age of the treatment group was 36.9 years old while of the placebo group was 38.7 years old, p=0.5. There were slightly more Caucasian in the treatment group 76.2% (16/21) compared to the placebo group 65% (13/20) and slightly more Hispanic in the placebo group 25% (5/20) compared to the treatment group 14.3% (3/21). Moreover, the treatment group included 2 Black (9.5%) while the placebo group included one Asian (5%) and one from another racial classification (5%), the differences in the ethnicity distribution did not reach significant level, p=0.3.

About 52.4% (11/21) of the treatment group and 60% (12/20) of the placebo group were married, 23.8% (5/21) of the treatment group and 25% (5/20) of the placebo group were never married and 19% (4/21) of the treatment and 5% (1/20) of the placebo group were divorced. The remainder proportions were either widowed or had other marital status (treatment group: 0% and 4.8%, placebo group: 5% and 5%, respectively).

Both groups had a similar level of education; the median years of education among the treatment group was 14 years and among the placebo group was 13.5 years, p=0.2. Although 81% (17/21) of the treatment group were employed compared to 75% (15/20) of the placebo group, the difference was not statistically significant, p=0.7.

Table 4-8: Baseline Demographic Characteristics by Study Group

CHARACTERISTICS	TREATMENT N = 21	PLACEBO N =20	P* VALUE
Age (Yrs) [189] Median (25th percentile, 75th percentile)	36.9 (32, 45.1)	38.7 (26, 42.7)	0.5
Ethnicity [189] % Caucasian Black Hispanic Asian Other	 76.2 9.5 14.3 0 0	 65 0 25 5 5	0.3
Marital Status % Married Widowed Divorced Never Married Other	 52.4 0 19 23.8 4.8	 60 5 5 25 5	0.8
Education (Yrs) Median (25th percentile, 75th percentile)	14 (12.5, 16)	13.5 (12, 14)	0.2
Employment % Employed Not Employed	 81 19	 75 25	0.7

* Mann-Whitney U test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

4.2.2.2 Reproductive and Lifestyle Profile

Table 4-9 summarizes the reproductive and lifestyle characteristics of the two study groups. No significant differences were found between the two groups in any of the studied variables. Both groups had comparable age at menarche (median was 13 years old among both of the treatment and the placebo groups, p=0.6). About 71.4% (15/21) of the treatment group and 80% (16/20) of the placebo group were ever pregnant, p=0.7. Furthermore, 53.3% (8/15) of those who were ever pregnant among the treatment group and 37.5% (6/16) among the placebo group had at least 3 pregnancies, p=0.7.

With regard to menopausal status, the majority of the placebo group 75% (15/20) and about 52% (11/21) of the treatment group were not currently menopausal (had menstrual period during the previous 12 months of the baseline interview), p=0.2. For those who reached menopause, the main type of menopause among the treatment group was the surgical menopause 70% (7/10) while natural menopause was the main type among the placebo group 60% (3/5), p=0.3. Most of the subjects in the two groups ever used oral contraceptive (18/21 (85.7%) of the treatment group, 18/20 (96%) of the placebo group, p=1). On the other hand, the majority of the subjects in the two groups were never used hormone replacement therapy (14/20 (70%) of the treatment group, 13/18 (72.2%) of the placebo group, p=0.8). Regarding smoking history of the two groups, 12 subjects from each group ever smoked (57.1% in the treatment group and 60% in the placebo group, p=0.9). The BMI was also comparable among the two groups; the median BMI in the treatment group was 24.7 Kg/m^2 compared to 23.7 Kg/m^2 among the placebo group, p=0.5.

Table 4-9: Baseline Reproductive and Lifestyle Characteristics by Study Group

CHARACTERISTICS	TREATMENT N = 21	PLACEBO N =20	P* VALUE
Age at Menarche (Yrs) Median (25th percentile, 75th percentile)	13 (12,13)	13 (12, 14)	0.6
Ever Pregnant % Yes No	 71.4 28.6	 80 20	0.7
Number of Pregnancy % 1-2 3-4 5+	 46.7 33.3 20	 62.5 25 12.5	0.7
Menopausal Status % Menopause Not Menopause	 47.6 52.4	 25 75	0.1
Type of Menopause % Surgical Natural Drug Therapy	 70 20 10	 40 60 0	0.3
Ever used OC % Yes No	 85.7 14.3	 90 10	0.9
Ever used HRT [A] % Yes No	 30 70	 27.8 72.2	0.8
Ever Smoke % Yes No	 57.1 42.9	 60 40	0.9
BMI [B] (Kg/m^2) Median (25th percentile, 75th percentile)	24.7 (22.5, 28,6)	23.7 (21.7, 27.1)	0.5

* Mann-Whitney U test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

[A] Three were missing at baseline; 1 in the treatment group and 2 in the placebo group

[B] BMI: body mass index. BMI was based on self-reported weight and height at week18

4.2.2.3 Clinical Characteristics Profile

Table 4-10 shows the main clinical characteristics of the two groups. Both groups had a comparable clinical history in relation to all the assessed characteristics. There was no significant difference in the level of severity of IC symptoms between the two groups. About 57.1% (12/21) of the treatment group and 45% (9/20) of the placebo group were classified as having severe IC symptoms while 42.9% (9/21) of the treatment group and 50% (10/20) of the placebo group were classified as having moderate symptoms, and only one subject of the placebo group was classified as having mild IC symptoms, (p=0.6).

In terms of the results from cystoscopy with hydrodistension, all the subjects in the two groups had glomerulations. Although 85% (17/20) of the placebo group compared to 66.7% (14/21) of the treatment group had severe glomerulations, the difference did not reach a significant level (p=0.2). Hunner's ulcer was reported among 25% (5/20) of the placebo group compared to only 4.8% (1/21) of the treatment group, however this noted difference was not significant (p=0.09).

Because the study subjects were allowed to continue using medications that help them in managing their condition, it was very important to be sure that the use of these medications was comparable among the two groups. Both groups showed similar use of narcotics and/or analgesics (52.4% (11/ 21) among the treatment group compared to 55% (11/20) among the placebo group, p= 0.9), antihistamines (85.7% (18/21) among the treatment group compared to 65% (13/20) among the placebo group, p=0.2), antispasmodics (33.3% (7/21) among the treatment group compared to 35% (7/20)among the placebo group, p=0.9) and of antidepressants (57.1% (12/21) among the treatment group compared to 55% (11/20) among the placebo group,

p=0.9). In terms of co-morbidity, the two groups reported comparable number of co-morbid conditions (median= 4 in the treatment group and 3 in the placebo group, p=0.4).

The bladder capacity measured by either urodynamics or cystometrogram indicated very small capacity among the two study groups. The median bladder capacity based on urodynamics was 149 ml among the treatment group and 174.5 ml among the placebo group, p=0.9. On the other hand, the median bladder capacity based on cystometrogram was 131 ml among the treatment group and 136 ml among the placebo group, p=0.7.

Table 4-10: Baseline Clinical Characteristics by Study Group

CHARACTERISTICS	TREATMENT N = 21	PLACEBO N =20	P* VALUE
Severity of IC Symptoms [A] %			0.6
Mild (0-6)	0	5	
Moderate (7-13)	42.9	50	
Severe (14-20)	57.1	45	
Severity of Glomerulations [B] %			0.2
Mild	19	0	
Moderate	14.3	15	
Severe	66.7	85	
Hunner's Ulcers [189] %			0.09
Yes	4.8	25	
No	95.2	75	
Types of Concomitant Medications [C] %			
Narcotics and/or Analgesics (yes)	52.4	55	0.9
Antihistamines (yes)	85.7	65	0.2
Antispasmodics (yes)	33.3	35	0.9
Antidepressants (yes)	57.1	55	0.9
Number of Co-morbid Condition [D]			0.4
Median (25^{th} percentile , 75^{th} percentile)	4 (2, 6)	3 (2, 4.8)	
Uroflow Volume (ml) [E] [189]			0.9
Median (25^{th} percentile , 75^{th} percentile)	149 (67, 231)	174.5 (91, 232)	
Cystometrogram (CMG) (ml) [F] [189]			0.7
Median (25^{th} percentile , 75^{th} percentile)	131 (58, 270)	136 (90, 227.5)	

* Mann-Whitney U test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

[A] Severity of IC symptoms was based on the O'Leary-Sant Interstitial Cystitis Symptom Index score, range from 0-20

[B] Severity of glomerulations was based on the following clinical definitions developed by the PI:
Glomerulations: Being a red, ulcerative bladder lesion that looks like a stain "glomerulations that is a collection of capillaries in one area. In the bladder these lesions are not a collection of capillaries but they are areas of local inflammation most likely caused by a collection of mast cells suddenly degranulating and causing an intense local inflammatory reaction, I.E. ulceration and bleeding
Mild glomerulations: Few submucosal glomerulations i.e. 0-2-5 lesions per cystoscopic view, associated with submucosal vascular injection. Vascular injection meaning that the mucosa turns red but there are none to only a few glomerulations
Moderate glomerulations: On hydrodistension, the bladder membrane turns red with vascular injection and there are greater than 10 but less than 15 glomerulations per cystoscopic view
Severe glomerulations: On hydrodistension, the bladder membrane turns red with vascular injection and there are submucosal glomerulations too numerous to count in nearly all of the bladder cystoscopic views. This can be with or without "Hunner's Ulcers", which are patches of bladder membrane where glomerulations blend into a large greater than 1.0cm, patch of bladder tissue

[C] The concomitant medications was defined as follows: **Antispasmodics** (Oxytrol, Detrol LA, Ditropan XL, Sanctrua, Vesicare), **Cyclic antidepressants** (Elavil, Zoloft), **Antihistamines** (Allerga, Clarinex,Nyquil, Atarax), **Analgesics and Narcotics** (Ultracet, pyridium, Vicodin, Darvocet, Ambien, Morphine, Lidocaine)

[D] Co-morbid conditions were conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc.

[E] Based on Uroflowmetry measures. Treatment (n=20) & placebo (n=20)

[F] CMG was too painful for 8 of the study participants. Treatment (n=15) & placebo (n=18)

4.2.2.4 Severity of IC Symptoms

Table 4-11 presents the baseline scores of IC symptoms (measured by O'Leary-Sant, PUF instruments, pain scale, urgency scale and voiding log) by the two groups. No significant difference was reported in any of these scores between the study groups. The results from both the O'Leary-Sant and the PUF instruments showed that the two groups had similar level of IC symptom severity. With regard to O'Leary-Sant instrument (0-36), the median total score was 26 among the treatment group and 23 among the placebo group, p=0.4. The scores from the two component of the O'Leary-Sant (ICSI (0-20) and ICPI (0-16)) were also comparable between the two groups. The median ICSI score was 14 among the treatment group and 12 among the placebo group (p=0.4), while the median ICPI score was 13 among the treatment group and 11.5 among the placebo group (p=0.2). In terms of the PUF score (1-35), the median total score was 23 among the treatment group and 21.5 among the placebo group, p=0.9. The results from both the PUF/symptom component and the PUF/bother component were not significantly different by the study group (median PUF symptom score =14 among the treatment group and 14 among the placebo group, p=0.9, median PUF bother score =8 among the treatment group and 7.5 among the placebo group, p=0.8).

With regard to the level of each symptom of IC, both pain (1-9) and Urgency (1-5) were evaluated as moderate by both groups (median pain score = 4 among the treatment and 4.8 among the placebo group; p= 0.3, median urgency score = 3.5 among the treatment and 3 among the placebo group, p= 0.1). Both groups reported approximately similar number of voids during waking hours (median= 12 among the treatment group and 14.5 among the placebo group, p= 0.3) and during sleeping hours (median= 2 among the treatment group and 2 among the placebo group, p= 0.7).

Table 4-11: Baseline IC Symptom Scores by Study Group* [189]

STUDY MAIN OUTCOMES	TREATMENT N = 21	PLACEBO N =20	P* VALUE
O'Leary-Sant Total Score (0-36) [A]	26 (18.5, 32)	23 (19.3, 30)	0.4
O'Leary-Sant ICSI [B] **Score (0-20)**	14 (10.5, 17)	12 (10, 16)	0.4
O'Leary-Sant ICPI [B] **Score (0-16)**	13 (8.5, 15)	11.5 (10, 14)	0.2
PUF [B] **Total Score (1-35)** [C]	23 (18.3, 25.5)	21.5 (18.3, 26.5)	0.9
PUF Symptom Score (1-23)	14 (11.5, 17)	14 (12.3, 17)	0.9
PUF Bother Score (0-12)	8 (6, 9)	7.5 (6, 9.8)	0.8
Pain Assessment Score (1-9) [D]	4 (4, 5)	4.8 (4, 5.8)	0.3
Urgency Scores (1-5) [E, F]	3.5 (2.6, 3.6)	3 (2.5, 3.2)	0.1
Number of Voids During Waking Hours	12 (9, 16)	14.5 (10, 18.8)	0.3
Number of Voids During Sleeping Hours	2 (1, 4)	2 (1, 4)	0.7

* Data were presented as median (25th percentile, 75th percentile). P values: Mann-Whitney U test for continuous variables.

A O'Leary et al. reported that almost no IC patients score less than 6 on either index (ICSI, or ICPI), while almost no controls score as high as 6 [23]

B ICSI: Intestinal Cystitis Symptom Index, ICPI: Intestinal Cystitis Problem Index, PUF: Pain and Urgency/ Frequency Patient Symptom Scale

C A PUF total score of 15 or more is associated with an 84% chance of having a positive PST, a strong indication that IC may be present [24]

D A score of 1 indicates no pain; a score of 9 indicates severe pain

E Mean of urgency scores from voiding log (24 hour period)

F A score of 1 indicates no urgency; a score of 5 indicates severe urgency

4.2.2.5 Quality of Life by Study Group (HRQL)

Tables 4-12 and **4-13** show the scores of SF-36 in the original format (0-100) and in the norm-based format (T-scores) for the two groups respectively**. Table 4-12** shows the scores of the SF-36' eight domains by study group in the original format: (0-100) as 0 indicates poor HRQL while 100 indicates excellent HRQL. There was no significant difference in any of the eight domain' scores between the two groups. The differences between groups in the scores of the physical functioning domain (median=65 among both the treatment group and the placebo group), the role-physical domain (median=0 among the treatment group and 37.5 among the placebo group),

the bodily pain domain (median=31 among the treatment group and 32 among the placebo group), the general health domain (median=42 among the treatment group and 57.3 among the placebo group), the social functioning domain (median=37.5 among the treatment group and 56.3 among the placebo group) and of the role-emotional domain (median=33.3 among the treatment group and 66.7 among the placebo group) did not reach significant level, $p \geq 0.1$. Interestingly, there was a marginal significant difference ($0.1 > p \geq 0.05$) in the score of the vitality domain (median=20 among the treatment group and 32.5 among the placebo group) and the score of the mental health domain (median=56 among the treatment group and 66 among the placebo group) between the study groups.

Table 4-12: Baseline Scores of the SF-36 Domains by Study Group* [189]

HEALTH RELATED QUALITY OF LIFE DOMAINS [A]	TREATMENT N = 21	PLACEBO N =20	P* VALUE
Physical Functioning	65 (45, 85)	65 (36.3, 89.7)	0.9
Role-Physical	0 (0, 50)	37.5 (0, 68.8)	0.3
Bodily Pain	31.0 (16, 41)	32 (22, 48.5)	0.5
General Health	42 (27.5, 67)	57.3 (40.5, 80.8)	0.1
Vitality	20 (10, 27.5)	32.5 (20, 57.5)	0.06
Social Functioning	37.5 (25, 62.5)	56.3 (28.1, 96.9)	0.2
Role-Emotional	33.3 (0, 100)	66.7 (33.3, 100)	0.2
Mental Health	56 (32, 68)	66 (56, 75)	0.07

* Data were presented as median (25^{th} percentile, 75^{th} percentile). P value: Mann-Whitney U test for continuous variables

A SF-36 includes eight different domains. The score of each domain ranges between 0 and 100. 0 = worse quality of life while 100 =excellent quality of life

Table 4-13 presents the norm-based scores of both the eight domains and the two components summary scales (PCS and MCS) of the SF-36 by study group. As it was reported earlier among the total study population, all the scores in the two groups were below the average (<50). Importantly, there was a significant difference in the mental component summary scale score between the two groups (median= 35.7 among the treatment group and 44.5 among the placebo group, p=0.03). On the other hand no significant difference was reported in the score of the physical component summary scale (median= 37.7 among the treatment group and 38.6 among the placebo group, p=0.9). Therefore, the reader should expect either a significant difference or a marginal significant difference between the two groups in relation to the scores of the domains that constitute the mental component summary scale. Both the differences between the two groups in the scores of vitality domain (median= 32.5 among the treatment group and 38.4 among the placebo group) and mental health domain (median= 39.1 among the treatment group and 44.8 among the placebo group) were marginal significant ($0.1 > p \geq 0.05$).

Table 4-13: Norm-Based Scores [A] of the 8 Domains, PCS and MCS/ SF-36 by Study Group*

HEALTH RELATED QUALITY OF LIFE DOMAINS	TREATMENT N = 21	PLACEBO N =20	P* VALUE
Physical Functioning	42.5 (34.1, 50.9)	42.5 (30.4, 52.8)	0.9
Role-Physical	28 (28, 42.1)	38.6 (28, 47.4)	0.3
Bodily Pain	33.2 (26.8, 37.5)	33.6 (29.3, 40.7)	0.5
General Health	36.8 (30.1, 48.5)	44 (36.1, 55)	0.1
Vitality	32.5 (27.8, 36)	38.4 (32.5, 50.2)	0.06
Social Functioning	30 (24.6, 40.9)	38.1 (25.9, 55.8)	0.2
Role-Emotional	34.3 (23.7, 55.3)	44.8 (34.3, 55.3)	0.2
Mental Health	39.1 (25.5, 45.9)	44.8 (39.1, 49.9)	0.08
PCS [B]	37.7 (32.6, 44.9)	38.6 (31.9, 48.3)	0.9
MCS [B]	35.7 (25.3, 43.7)	44.5 (37.2, 51.9)	0.03

* Data were presented as median (25th percentile, 75th percentile). P value: Mann-Whitney U test for continuous variables

[A] Norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] PCS: Physical Component Summary, MCS: Mental component summary

4.2.2.6 Sexual Function Characteristics by Study Group

Table 4-14 presents the main sexual function characteristics at baseline for the two groups in the study. Both groups reported having sexual intercourse during the previous month of the baseline assessment in a comparable manner (76.2% (16/21) among the treatment group and 68.4% (13/19) among the placebo group, p=0.6). The difference in the distribution of experiencing painful sexual intercourse was not significant among those who were sexually active in the two groups, p=0.3.

About 37.5% (6/16) of those who were sexually active in the treatment group and 38.5% (5/13) of those in the placebo group stated that they experienced painful intercourse always. Interestingly, the placebo group showed more sexual desire compared to the treatment group (medians= 3.9 cm and 1.7 cm respectively) and this difference reach a marginal significant level, p=0.08. On the other hand, the two groups reported similar level of sexual arousal (median=2.4 cm among the treatment group and 3 cm among the placebo group, p=0.5).

Table 4-14: Baseline Sexual Function Characteristics by Treatment Group

SEXUAL FUNCTION VARIABLES	TREATMENT N = 21	PLACEBO N =19 *	P* VALUE
Had Sexual Intercourse [A] **%**			0.6
Yes	76.2	68.4	
No	23.8	31.6	
Experience Painful Intercourse [A] **%**			0.3
Not at all	6.3	0	
Sometimes, less than 25% of the time	31.3	7.7	
Sometimes, about 50% of the time	12.5	15.4	
Usually, about 75% of the time	12.5	38.5	
Always	37.5	38.5	
Sexual Desire (0-10cm) [A, B] 189			0.08
Median (25th percentile, 75th percentile)	1.7 (0.5, 4.5)	3.9 (2.2, 5.5)	
Sexual Arousal (0-10cm) [A, B] 189			0.5
Median (25th percentile, 75th percentile)	2.4 (0.7, 4.9)	3 (1.2, 5.8)	

* One was missing at baseline. P value: Mann-Whitney U test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

[A] All sexual assessments were assessed for the previous month to the baseline visit

[B] Both sexual desire and sexual arousal were based on visual analog scale (0-10cm), 0 = none while 10 = high

4.2.3 Oral PPS Compliance During the Study Period

Table 4-15 shows oral PPS compliance during the study period for all the study subjects. Compliance was defined as the percentage of the oral PPS administered dose per each study week as described previously in the method section. About 50% of the study population administered 96.4% or less during the entire period of the study. The medians of compliance during the first, second and third six weeks period were comparable (median= 96.4 during first six weeks, 97.6 during second six weeks, 97.6 during third six weeks).

Table 4-15: Oral PPS Compliance of the Total Study Population (n=41) by Study Period*

DESCRIPTION	PERCENTAGE
Total Compliance [A]	96.4 (81.7, 99.2)
Compliance During Week 1 to Week 6 [B]	96.4 (90.5, 98.8)
Compliance During Week 7 to Week 12[C]	97.6 (88.7, 100)
Compliance During Week 13 to Week 18 [D]	97.6 (81, 100)

* Data were presented as median (25th percentile, 75th percentile)

[A] The average of weekly compliance for 18 weeks; compliance was calculated for each week of the trial by dividing the total number of capsules that were administered during that week by 28 capsules (the total number of capsules that the participants should administer during each week).

[B] The average of weekly compliance for the first six weeks (week 1 to week 6)

[C] The average of weekly compliance for the second six weeks (week 7 to week 12)

[D] The average of weekly compliance for the third six weeks (week 13 to week 18)

Table 4-16 summarizes oral PPS compliance by study group during the entire period of the study as well as during the first, second and the third six weeks of the study. Both groups administered more than 95% of the required oral PPS therapy during the 18 weeks period. Importantly, no significant differences were reported among the two groups in terms of total compliance during the entire study period (median= 96 among the treatment group and 97 among the placebo group, p=0.6), compliance during week 1 to week 6 (median= 95.2 among the

treatment group and 97 among the placebo group, p=0.6), compliance during week 7 to week 12 (median= 96.4 among the treatment group and 98.8 among the placebo group, p=0.1), and compliance during week 13 to week 18 (median= 96.4 among the treatment group and 98.2 among the placebo group, p=0.5).

Table 4-16: Oral PPS Compliance During Study Period by Study Group*

DESCRIPTION	TREATMENT N = 21	PLACEBO N =20	P* VALUE
Total Compliance [A]	96 (80.4, 99.2)	97 (92.1, 99.1)	0.6
Compliance During Week 1 to Week 6 [B]	95.2 (86.3, 100)	97 (90.8, 98.8)	0.6
Compliance During Week 7 to Week 12[C]	96.4 (78, 100)	98.8 (95.2, 100)	0.1
Compliance During Week 13 to Week 18 [D]	96.4 (72, 100)	98.2(87.4, 100)	0.5

* Data were presented as median (25th percentile, 75th percentile). P value: Mann-Whitney U test for continuous variables.

[A] The average of weekly compliance for 18 weeks; compliance was calculated for each week of the trial by dividing the total number of capsules that were administered during that week by 28 capsules (the total number of capsules that the participants should administer during each week).

[B] The average of weekly compliance for the first six weeks (week 1 to week 6)

[C] The average of weekly compliance for the second six weeks (week 7 to week 12)

[D] The average of weekly compliance for the third six weeks (week 13 to week 18)

4.3 ASSOCIATION RESULTS

4.3.1 Factors that Were Found to be Associated With the Severity of IC Symptoms (Univariate Analysis)

4.3.1.1 Socio-Demographic Factors

Table 4-17 presents the univariate associations between ICSI score (measures the severity of IC symptoms) and certain demographic factors at baseline. Interestingly, there were no significant differences among the four age categories of the study population in terms of ICSI scores. The median, the 25th percentile and the 75th percentile were comparable and indicated no significant association between age and the severity of IC symptoms, p=0.7. Although, Caucasian subjects reported higher score of ICSI (score ≥ 14 equates severe level of IC symptoms) compared to not Caucasian subjects (median=15, median=11, respectively), the difference was not significant, p=0.1. Interestingly enough, martial status was found to be univariately, significantly associated with ICSI score; married subjects reported a lower ICSI score (median=11) compared to currently not married subjects (median=16), p=0.02. On the other hand, both educational level and employment status were not found to be associated with ICSI score. Subjects who had either an elementary or secondary educational level reported comparable ICSI score (median=13) to those who had post-secondary level of education (median=14), p=0.9. Moreover, the ICSI score of those who were currently employed (median=13.5) was not significantly different from those who were not employed (median=14), p=0.8.

Table 4-17: Univariate Associations Between the Severity of IC Symptoms (ICSI Scores) and Certain Demographic Factors at Baseline (n=41)

DEMOGRAPHIC FACTORS	N	ICSI SCORES (RANGE: 0-20)*	P* VALUE
Age Categories	**41**		0.7
20-29	11	14 (10, 16)	
30-39	12	14 (8.5, 16.8)	
40-49	10	12 (9.5, 15.3)	
50+	8	14.5 (11.5, 17.8)	
Ethnicity	**41**		0.1
Caucasian	29	15 (10.5, 16.5)	
Not Caucasian [A]	12	11 (8.5, 14.8)	
Marital Status	**41**		0.02
Married	23	11 (8, 15)	
Currently not married [B]	18	16 (12.8, 17)	
Educational Levels	**41**		0.9
Elementary & Secondary	13	13 (10.5, 17)	
Post-Secondary	28	14 (10, 16)	
Employment Status	**41**		0.8
Employed	32	13.5 (10, 16)	
Not Employed	9	14 (10.5, 16.5)	

* Data were presented as median (25^{th} percentile, 75^{th} percentile). P value: Mann-Whitney U test or Kruskal-Wallis test

[A] Not Caucasian = Black, Hispanic, Asian and other

[B] Currently not married = widowed, divorced, never married and other

4.3.1.2 Reproductive and Lifestyle Factors

Table 4-18 shows the univariate associations between the ICSI score and certain reproductive and lifestyle factors. With the exception of menopausal status, all the other assessed factors were not found to be associated with the ICSI score. Subjects who were ever pregnant had a slightly lower ICSI score (median=13) than those who were not' (median=15), p=0.7. Moreover, subjects who experienced from 1 to 2 pregnancies reported a higher, but not significant, ICSI score (median=14) compared to those who had 3 or more pregnancies (median=12), p=0.6. Interestingly, IC cases who were not currently menopausal reported significant lower ICSI score (median=11.5) compared to the menopausal cases (median=16), p=0.02.

Both the use of OC and HRT were not found to be associated with ICSI score. Subjects who had ever used OC or HRT reported a comparable score (median=13.5, 15, respectively) to those who had never used OC or HRT (median=14, 13, respectively), p=0.9, 0.3, respectively. In addition, the median ICSI score for those who had ever smoked (median=14) was not significantly different from those who had never smoked (median=13), p=0.8.

Table 4-18: Univariate Associations Between the Severity of IC Symptoms (ICSI Scores) and Certain Reproductive History and Lifestyle Factors at Baseline (n=41)

REPRODUCTIVE & LIFESTYLE FACTORS	N	ICSI SCORES (RANGE: 0-20)*	P* VALUE
Ever Pregnant	**41**		0.7
Yes	31	13 (10, 16)	
No	10	15 (10, 16.3)	
Number of Pregnancies	**31**		0.6
1-2	17	14 (10, 17)	
3+	14	12 (8.8, 16)	
Menopausal Status	**41**		0.02
Menopause	15	16 (13, 17)	
Not Menopause	26	11.5 (9.5, 16)	
Ever Used OC	**41**		0.9
Yes	36	13.5 (10, 16.7)	
No	5	14 (10.5, 16)	
Ever Used HRT [A]	**38**		0.3
Yes	11	15 (11, 18)	
No	27	13 (10, 16)	
Ever Smoked	**41**		0.8
Yes	24	14 (10, 16)	
No	17	13 (10.5, 16.5)	

* Data were presented as median (25th percentile, 75th percentile). P value: Mann-Whitney U test

[A] Three were missing at baseline

4.3.1.3 Clinical and Sexual History Factors

Table 4-19 shows the univariate associations between ICSI score and certain clinical and sexual history factors. We were not able to determine if the presence of glomerulations was associated with the severity of IC symptoms score, as all our study population had glomerulations. Although, we expected to find significant associations between either the severity of glomerulations or the presence of Hunner's ulcer and ICSI score, none of these were significant. The median ICSI score was 15.5 among those who had mild glomerulations; 15.5 among those who had moderate glomerulations and 13 among those who had severe glomerulations, p=0.4. Furthermore, those who had Hunner's ulcer reported a comparable ICSI score (median=14) to those who had not' (median=14), p=0.8. Interestingly, there were a significant association between ICSI score and having sexual intercourse during the month before the baseline interview. IC cases who had sexual intercourse during the month before the baseline interview reported significantly lower ICSI scores (median=13) than those who had not' (median=17), p=0.03.

Table 4-19: Univariate Associations Between the Severity of IC Symptoms (ICSI Scores) and Certain Clinical and Sexual History Factors at Baseline (n=41)

CLINICAL AND SEXUAL HISTORY FACTORS	N	ICSI SCORES (RANGE: 0-20)*	P* VALUE
Severity of Glomerulations [A]	**41**		0.4
Mild	4	15.5 (9, 18.3)	
Moderate	6	15.5 (12.3, 17.3)	
Severe	31	13 (10, 16)	
Presence of Hunner's Ulcer	**41**		0.8
Yes	6	14 (8.3, 16.5)	
No	35	14 (10, 16)	
Had Sexual Intercourse [B]	**40**		0.03
Yes	29	13 (10, 15.5)	
No	11	17 (11, 18)	

* Data were presented as median (25th percentile, 75th percentile). P value: Mann-Whitney U test or Kruskal-Wallis test

[A] Severity of glomerulations was based on the following clinical definitions developed by the PI:
Glomerulations: Being a red, ulcerative bladder lesion that looks like a stain "glomerulations that is a collection of capillaries in one area. In the bladder these lesions are not a collection of capillaries but they are areas of local inflammation most likely caused by a collection of mast cells suddenly degranulating and causing an intense local inflammatory reaction, I.E. ulceration and bleeding
Mild glomerulations: Few submucosal glomerulations i.e. 0 -2-5 lesions per cystoscopic view, associated with submucosal vascular injection. Vascular injection meaning that the mucosa turns red but there are none to only a few glomerulations
Moderate glomerulations: On hydrodistension, the bladder membrane turns red with vascular injection and there are greater than 10 but less than 15 glomerulations per cystoscopic view
Severe glomerulations: On hydrodistension, the bladder membrane turns red with vascular injection and there are submucosal glomerulations too numerous to count in nearly all of the bladder cystoscopic views. This can be with or without "Hunner's Ulcers", which are patches of bladder membrane where glomerulations blend into a large greater than 1.0cm, patch of bladder tissue

[B] One was missing at baseline. Subjects were asked if they had sexual intercourse during the month previous to the baseline assessment

4.3.1.4 Co-morbidity, BMI and Sexual Function Domains

Table 4-20 presents both the spearman correlation coefficients and the p values for the bivariate correlations between ICSI scores and each of the number of co-morbid conditions, BMI, sexual desire and sexual arousal. A weak non-significant positive correlation was found between the number of co-morbid conditions and ICSI score (ρ=0.2, p=0.3). Moreover, weak non-significant correlations were found between ICSI score and each of the BMI (ρ= -0.1, p=0.6), sexual desire score (ρ= -0.3, p=0.09) and sexual arousal score (ρ= -0.2, p=0.1).

Table 4-20: Correlations Between the Severity of IC Symptoms (ICSI* Score: 0-20), Co-morbidity, BMI and Sexual Function Domains at Baseline (n=41)

FACTORS	SPEARMAN CORRELATION COEFFICIENTS	P VALUE
Number of Co-morbid Conditions [A]	0.2	0.3
BMI [B]	-0.1	0.6
Sexual Desire [C]	-0.3	0.09
Sexual Arousal [C]	-0.2	0.1

* ICSI: interstitial cystitis symptom index, 0 indicates no symptoms, 20 indicates severe symptoms

[A] Four subjects had no co-morbid conditions. Co-morbid conditions were conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc.

[B] BMI: body mass index. BMI was based on self-reported weight and height at week18

[C] One was missing at baseline. Sexual desire and sexual arousal were based on visual analog scale (0-10 cm), 0= none while 10 = high. Subjects were asked to evaluate their sexual desire and sexual arousal during the month previous to the baseline assessment

4.3.2 Factors that Were Found to be Associated With the Severity of IC Symptoms (Multivariate Regression)

Because of sample size limitation we were not able to include more than 4 predictors in the multivariate model. When we included sexual activity to the model, standard errors changed significantly and at the same time sexual activity became no longer associated with symptom severity. Therefore, the final model only tested marital status and menopausal status adjusting for age and co-morbidity using multivariate median regression.

Table 4-21 shows the regression coefficients, 95% CI and p values for each of the previously identified factors that were found to be associated with ICSI score (in the univariate assessments) after adjusting for age and co-morbidity. According to the univariate assessments, both being currently not married and menopausal were found to be significantly associated with greater severity of IC symptoms. Before adjusting for the well known covariates (age and number of co-morbid conditions), [21, 203] both factors (marital status: being married and menopausal status: being menopausal) in the primary model were found to have an independent significant association with the severity of IC symptoms (β= -4, p=0.03, β= 4, p=0.04, respectively). Interestingly, after adjusting for age and co-morbidity, only marital status remained highly significant in the model. The median ICSI score for married subjects was found to be ~ 4 points less than the median score for currently not married subjects, p=0.03. On the other, the association between menopausal status and the severity of IC symptoms was no longer significant after including both age and number of co-morbid conditions in the final model, p=0.2. This indicates that both age and co-morbidity may be considered as important confounders for this association.

Table 4-21: Results of Multivariate Median Regression for ICSI (0-20) Score and the Factors that Were Found to be Associated With ICSI Score in the Univariate Assessment after Adjusting for Both Age and Co-morbidity (n=41)

INDEPENDENT VARIABLE[A]	DEPENDENT VARIABLE ICSI SCORES[*]			
	β	SE	P Value	95%CI
Age	0.04	0.09	0.7	-0.15 , 0.23
Number of Co-morbid Conditions [A]	0.15	0.27	0.6	-0.39 , 0.70
Marital status [B]	-3.85	1.75	0.03	-7.41 , -0.29
Menopausal Status [B]	3.38	2.51	0.2	-1.72 , 8.47

[*] ICSI: interstitial cystitis symptom index, 0 = no symptoms; 20 = severe symptoms

[A] Four subjects had no co-morbid conditions. Co-morbid conditions are conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc

[B] Reference category: currently not married; currently not menopausal

4.3.3 Factors that Were Found to be Associated With HRQL in IC Subjects (Univariate Analysis)

Because we used the norm-based score format for all the SF-36 domains in our analysis, it was very easy to define the impairment (below average) in any of the SF-36' domains. All scores above or below the 50 are above or below the average in the 1998 general US population.[184] Therefore, any score below 50 indicates an impairment in HRQL.

4.3.3.1 Socio-Demographic Factors

Table 4-22 presents the results of the univariate associations between each of the eight domains of the SF-36 and certain demographic factors at baseline. Interestingly, only employment status was found to be significantly associated with the physical functioning domain. Subjects who

were currently employed reported a better physical functioning score (median=46) than those who were not' (median=24), p=0.03. Moreover, marital status showed a marginal significant association with the physical functioning domain. Married subjects reported a better physical functioning score (median=49) compared to currently not married subjects (median=37), p=0.06.

With regard to role-physical, bodily pain, general health and social function domains, only marital status was found to be significantly associated with each one of these domains. Interestingly, married IC cases consistently reported a greater (better) score of role-physical, bodily pain, general health and social function domains (median scores = 42, 37, 46, 37 and 41, respectively) compared to currently not married cases (median scores = 28, 29, 36, 32, and 27, respectively), p=0.001, 0.003, 0.01, 0.03 and 0.01, respectively. In terms of role-emotional domain, none of the tested factors was found to be associated. However, both marital status and educational level showed marginally significant associations. Similar to what we reported above, married IC cases showed greater role-emotional score (median= 45) than currently not married cases (median= 34), p=0.08. Moreover, cases who had an elementary and/or secondary level of education reported greater role-emotion score (median= 55) compared to those who had post-secondary level of education (median= 34), p=0.06.

Finally, none of the tested variables was found to be significantly associated with mental health domain. The associations between mental health score and age and/or marital status were found to be marginally significant. IC cases who were 50 years old or more reported the highest mental health score among all the 4 age categories (20-29: median=39; 30-39: median= 36; 40-49: median= 45; 50+: median= 49), p=0.06. Furthermore, married IC cases showed a better mental health score (median= 46) than currently not married IC cases (median= 39), p=0.08.

In summary, it would appear that marital status is a very important factor that found to be associated either significantly or marginally significantly with each of the SF-36 domains in the univariate assessments at baseline.

Table 4-22: Univariate Associations Between Each of the Eight Domains of the SF-36 and Certain Demographic Factors at Baseline (n=41)

DEMOGRAPHIC FACTORS	N	SF-36 DOMAINS [A]							
		PF	RP	BP	GH	VT	SF	RE	MH
Age Categories	**41**								
20-29	11	47 (32, 53)	35 (28, 42)	33.6 (25, 37)	39 (34, 46)	37 (32, 51)	35 (25, 46)	34 (34, 45)	39 (30, 44)
30-39	12	43 (25, 52)	32 (28, 49)	29 (24, 41)	38 (29, 55)	32 (28, 42)	33 (21, 41)	29 (24, 53)	36 (23, 46)
40-49	10	43 (34, 55)	35 (28, 42)	36 (29, 40)	41 (31, 52)	36 (29, 48)	35 (25, 57)	34 (32, 55)	45 (31, 49)
50+	8	40 (24, 49)	28 (28, 53)	38 (29, 41)	46 (38, 51)	35 (26, 39)	33 (25, 54)	55 (29, 55)	49 (46, 52)
P* values		0.8	0.9	0.5	0.6	0.6	0.8	0.4	0.06
Ethnicity	**41**								
Caucasian	29	42 (34, 51)	28 (28, 42)	34 (29, 37)	39 (31, 51)	32 (29, 42)	35 (25, 44)	34 (24, 55)	44 (31, 49)
Not Caucasian[B]	12	47 (20, 55)	39 (28, 49)	33 (29, 46)	43 (35, 53)	37 (27, 51)	30 (26, 50)	40 (26, 55)	36 (28, 46)
P* values		0.9	0.4	0.5	0.4	0.4	0.9	0.9	0.4
Marital Status	**41**								
Married	23	49 (34, 55)	42 (28, 49)	37 (29, 46)	46 (36, 56)	37 (32, 51)	41 (25, 57)	45 (34, 55)	46 (32, 53)
Currently not married[B]	18	37 (31, 47)	28 (28, 30)	29 (24, 35)	36 (29, 44)	32 (27, 37)	27 (23, 35)	34 (24, 47)	39 (27, 46)
P* values		0.06	0.001	0.003	0.01	0.03	0.01	0.08	0.08
Education Levels	**41**								
Elementary & Secondary	13	42 (24, 52)	35 (28, 46)	37 (29, 44)	51 (36, 56)	37 (27, 49)	30 (25, 57)	55 (34, 55)	48 (29, 52)
Post-Secondary	28	42 (32, 52)	31 (28, 42)	33 (29, 37)	38 (32, 48)	34 (32, 42)	35 (25, 41)	34 (24, 45)	39 (30, 46)
P* values		0.7	0.8	0.3	0.1	0.7	0.7	0.06	0.1
Employment Status	**41**								
Employed	32	46 (35, 53)	31 (28, 42)	34 (29, 37)	40 (33, 51)	34 (28, 42)	33 (25, 45)	34 (24, 55)	40 (31, 46)
Not Employed	9	24 (20, 48)	42 (28, 49)	29 (27, 42)	42 (30, 56)	40 (30, 54)	41 (22, 57)	45 (29, 55)	46 (27, 53)
P* values		0.03	0.5	0.9	0.8	0.2	0.6	0.5	0.6

* P value: Mann-Whitney U test or Kruskal-Wallis test

[A] Norm-based scores were presented as median (25^{th} percentile, 75^{th} percentile), all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation. PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social function, RE: role-emotional, MH: mental health

[B] Not Caucasian = Black, Hispanic, Asian and others. Currently not married = widowed, divorced, never married and others

4.3.3.2 Reproductive and Lifestyle Factors

Table 4-23 shows the results of the univariate associations between each of the eight domains of the SF-36 and certain reproductive and lifestyle factors at baseline. With the exception of being sexually active during the previous month of the baseline interview, none of the tested reproductive and lifestyle factors was found to be significantly associated with physical functioning domain of the SF-36. IC cases who indicated that they had sexual intercourse during the month before the baseline interview reported a significantly better physical functioning domain score (median= 47) compared to those who had not any sexual intercourse during the same period (median=30), p=0.02.

None of the tested variables was found to be significantly associated with the role-physical domain score, however, both ever use of OC and HRT showed marginal significant associations with role-physical domain score. IC subjects who never used either OC or HRT reported a better role-physical score (median= 49; 42, respectively) compared to those who ever used OC or HRT (median= 28; 28, respectively), p=0.05, 0.06, respectively.

With regard to bodily pain, general health, social functioning and role-emotion domains, none of the tested factors was found to be significantly associated with any of them. Only, "having sexual intercourse during the month before the baseline interview" was found to be significantly associated with vitality domain score. Subjects who had sexual intercourse during the month previous to baseline interview reported a better vitality domain score (median= 35) than those who had not' (median= 28), p=0.01.

Interestingly, being ever pregnant was found to be significantly associated with mental health domain score. IC cases who indicated that they were ever pregnant showed better mental health score (median= 44) than those who were not (median= 31), p=0.04.

4.3.3.3 Co-morbidity, BMI and Sexual Function Domains

Table 4-24 presents both the spearman correlation coefficients and the p values for the bivariate correlations between each of the eight domains of SF-36, co-morbidity, BMI and sexual function domains at baseline. Weak significant negative correlations were found between the number of co-morbid conditions and each of the physical functioning (ρ= -0.4, p=0.02), bodily pain (ρ= -0.4, p=0.02) and role-emotional (ρ= -0.3, p=0.04) domains. On the other hand, BMI was found to be negatively correlated with each of the general health domain (ρ= -0.3, p=0.05) and vitality domain (ρ= -0.3, p=0.02). None of the tested variables was found to be significantly correlated with any of the role-physical, social functioning and/or mental health domains.

Table 4-23: Univariate Associations Between Each of the Eight Domains of SF-36 and Certain Reproductive History and Lifestyle Factors at Baseline (n=41)

REPRODUCTIVE & LIFESTYLE FACTORS	N	SF-36 DOMAINS [A]							
		PF	RP	BP	GH	VT	SF	RE	MH
Ever Pregnant	**41**								
Yes	31	43 (34, 52)	35 (28, 49)	34 (29, 42)	44 (32, 53)	35 (32, 44)	41 (25, 52)	45 (34, 55)	44 (32, 50)
No	10	34 (28, 51)	28 (28, 37)	31 (20, 37)	36 (31, 44)	32 (27, 42)	27 (18, 37)	29 (24, 47)	31 (25, 41)
P* values		0.4	0.2	0.08	0.1	0.4	0.1	0.1	0.04
Number of Pregnancies	**31**								
1-2	17	43 (29, 50)	35 (28, 42)	29 (29, 42)	44 (32, 54)	35 (32, 44)	30 (26, 44)	45 (34, 55)	41 (36, 47)
3+	14	46 (34, 55)	35 (28, 56)	37 (29, 46)	44 (34, 54)	36 (27, 47)	41 (29, 57)	40 (24, 55)	46 (31, 53)
P* values		0.4	0.4	0.3	0.7	0.8	0.2	0.8	0.2
Menopausal Status	**41**								
Menopause	15	38 (24, 49)	28 (28, 42)	29 (29, 37)	42 (29, 51)	35 (28, 40)	30 (25, 46)	34 (24, 55)	48 (25, 53)
Not Menopause	26	47 (34, 53)	35 (28, 44)	34 (28, 39)	42 (32, 51)	35 (33, 45)	35 (25, 48)	40 (32, 55)	39 (30, 46)
P* values		0.2	0.1	0.9	0.9	0.4	0.9	0.9	0.1
Ever Used OC	**41**								
Yes	36	42 (32, 52)	28 (28, 42)	33 (29, 37)	43 (33, 51)	34 (28, 42)	30 (25, 41)	34 (24, 55)	40 (31, 48)
No	5	42 (20, 51)	49 (35, 56)	37 (29, 49)	36 (29, 47)	36 (31, 55)	57 (30, 57)	55 (34, 55)	46 (27, 55)
P* values		0.5	0.05	0.2	0.3	0.3	0.1	0.2	0.6
Ever Used HRT [B]	**38**								
Yes	11	38 (24, 51)	28 (28, 35)	37 (29, 37)	46 (37, 56)	35 (25, 42)	30 (25, 41)	34 (24, 55)	48 (25, 50)
No	27	47 (34, 53)	42 (28, 49)	34 (29, 42)	39 (32, 51)	35 (32, 44)	41 (25, 52)	45 (34, 55)	39 (30, 46)
P* values		0.3	0.06	0.8	0.3	0.6	0.5	0.6	0.1
Ever Smoked	**41**								
Yes	24	42 (32, 48)	31 (28, 42)	31 (25, 37)	38 (32, 47)	35 (31, 44)	33 (21, 54)	34 (24, 45)	40 (31, 46)
No	17	49 (33, 54)	35 (28, 49)	37 (29, 42)	46 (35, 56)	35 (28, 48)	35 (27, 44)	45 (29, 55)	46 (28, 52)
P* values		0.2	0.6	0.1	0.08	0.9	0.5	0.3	0.5

Table 4-23 Cont'd

REPRODUCTIVE & LIFESTYLE FACTORS	N	SF-36 DOMAINS[A]							
		PF	RP	BP	GH	VT	SF	RE	MH
Had Sexual Intercourse[C]	**40**								
Yes	29	47 (34, 53)	35 (28, 49)	34 (29, 40)	44 (32, 53)	35 (32, 46)	35 (25, 46)	34 (29, 55)	39 (30, 46)
No	11	30 (19, 42)	28 (28,35)	29 (20, 37)	37 (32, 46)	28 (25, 36)	30 (19, 41)	34 (24, 55)	46 (25, 48)
P* values		0.02	0.09	0.4	0.3	0.01	0.3	0.8	0.8

* P value: Mann-Whitney U test or Kruskal-Wallis test

[A] Norm-based scores were presented as median (25th percentile, 75th percentile), all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation. PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

[B] Three were missing at baseline

[C] One was missing at baseline. Subjects were asked if they had sexual intercourse during the month previous to the baseline assessment

Table 4-24: Correlations Between Each of the Eight Domains of SF-36 and Co-morbidity, BMI and Sexual Function Domains at Baseline (n=41)

FACTORS	SPEARMAN CORRELATION COEFFICIENTS SF-36 DOMAINS [A]															
	PF		RP		BP		GH		VT		SF		RE		MH	
	ρ*	p	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
Number of Co-morbid Conditions [B]	-0.4	0.02	-.3	0.1	-0.4	0.02	-0.1	0.3	-0.2	0.1	-0.3	0.1	-0.3	0.04	-0.2	0.3
BMI [C]	0.06	0.7	0.1	0.5	0.0	0.9	-0.3	0.05	-0.3	0.02	0.06	0.7	0.2	0.3	0.03	0.8
Sexual Desire [D]	0.02	0.9	-0.1	0.4	0.06	0.7	0.06	0.7	0.2	0.2	0.2	0.2	-0.04	0.8	-0.05	0.8
Sexual Arousal [D]	0.1	0.5	-0.2	0.2	-0.02	0.9	-0.02	0.9	0.2	0.3	0.09	0.6	-0.1	0.5	-0.06	0.7

* Spearman correlation coefficient

A Norm-based scores, all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation. PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

B Four subjects had no co-morbid conditions. Co-morbid conditions are conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc.

C BMI: body mass index. BMI was based on self-reported weight and height at week18

D One was missing at baseline. Both sexual desire and sexual arousal were based on visual analog scale (0-10 cm), = none while 10 = high. Subjects were asked to evaluate their sexual desire and sexual arousal during the month previous to the baseline assessment

4.3.4 Factors that Were Found to be Associated With the Impairment in HRQL (Multivariate Regression)

In order to assess if the above defined associations between each of the eight domains of SF-36 and the determined factors from the univariate assessments were confounded by age or co-morbidity, and can independently explain the variation in SF-36 domain scores, multivariate median regressions were performed.

Table 4-25 shows the regression coefficients and p values for each of the previously identified factors that were found to be significantly associated with each domain of SF-36 (in the univariate assessments) after adjusting for age and co-morbidity. In the univariate assessments, both being sexually active and currently employed were found to be significantly associated with a better physical functioning score. In the primary multivariate model which included only those two factors (being employed and being sexually active), only employment status was found to be significantly associated with physical functioning score after adjusting for being sexually active (β= 18.9, p=0.004). Interestingly, when we included both age and number of co-morbid conditions to the primary model, the same results were obtained. In particular, only employment status remained a highly significant factor after adjusting for age, co-morbidity and being sexually active. The median physical functioning score for an employed subject was found to be ~ 21 points more than the median score for a currently unemployed subject, p=0.01.

For the role-physical domain, only marital status was found to be significantly associated in the univariate analysis. Moreover, never used oral contraceptive was found to be marginally significantly associated with role-physical in the univariate analysis. Interestingly in the primary

model which included both marital status and never used OC only marital status remained significant in the model. After adjusting for age and co-morbidity both marital status (being married) and never used OC were found to be independently associated with better role-physical domain score.

With regard to bodily pain, both increase in number of co-morbid conditions and being currently not married were found to be significantly associated with lower bodily pain score in the univariate assessments.

After adjusting for age in the final model, only number of co-morbid conditions was significantly associated with bodily pain score. The median bodily pain score was found to be reduced by approximately 1.47 point for a subject whose number of co-morbid conditions is one higher than another subject's, p=0.01. In addition, marital status was not significantly associated with bodily pain score after adjusting for age and co-morbidity.

General health domain was found to be significantly affected by both marital status and BMI in the univariate assessments. Both factors (marital status and BMI) were found to be independently associated with the general health domain in the primary multivariate model (β= 12.7, p=0.02; β= -1.06, p=0.008, respectively) Interestingly, after including both age and co-morbidity to the final model, only BMI was a highly significant factor that can independently explain the variation in the general health domain. The median general health score was found to be reduced by approximately 1.05 point for a subject whose BMI is 1 Kg/m^2 higher than another subject's, p=0.007. Moreover, marital status was no longer an independent factor that may explain the variation in the general health score based on the final model.

On the other hand, none of the variables which were found to be significantly associated with vitality score in the univariate assessments (marital status, being sexually active and BMI)

was significant either in the primary model or in the final model, after adjusting for age and co-morbidity.

In terms of social functioning, only marital status was found to be significantly associated with it in the univariate assessments. Interestingly, after adjusting for both age and co-morbidity, marital status remained an important factor that can independently explain the variation in social functioning domain. The median social functioning score for a married subject was found to be ~13 points more than the score for a currently not married subject, p=0.01.

With regard to role-emotion domain, only number of co-morbid conditions was found to be significantly associated with it univariately. After adjusting for age, co-morbidity remained an independent factor that can explain the variation in the role-emotion domain. Furthermore, the median role-emotion score was found to be reduced by approximately 2.87 point for a subject whose number of co-morbid conditions is one higher than another subject's, p=<0.001.

Finally, mental health score was found to be associated with ever pregnant in the univariate assessments. This association was significant, even, after adjusting for both age and co-morbidity. The median mental health score for a never pregnant subject was found to be ~9 points less than the median score of an ever pregnant subject, p=0.003.

In summary, the results from multivariate median regression showed that marital status can no longer be considered as an independent variable that may explain the variation in any of the bodily pain, general health, vitality, role-emotion and the mental health domains after adjusting for age and co-morbidity, in particular. Marital status was found to be an independent factor that can explain only the variation in social functioning domain of the HRQL in IC cases.

Table 4-25: Results of Multivariate Median Regression for Each Domain of the SF-36 and the Factors that Were Found to be Associated With Each Domain in the Univariate Assessments after Adjusting for Both Age and Co-morbidity (n=41)

INDEPENDENT VARIABLE AND COVARIATES	SF-36 DOMAINS [A]															
	PF		RP		BP		GH		VT		SF		RE		MH	
	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value
Age	0.08	0.8	-0.06	0.13	0.14	0.4	0.29	0.2	0.23	0.4	0.11	0.6	0.53	0.01	0.35	0.002
Number of Co-morbid Conditions [B]	0.19	0.9	-0.94	0.008	-1.47	0.01	-0.29	0.7	-084	0.3	-1.64	0.04	-2.87	<0.001	-0.65	0.03
Employed [C]	21.1	0.01	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Had Sex [C,D]	8.69	0.3	------	------	------	------	------	------	4.47	0.5	------	------	------	------	------	------
Married [C]	------	------	8.49	0.006	7.34	0.06	9.14	0.08	6.9	0.2	13.09	0.01	------	------	------	------
BMI[E]	------	------	------	------	------	------	-1.05	0.007	-0.37	0.3	------	------	------	------	------	------
Never Use OC [C]	------	------	12.7	0.007	------	------	------	------	------	------	------	------	------	------	------	------
Never Pregnant [C]	------	------	------	------	------	------	------	------	------	------	------	------	------	------	-9.52	0.003

[A] Norm-based scores, all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation. PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

[B] Four subjects had no co-morbid conditions. Co-morbid conditions are conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc.

[C] Reference category: Not employed; did not have sex; currently not married; ever use oral contraceptive; ever pregnant

[D] One was missing at baseline (n=40). Subjects were asked if they had sexual intercourse during the month previous to the baseline assessment

[E] BMI: body mass index. BMI was based on self-reported weight and height at week18

4.3.5 Associations Between the Severity of IC Symptoms (ICSI Score) and the Eight Domains of the SF-36

The following sections present our main findings of assessing the second aim of this dissertation. After determining to what extent socio-demographic, lifestyle, reproductive and clinical history factors were associated with both the severity of IC symptoms as well as the quality of life in IC patients, it was crucial to examine the association between the severity of IC symptoms and the HRQL after adjusting for the main covariates that were identified from assessing the first aim of this study.

4.3.5.1 Unadjusted Associations

Table 4-26 shows the Spearman correlation coefficients and the p values for the bivariate correlations between the ICSI score and each of the eight domains of the SF-36. Interestingly, the severity of IC symptoms was found to be negatively correlated with each of the physical functioning (ρ = -0.4, p=0.007), role-physical (ρ = -0.4, p=0.005), bodily pain (ρ = -0.5, p=0.001), and the social functioning domain (ρ = -0.5, p=0.001). Moreover, both bodily pain and social functioning domains showed the greatest impairments as a result of the increase in the severity of IC symptoms score. Another weaker negative correlation was found between the severity of IC symptoms and the general health domain; however, it was marginally significant (ρ = -0.3, p=0.06).

Table 4-26: Unadjusted Correlations Between the ICSI (0-20) Score and the Eight Domains of SF-36 at Baseline (n=41)

SF-36 DOMAINS [A]	SEVERITY OF IC SYMPTOMS ICSI SCORES [B]	
	Spearman Correlation Coefficients ρ	P Value
Physical Functioning	-0.4	0.007
Role-Physical	-0.4	0.005
Bodily Pain	-0.5	0.001
General Health	-0.3	0.06
Vitality	-0.3	0.1
Social Functioning	-0.5	0.001
Role-Emotional	-0.1	0.6
Mental Health	-0.1	0.5

[A] Norm-based scores, all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation.

[B] ICSI: interstitial cystitis symptom index, 0 = no symptoms; 20 = severe symptoms

4.3.5.2 Adjusted Associations

Table 4-27 presents the results of the multivariate regressions between each domain of the SF-36 and the ICSI score after adjusting for the well known covariates in the literature (age and co-morbidity) [21, 203] and the covariates which were identified for each quality of life domain from the univariate analyses (**section 4.3.3)**.

After adjusting for age, number of co-morbid conditions and employment status, ICSI score remained negatively associated with physical functioning score. The median physical functioning score was found to be reduced by approximately 1.54 point for a subject whose ICSI score is 1 point greater than another subject's. Although this magnitude of variation in the median physical functioning score was very small, it was highly significant, p=0.007. On the other hand, after adjusting for age, co-morbidity, marital status and ever use of oral contraceptive, ICSI score was no longer a significant independent factor that may explain the variation in role-physical functioning score.

With regard to the effect of the severity of IC symptoms on bodily pain domain, even after adjusting for age, co-morbidity and marital status, ICSI score remained a significant factor in the model. The median bodily pain score was found to be reduced by approximately 0.83 point for a subject whose ICSI score is 1 point greater than another subject's, p=0.04.

In the unadjusted analysis, ICSI score was found to be negatively correlated with general health score, this correlation was marginally significant **(Table 4-25)**. After adjusting for age, number of co-morbid conditions, marital status and BMI, ICSI score was a significant predictor of general health score. The median general health score was found to be reduced by approximately 1.62 point for a subject whose ICSI score is 1 point greater than another subject's, p=0.001.

On the other hand, similar to what we reported in the unadjusted analysis **(Table 4-25)**, ICSI score was not found to be associated with the variation in either vitality domain or role-emotion domain after adjusting for study covariates. However, the magnitude of variation in vitality score was found to be significantly explained by marital status (ß=8.8, p=0.002) when ICSI score, age, co-morbidity and BMI were included in the model. Moreover, the magnitude of variation in role-emotion was found to be significantly explained by number of co-morbid conditions (ß=-2.68, p<0.001) after adjusting for ICSI score and age. Interestingly, ICSI score was found to be negatively associated with social functioning score in the unadjusted analyses **(Table 4-25)**. After adjusting for age, number of co-morbid conditions, and marital status, this association was no longer significant. The reverse was found with mental health domain; there was no significant association between ICSI score and mental health score in the unadjusted analysis **(Table 4-25).** However, after adjusting for age, co-morbidity, and ever pregnant, ICSI score was a significant predictor of mental health domain. The median mental health score was

found to be reduced by approximately 0.56 point for a subject whose ICSI score is 1 point greater than another subject's, p=0.01.

In summary, the results from multivariate median regression showed that the severity of IC symptoms (represented by ICSI score) is significantly associated with the impairment (reduction) in physical functioning, bodily pain, general health and mental health domains of HRQL in IC patients after adjusting for study covariates as well as age and co-morbidity.

Table 4-27: Results of Multivariate Median Regression for each Domain of the SF-36 and the ICSI (0-20) Score after Adjusting for Certain Covariates at Baseline (n=41)

INDEPENDENT VARIABLE AND COVARIATES	SF-36 DOMAINS [A]															
	PF		RP		BP		GH		VT		SF		RE		MH	
	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value
ICSI [B]	-1.54	0.007	-0.57	0.08	-0.83	0.04	-1.62	0.001	0.18	0.6	-1.27	0.3	-0.48	0.4	-0.56	0.01
Age	0.31	0.08	-0.04	0.7	0.06	0.6	0.30	0.03	0.07	0.5	-0.09	0.8	0.47	0.02	0.48	<0.001
Number of Co-morbid Conditions [C]	-1.33	0.05	-0.80	0.003	-1.33	0.003	-0.21	0.6	-0.86	0.03	-1.67	0.2	-2.68	<0.001	-0.86	0.003
Employed [D]	4.07	0.4	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Married [D]	------	------	9.19	<0.001	6.47	0.04	3.94	0.3	8.8	0.002	7.7	0.3	------	------	------	------
BMI [E]	------	------	------	------	------	------	-0.69	0.004	-0.32	0.09	------	------	------	------	------	------
Never use OC [D]	------	------	12.57	0.001	------	------	------	------	------	------	------	------	------	------	------	------
Never Pregnant [D]	------	------	------	------	------	------	------	------	------	------	------	------	------	------	-4.0	0.05

[A] Norm-based scores, all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation. PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

[B] ICSI: interstitial cystitis symptom index, 0 indicates no symptoms, 20 indicates severe symptoms

[C] Four subjects had no co-morbid conditions. Co-morbid conditions are conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc

[D] Reference category: Not employed; currently not married; ever use oral contraceptive; ever pregnant

[E] BMI: body mass index. BMI was based on self-reported weight and height at week18

4.3.6 Effect of IC Symptoms on PCS and MCS of HRQL

In the previous section **(4.3.5)** we described how the severity of IC symptoms (ICSI score: cumulative score that reflects the severity of pain, urgency, urinary frequency and nocturia together) can affect each domain of the quality of life in IC patients (eight domains of the SF-36 instrument). This section shows which IC symptom, in particular, is significantly associated with the quality of life represented by the two summary component scales: the physical component summary (PCS) and the mental component summary (MCS) scales. Results from simple non-parametric correlations as well as multivariate median regression were presented in the following sections.

4.3.6.1 Bivariate Correlations Between IC Symptoms

Because we expected that the occurrence of each symptom of IC is not an independent event, it was very important to assess the degree and significance level of co-linearity between IC symptoms. **Table 4-28** shows both the correlation coefficients and the p values for bivariate correlations between IC symptoms (pain, urinary frequency, nocturia and urgency). Interestingly, there were significant positive correlations between pain and urgency ($\rho = 0.4$, $p=0.01$) and between urinary frequency and nocturia ($\rho = 0.4$, $p=0.01$). Furthermore, a marginal significant positive correlation was observed between pain and urinary frequency ($\rho = 0.3$, $p=0.07$). This in fact, indicates that we cannot include either both pain and urgency or both urinary frequency and nocturia in the same model if we want to determine which symptom can independently explain the variation in any of quality of life summary component scales (PCS and MCS).

Table 4-28: Bivariate Correlations Between IC Symptoms at Baseline (n=41)

	PAIN SCORE [A]		URINARY FREQUENCY		NOCTURIA [B]	
	ρ*	p	ρ	p	ρ	p
Pain Score [A]	_____	_____	_____	_____	_____	_____
Urinary Frequency	0.3	0.07	_____	_____	_____	_____
Nocturia	0.2	0.2	04	0.004	_____	_____
Urgency Score [B]	0.4	0.01	0.02	0.9	0.1	0.5

* Spearman correlation coefficient

[A] A score of 1 indicates no pain; a score of 9 indicates severe pain. Pain during voididng shows the same correlations as general pain

[B] A score of 1 indicates no urgency; a score of 5 indicates severe urgency

4.3.6.2 Factors that Were Found to be Associated With PCS and/ or MCS Scales

Although, we determined the factors that were associated with the quality of life in IC patients previously in this chapter **(sections: 4.3.3 and 4.3.4)**, it was important to know how these factors will affect the component summary scales of the SF-36 as well. This step was crucial to determine the covariates that we will need to adjust for when assessing how each symptom of IC affects each summary component of quality of life.

4.3.6.2.1 Socio-Demographic Factors

Table 4-29 presents the univariate associations between each of the quality of life summary component scales and certain demographic factors at baseline. It was not a surprise for us to find that marital status was the only demographic factor found to be associated with PCS as we previously, in this chapter, reported that marital status was significantly associated with the component domains of this summary scale (role-physical, bodily pain, general health**), Table 4-22.** Similar to what we observed earlier, married subjects showed a better physical component

scale score (median = 40.6) compared to currently not married subjects (median = 33.7), p=0.03. On the other hand, marital status was not found to be associated with the MCS, although, it was found to be significantly associated with two component domains (vitality and social functioning) of this summary scale, **Table 4-22.**

Table 4-29: Univariate Associations Between Each of the Quality of Life Summary Component Scales and Certain Demographic Factors at Baseline (n=41)

DEMOGRAPHIC FACTORS	N	PCS [A]		MCS [A]	
		Median (25th percentile, 75th percentile)	P* value	Median (25th percentile, 75th percentile)	P* value
Age Categories	**41**		0.9		0.3
20-29	11	37.7 (33.4, 47.5)		38.2 (32.7, 39.8)	
30-39	12	35.4 (28.2, 50.4)		34.9 (24.7, 47.2)	
40-49	10	37.4 (32.9, 44.8)		39.1 (28.2, 57.3)	
50+	8	39.1 (26.7, 41.1)		48.2 (39.8, 51.5)	
Ethnicity	**41**		0.4		0.8
Caucasian	29	36.8 (31.9, 44.7)		39.8 (28.9, 49.5)	
Not Caucasian [B]	12	39.2 (32.5, 51.1)		38.6 (27.8, 51.2)	
Marital Status	**41**		0.03		0.1
Married	23	40.6 (33.5, 51.0)		42.2 (38.2, 51.5)	
Currently not married [C]	18	33.7 (26.5, 38.8)		34.2 (25.9, 42.3)	
Education Levels	**41**		0.8		0.07
Elementary & Secondary	13	37.6 (29.3, 44.9)		49.2 (31.2, 54.6)	
Post-Secondary	28	38.1 (32.3, 47.4)		38.0 (27.9, 41.6)	
Employment Status	**41**		0.2		0.2
Employed	32	39.1 (33.4, 48.3)		38.8 (27.1, 48.4)	
Not employed	9	32.0 (26.6, 41.9)		49.2 (34.5, 54.6)	

* P value: Mann-Whitney U test or Kruskal-Wallis test

[A] PCS: Physical Component Summary, MCS: Mental component summary. Both PCS and MCS are norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] Not Caucasian = Black, Hispanic, Asian and other

[C] Currently not married = widowed, divorced, never married and other

4.3.6.2.2 Reproductive and Lifestyle Factors

Table 4-30 shows the univariate associations between each of the quality of life summary component scales and certain reproductive history and lifestyle factors at baseline. Only being sexually active during the month previous to the baseline interview was found to be significantly associated with a better PCS score. Subjects who had sexual intercourse during the month previous to the baseline interview reported a greater PCS score (median = 48.5) compared to those who had not' (median = 39.6), p=0.006. On the other hand, none of the assessed factors was found to be significantly associated with MCS score.

Table 4-30: Univariate Associations Between Each of the Quality of Life Summary Component Scales and Certain Reproductive History and Lifestyle Factors at Baseline (n=41)

REPRODUCTIVE & LIFESTYLE FACTORS	N	PCS [A]		MCS [A]	
		Median (25th percentile, 75th percentile)	P* value	Median (25th percentile, 75th percentile)	P* value
Ever Pregnant	**41**		0.3		0.06
Yes	31	37.7 (33.2, 47.5)		39.8 (31.7, 50.0)	
No	10	36.1 (25.8, 47.4)		29.9 (24.5, 40.9)	
Number of Pregnancies	**31**		0.5		0.6
1-2	17	37.6 (32.7, 42.4)		39.5 (33.7, 47.3)	
3+	14	40.1 (32.9, 52.4)		48.0 (28.5, 52.0)	
Menopausal Status	**41**		0.1		0.5
Menopause	15	33.6 (26.7, 40.6)		45.3 (30.0, 50.0)	
Not Menopause	26	38.8 (33.4, 48.6)		38.6 (27.1, 49.0)	
Ever Used OC	**41**		0.9		0.1
Yes	36	37.6 (32.3, 47.4)		38.8 (27.9, 49.1)	
No	5	39.6 (29.1, 47.7)		54.6 (31.6, 57.4)	
Ever Used HRT [B]	**38**		0.1		0.6
Yes	11	33.2 (26.6, 41.2)		45.3 (24.2, 50.0)	
No	27	39.9 (33.7, 48.5)		38.9 (27.1, 48.8)	
Ever Smoked	**41**		0.2		0.7
Yes	24	34.1 (32.3, 41.1)		38.8 (27.1, 49.5)	
No	17	40.6 (29.4, 49.9)		39.4 (30.4, 50.6)	

Table 4-30 Cont'd

REPRODUCTIVE & LIFESTYLE FACTORS	N	PCS [A]		MCS [A]	
		Median (25th percentile, 75th percentile)	P* value	Median (25th percentile, 75th percentile)	P* value
Had Sexual Intercourse [C]	**40**		0.006		0.9
Yes	29	48.5 (39.9, 8.7)		49.0 (38.9, 11.3)	
No	11	39.6 (26.7, 9.1)		52.0 (40.0, 14.2)	

* P value: Mann-Whitney U test or Kruskal-Wallis test

[A] PCS: Physical Component Summary, MCS: Mental component summary. Both PCS and MCS are norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] Three were missing at baseline

[C] One was missing at baseline. Subjects were asked if they had sexual intercourse during the month previous to the baseline assessment

4.3.6.2.3 Co-morbidity, BMI and Sexual Function Domains

Table 4-31 describes the bivariate correlations between each of the quality of life summary component scales and certain factors (co-morbidity, BMI and sexual domains) at baseline. Interestingly, none of these factors was found to be significantly correlated with any of the two summary component scales. Moreover, a negative marginally significant correlation was found between the PCS score and the number of co-morbid conditions ($\rho = -0.3$, $p=0.09$).

Table 4-31: Correlations Between Each of the Quality of Life Summary Component Scales and Co-morbidity, BMI and Sexual Function Domains at Baseline (n=41)

FACTORS	SF-36 SUMMARY COMPONENETS			
	PCS [A]		MCS [A]	
	ρ*	p	ρ*	p
Number of Co-morbid Conditions [B]	-0.3	0.09	-0.2	0.1
BMI [C]	-0.1	0.6	0.04	0.8
Sexual Desire [D]	-0.01	0.9	0.1	0.8
Sexual Arousal [D]	0.03	0.9	-0.03	0.9

* Spearman correlation coefficients

A PCS: Physical Component Summary, MCS: Mental component summary. Both PCS and MCS are norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

B Four subjects had no co-morbid conditions. Co-morbid conditions are conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc

C BMI: body mass index. BMI was based on self-reported weight and height at week18

D One was missing at baseline. Both sexual desire and sexual arousal were based on visual analog scale (0-10cm), 0 = none while 10 = high. Subjects were asked to evaluate their sexual desire and sexual arousal during the month previous to the baseline assessment

4.3.6.3 Unadjusted Bivariate Correlations Between Each of the PCS and MCS Scales and Each of the IC Symptoms

Table 4-32 shows the bivariate correlations between each of the quality of life component summary scales and each symptom of IC. Interestingly, all symptoms were found to be significantly negatively correlated with the PCS score, but not with the MCS score. Both pain and urinary frequency symptoms showed the strongest negative correlations with PCS score (ρ= -0.5, p=0.002 and ρ= -0.5, p=0.003, respectively) among the IC symptoms. On the other hand, a weak negative correlation was reported between pain and MCS, however, it was not significant (ρ= -0.3, p=0.09). In fact, these results were consistent with what we reported previously **(Table 4-26, 4-27)**; severity of IC symptoms was found to be significantly associated with the reduction in the scores of three of the component domains of the PCS (physical functioning, bodily pain

and general health domains) and only one of the component domains of the MCS (Mental health).

Table 4-32: Correlation Coefficients and P values for Correlations Between Each of the PCS and MCS scale and IC Symptoms at Baseline (n=41)

FACTORS	SF-36 SUMMARY COMPONENETS			
	PCS [A]		MCS [A]	
	ρ*	p	ρ*	p
Pain Score [B]	-0.5	0.002	-0.3	0.09
Urinary Frequency	-0.5	0.003	0.1	0.8
Nocturia	-0.3	0.03	0.2	0.2
Urgency Score [C]	-0.4	0.02	0.1	0.6

* Spearman correlation coefficients

[A] PCS: Physical Component Summary, MCS: Mental component summary. Both PCS and MCS are norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] A score of 1 indicates no pain; a score of 9 indicates severe pain. Voiding pain was found to be significantly correlated with PCS (ρ=-0.4, P=0.004) and not significantly correlated with MCS (ρ=-0.2, P=0.1)

[C] A score of 1 indicates no urgency; a score of 5 indicates severe urgency

4.3.6.4 Adjusted Associations Between Physical Component Summary Scale and Each of the IC Symptoms

Because none of the IC symptoms showed any significant correlation with MCS scale in the unadjusted analysis **(section 4.3.6.3)**, we did not expect that these results will be significantly changed after adjusting for age and co-morbidity. On the other hand, it was crucial to perform further examination to determine if the significant associations which we reported in the previous section **(section 4.3.6.3)** between the PCS scale and each of the IC symptoms will be altered after adjusting for age, co-morbidity and the main study covariates.

Table 4-33 shows the results of the multivariate median regression models between PCS scale score and each of the IC symptoms after adjusting for age, co-morbidity and marital status. Importantly, because our sample size is small, each time we fit a model and found that the addition of a certain covariate had not a significant effect on either the regression coefficients or the p values, we selected the parsimonious model (model with the least number of covariates) as our final model. This was the case when we included being sexually active variable into each model.

Interestingly, after adjusting for age, co-morbidity and marital status in each model, only pain during voiding (model 1) and nocturia (model 3) were found to be significantly associated with lower PCS score. The median PCS score was found to be reduced by approximately 2.79 point for a subject whose score of pain during voiding is 1 point higher than another subject's, p=0.04. On the other hand, the median PCS score was found to be reduced by approximately 1.8 point for a subject whose average number of nocturia during an 24 hour period is 1 greater than

another subject's, p=0.01. Importantly, the magnitude of variation in PCS score that can be explained by urgency (model 4: ß=-5.45, p=0.1) was large, however, not statistically significant.

Table 4-33: Multivariate Median Regression Models for the PCS and Each Symptom of IC after Adjusting for Age, Co-morbidity and Marital Status at Baseline (n=41)

INDEPENDENT VARIABLE	PCS [A]	
	β	P Value
Model (1)		
Pain [B]	-2.79	0.04
Age	-0.07	0.7
Number of Co-morbid Conditions[C]	0.05	0.9
Marital Status [D]	8.92	0.05
Model (2)		
Urinary Frequency	-0.49	0.09
Age	-0.03	0.8
Number of Co-morbid Conditions	-0.63	0.1
Marital Status	6.76	0.1
Model (3)		
Nocturia	-1.80	0.01
Age	0.19	0.3
Number of Co-morbid Conditions	-0.76	0.2
Marital Status	6.50	0.1
Model (4)		
Urgency [E]	-5.45	0.1
Age	-0.01	0.9
Number of Co-morbid Conditions	-0.48	0.4
Marital Status	4.79	0.3

[A] PCS: Physical Component Summary, a norm-based score. All scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation.

[B] Pain during voiding. A score of 1 indicates no pain; a score of 9 indicates severe pain

[C] Four subjects had no co-morbid conditions. Co-morbid conditions are conditions that were active during the trial or may exacerbate IC symptoms e.g.: endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes...etc.

[D] Marital status: married or currently not married (widowed, divorced, never married and other). Currently not married is the reference group.

[E] A score of 1 indicates no urgency; a score of 5 indicates severe urgency.

4.4 EFFICACY RESULTS

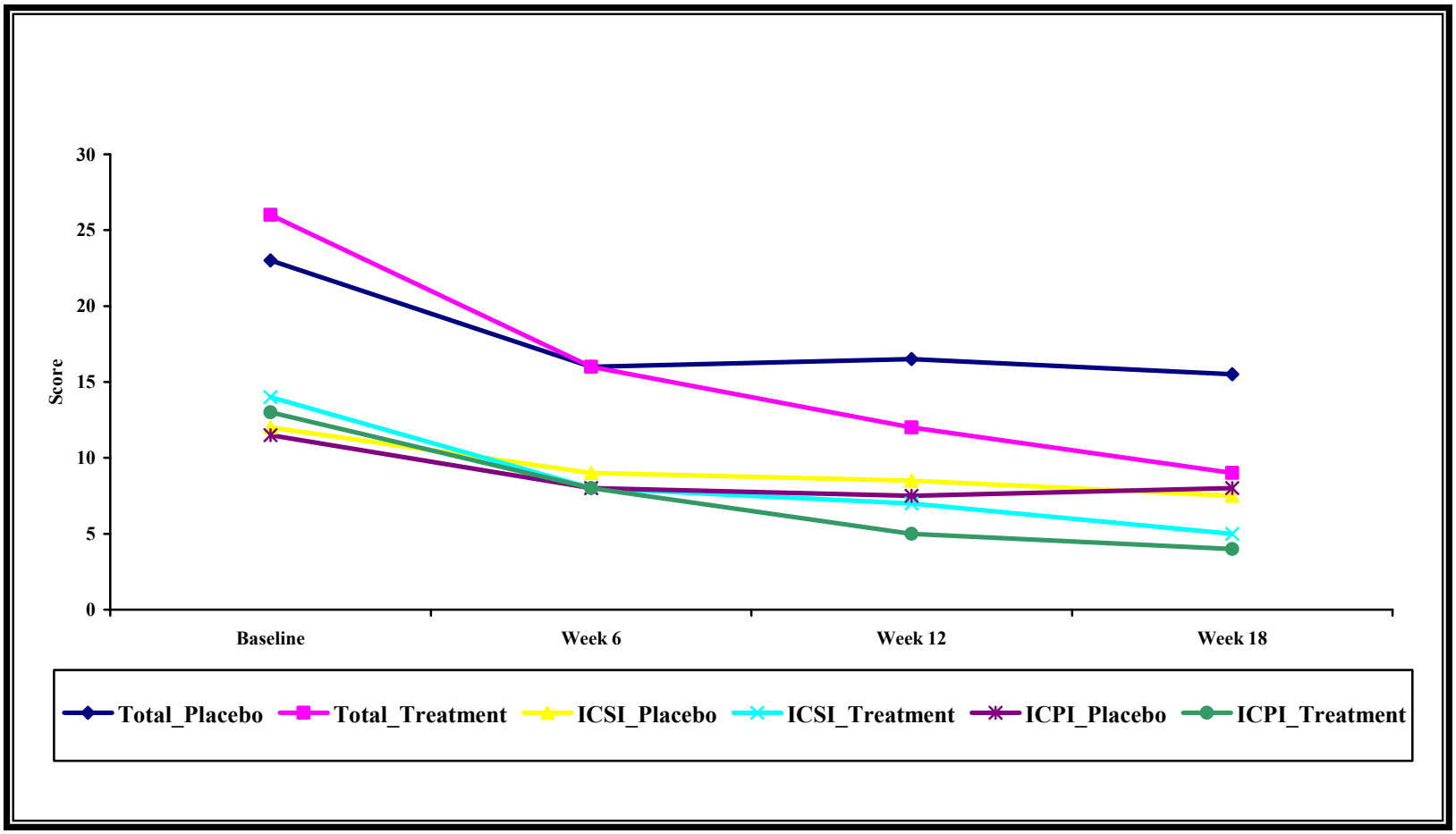
4.4.1 Severity of IC Symptoms

As mentioned previously in chapter three of this dissertation, severity of IC symptoms was measured using two well-known validated instruments: O'Leary-Sant interstitial cystitis symptom and problem index and PUF instrument. Both total score from O'Leary-Sant instrument and from PUF instrument were used as well as their components: ICSI score and ICPI score of the O'Leary-Sant instrument and symptoms score and bother score of the PUF instrument.

4.4.1.1 Changes in the Severity of IC Symptoms Among Treatment and Placebo Groups Over the Study Period

Figure 4-2 shows time plots of O'Leary-Sant total score, ICSI score and ICPI score for both study groups. Both treatment and placebo groups showed a decreasing trend in the severity of IC symptoms over the study period. Interestingly, the reduction in O'Leary-Sant total score as well as in ICSI and ICPI scores appeared to be more among the treatment group compared to the placebo group. The same decreasing trend can be observed in **Figure 4-3** which shows time plots of PUF total score, symptoms score and bother score for both study groups. Once again, the

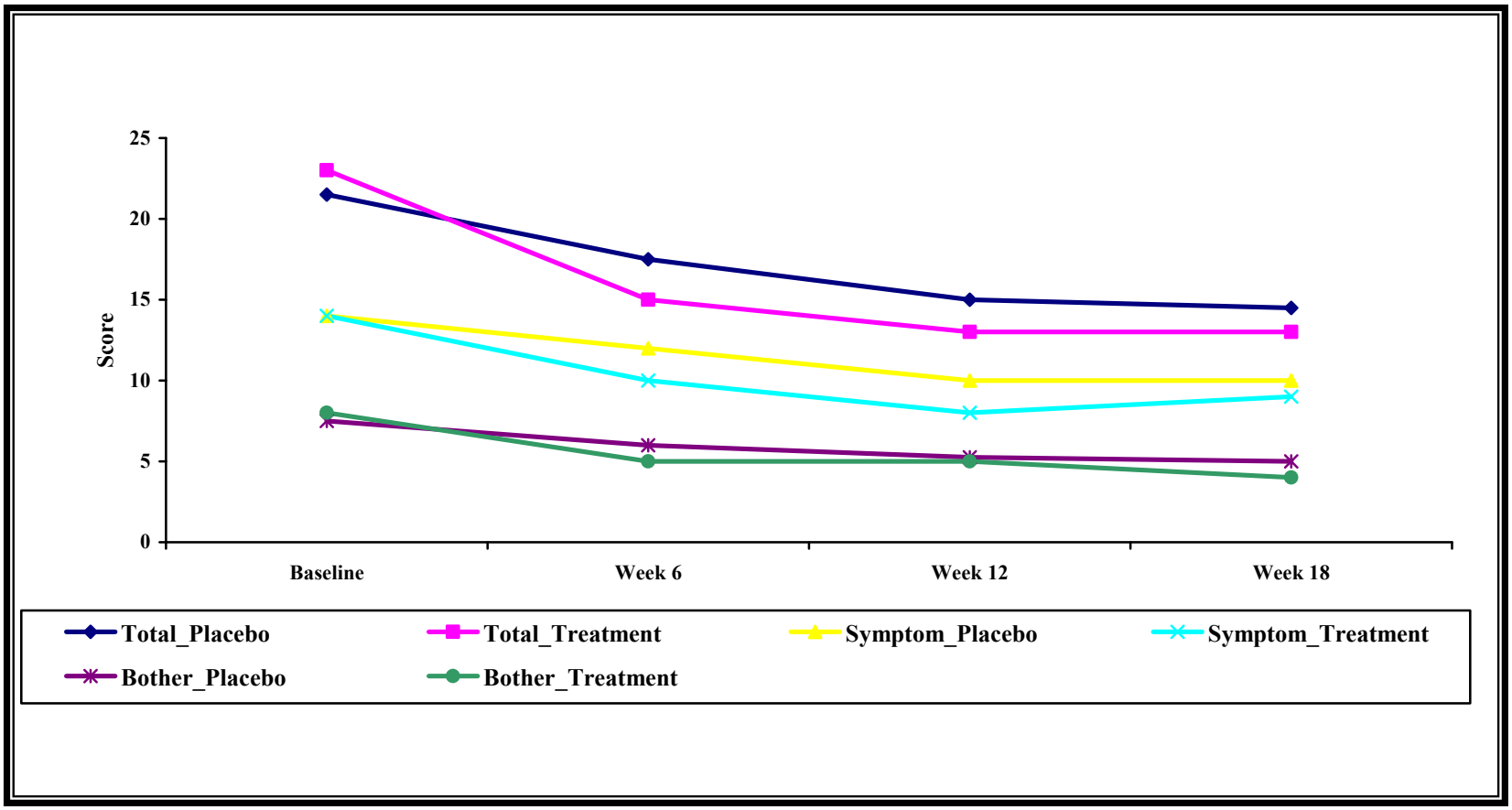
reductions in PUF total score as well as in symptoms score and bother score appear to be more among the treatment group in comparison to the placebo group.



* Scores were presented as median.

* Total_Placebo: Total O'Leary_Sant score for placebo, Total_Treatment: Total O'Leary_Sant score for treatment, ICSI_Placebo: Interstitial cystitis symptom index score for placebo, ICSI_Treatment: Interstitial cystitis symptom index score for treatment, ICPI_Placebo: Interstitial cystitis problem index score for placebo, ICPI_Treatment: Interstitial cystitis problem index score for treatment

Figure 4-2: Time Plots of the O'Leary-Sant Total Score, ICSI Score and ICPI Score by Study Group



* Scores were presented as median
* Total_Placebo: Total PUF score for placebo, Total_Treatment: Total PUF score for treatment, Symptom_Placebo: Symptom score for placebo, Symptom_Treatment: Symptom score for treatment, Bother_Placebo: Bother score for placebo, Bother_Treatment: Bother score for Treatment

Figure 4-3: Time Plots of the PUF Total Score, Symptom Score and Bother Score by Study Group

4.4.1.2 Effect of Trial Treatment and Placebo on the Severity of IC Symptoms

Both study groups showed statistically significant improvement in the severity of IC symptoms at each endpoint (week 6, week 12 and week 18) in comparison to the baseline, ($p<0.05$). **Table 4-34** presents the changes in the scores of the severity of IC symptoms (O'Leary-Sant index and PUF instrument) from baseline to each endpoint among the treatment group. At each endpoint, the treatment group showed statistically significant improvement (reduction) in the severity of IC symptoms, measured by both O'Leary-Sant and PUF instruments, compared to the baseline. Moreover, by the end of the trial, treatment group showed ~46% reduction in O'Leary-Sant total score and ~30% reduction in PUF total score compared to the baseline ($p<0.001$).

Significant improvement in the severity of IC symptoms was also reported among the placebo group at each endpoint in comparison to the baseline, **Table 4-35**. At week 18, placebo group showed ~ 35% reduction in O'Leary-Sant total score and ~28% reduction in PUF total score in comparison to the baseline ($p<0.001$).

Table 4-36 shows the changes in the scores of the severity of IC symptoms from baseline to week 6, week 12 and week 18 between study groups. Interestingly, the treatment group reported statistically significant changes from baseline to week 12 in both O'Leary-Sant total score and ICSI score compared to the placebo, (changes in O'Leary-Sant total score: -12 vs -5.5 , p value =0.04, respectively; changes in ICSI score: -6 vs -3, p value =0.03, respectively).

Moreover, greater reduction in the changes in O'Leary-Sant total score as well as in ICPI score from baseline to week 18 were reported among the treatment group in comparison to the placebo group, (changes in O'Leary-Sant total score: -12 vs -8 , p value =0.07, respectively; changes in ICPI score: -6 vs -4, p value =0.05, respectively).

No significant differences were observed in PUF total score, PUF symptoms score and/or PUF bother score from baseline to any endpoint between the study groups.

Table 4-34: Changes in IC Symptom Severity Scores from Baseline to Week 6, Week 12 and Week 18 in the Treatment Group*

OUTCOMES	SCORES OF TREATMENT GROUP (N=21) AT :									
	Baseline	Week 6	Change B-W6*	P [B]	Week 12	ChangeB-W12*	P [B]	Week 18	ChangeB-W18*	P [B]
O'Leary-Sant Total Score (0-36)	26 (18.5, 32)	16 (8.5, 26)	-7 (-3, -14.5)	<0.001	12 (7.5, 20.5)	-12 (-6.5, -16.5)	<0.001	9 (6.5, 22)	-12 (-7.5, -16.3)	<0.001
O'Leary-Sant ICSI [A] (0-20)	14 (10.5, 17)	8 (4.5, 14)	-4 (-1.5, -8)	<0.001	7 (5,10.5)	-6 (-3, -7.5)	<0.001	5 (4, 11)	-6 (-3.5, -9)	<0.001
O'Leary-Sant ICPI [A] (0-16)	13 (8.5, 15)	8 (3.5, 13)	-3 (-1.5, -7)	<0.001	5 (3, 10)	-6 (-3, -8.5)	<0.001	4 (2.5, 11)	-6 (-3.5, -8.5)	<0.001
PUF[I] Total Score (1-35)	23 (18.3, 25.5)	15 (12, 21.8)	-4 (0, -8.8)	0.002	13 (10, 19.5)	-6 (-3, -10.5)	<0.001	13 (8.5, 19)	-7 (-4, -13)	<0.001
PUF Symptom Index (1-23)	14 (11.5, 17)	10 (8, 15.3)	-3 (0, 5.5)	0.002	8 (7, 12.5)	-5 (-2, -7)	<0.001	9 (6, 12)	-4 (-2, -7.5)	<0.001
PUF Bother Index (0-12)	8 (6, 9)	5 (4, 8)	-1 (0, -2.8)	0.005	5 (3, 7)	-2.5 (-1, -3.5)	0.001	4 (3, 7)	-3 (-1.8, -4.5)	<0.001

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates improvement)

[A] ICSI: interstitial cystitis symptom index, ICPI: interstitial cystitis problem index, PUF: pain and urgency/frequency patient symptom scale

[B] Wilcoxon Sign Rank test

Table 4-35: Changes in IC Symptom Severity Scores from Baseline to Week 6, Week 12 and Week 18 in the Placebo Group*

OUTCOMES	SCORES OF PLACEBO GROUP (N=20) AT :									
	Baseline	Week 6	Change B-W6*	P [B]	Week 12	ChangeB-W12*	P [B]	Week 18	ChangeB-W18*	P [B]
O'Leary-Sant Total Score (0-36)	23 (19.3, 30)	16 (10, 25.5)	-4 (-1.3, -12)	0.001	16.5 (10, 25)	-5.5 (-3, -9)	0.001	15.5 (7, 21)	-8 (-3.3, -13)	<0.001
O'Leary-Sant ICSI [A] (0-20)	12 (10, 16)	9 (6, 14.3)	-2 (0, -4.8)	0.003	8.5 (6, 13.8)	-3 (-1.3, -4)	0.001	7.5(4.3, 12)	-4 (-3, -7.5)	<0.001
O'Leary-Sant ICPI [A] (0-16)	11.5 (10, 14)	8 (4.5, 11.8)	-2 (-1, -5)	0.002	7.5 (4, 11)	-3 (-1, -5)	0.001	8 (2.5, 10.8)	-4 (-0.3, -5)	0.001
PUF[1] Total Score (1-35)	21.5 (18, 26.5)	17.5 (10, 22)	-3.8 (-1.3, -7.8)	<0.001	15 (11, 20)	-5.8 (-3, -10)	<0.001	15 (10, 18.5)	-6 (-3, -13)	<0.001
PUF Symptom Index (1-23)	14 (12.3, 17)	12 (6.5,14.8)	-2 (-1, -5.5)	0.001	10 (7, 13.8)	-4 (-2, -6.5)	<0.001	10 (6.3, 12.8)	-4.5 (-2.3, -8)	<0.001
PUF Bother Index (0-12)	7.5 (6, 9.8)	6 (3, 7.8)	-1.8 (-1, -3)	0.001	5.2 (4, 7)	-1.8 (-1, -3.8)	0.001	5 (3, 6)	-3 (-1, -5)	<0.001

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates improvement)

[A] ICSI: interstitial cystitis symptom index, ICPI: interstitial cystitis problem index, PUF: pain and urgency/frequency patient symptom scale

[B] Wilcoxon Sign Rank test

Table 4-36: Changes in IC Symptom Severity Scores from Baseline to Week 6, Week 12 and Week 18 Between Study Groups* [189]

OUTCOMES	BASELINE TO WEEK 6*			BASELINE TO WEEK 12*			BASELINE TO WEEK 18*		
	Treatment	Placebo	P [B]	Treatment	Placebo	P [B]	Treatment	Placebo	P [B]
O'Leary-Sant Total Score (0-36)	-7 (-3, -14.5)	-4 (-1.3, -12)	0.2	-12 (-6.5, -16.5)	-5.5 (-3, -9)	0.04	-12 (-7.5, -16.3)	-8 (-3.3, -13)	0.07
O'Leary-Sant ICSI [A] (0-20)	-4 (-1.5, -8)	-2 (0, -4.8)	0.2	-6 (-3, -7.5)	-3 (-1.3, -4)	0.03	-6 (-3.5, -9)	-4 (-3, -7.5)	0.1
O'Leary-Sant ICPI [A] (0-16)	-3 (-1.5, -7)	-2 (-1, -5)	0.3	-6 (-3, -8.5)	-3 (-1, -5)	0.06	-6 (-3.5, -8.5)	-4 (-0.3, -5)	0.05
PUF[I] Total Score (1-35)	-4 (0, -8.8)	-3.8 (-1.3, -7.8)	0.8	-6 (-3, -10.5)	-5.8 (-3, -10)	0.6	-7 (-4, -13)	-6 (-3, -13)	0.7
PUF Symptom Index (1-23)	-3 (0, 5.5)	-2 (-1, -5.5)	0.9	-5 (-2, -7)	-4 (-2, -6.5)	0.6	-4 (-2, -7.5)	-4.5 (-2.3, -8)	0.8
PUF Bother Index (0-12)	-1 (0, -2.8)	-1.8 (-1, -3)	0.6	-2.5 (-1, -3.5)	-1.8 (-1, -3.8)	0.7	-3 (-1.8, -4.5)	-3 (-1, -5)	0.9

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates improvement)

[A] ICSI: interstitial cystitis symptom index, ICPI: interstitial cystitis problem index, PUF: pain and urgency/frequency patient symptom scale

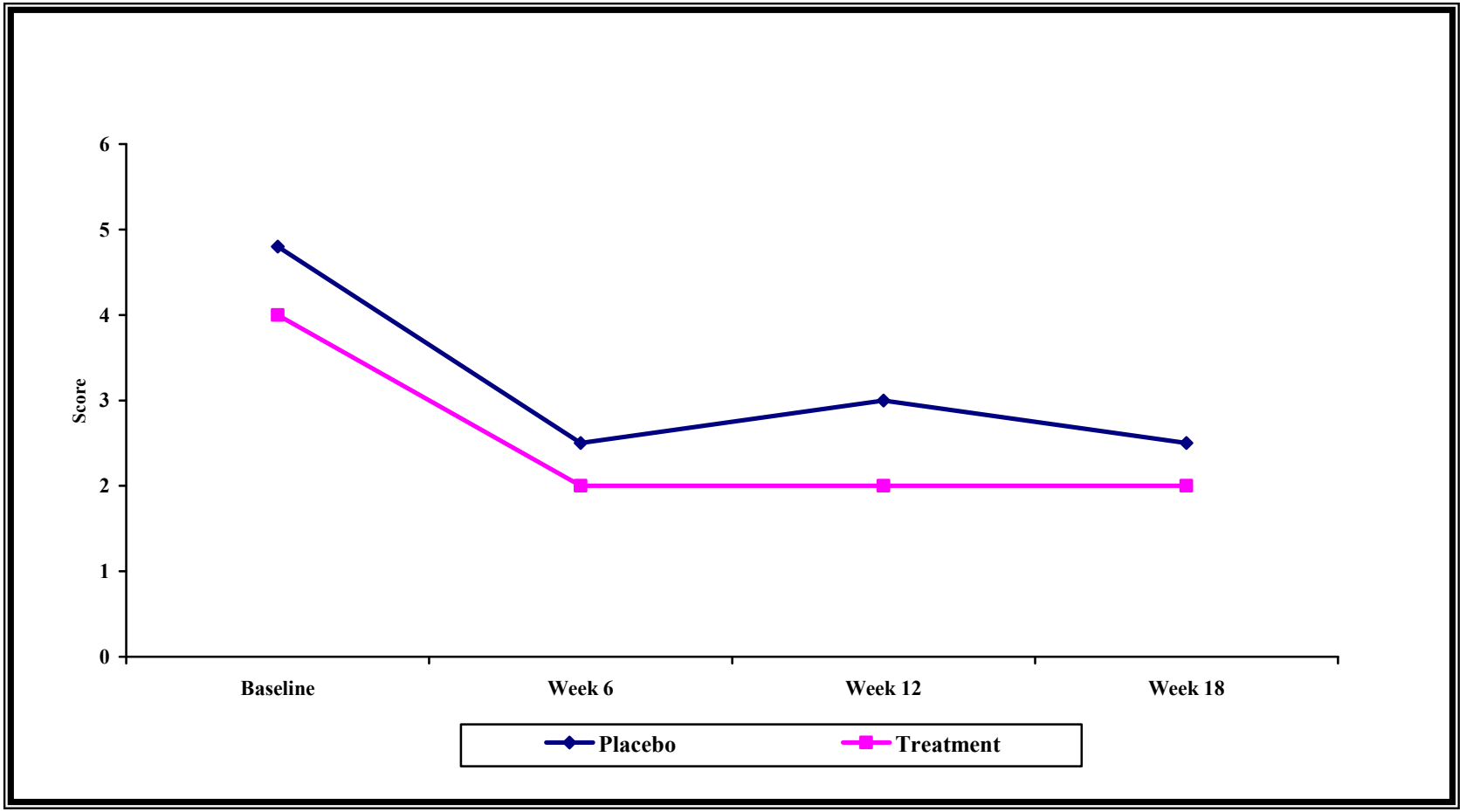
[B] Mann-Whitney test

4.4.2 IC Symptoms (Pain, Urgency, Urinary Frequency and Nocturia)

In the previous section **(4.4.1)**, we presented the effect of the trial interventions on the severity of IC symptoms in general. In this section we present the effect of the trial interventions on each IC symptom separately, in order to determine which symptom (pain, urgency, urinary frequency and/or nocturia) is most likely to be improved as a result of administering either intravesical PPS plus oral PPS or intravesical placebo plus oral PPS at the following endpoints: week 6, week 12, and/or week 18 of the trial.

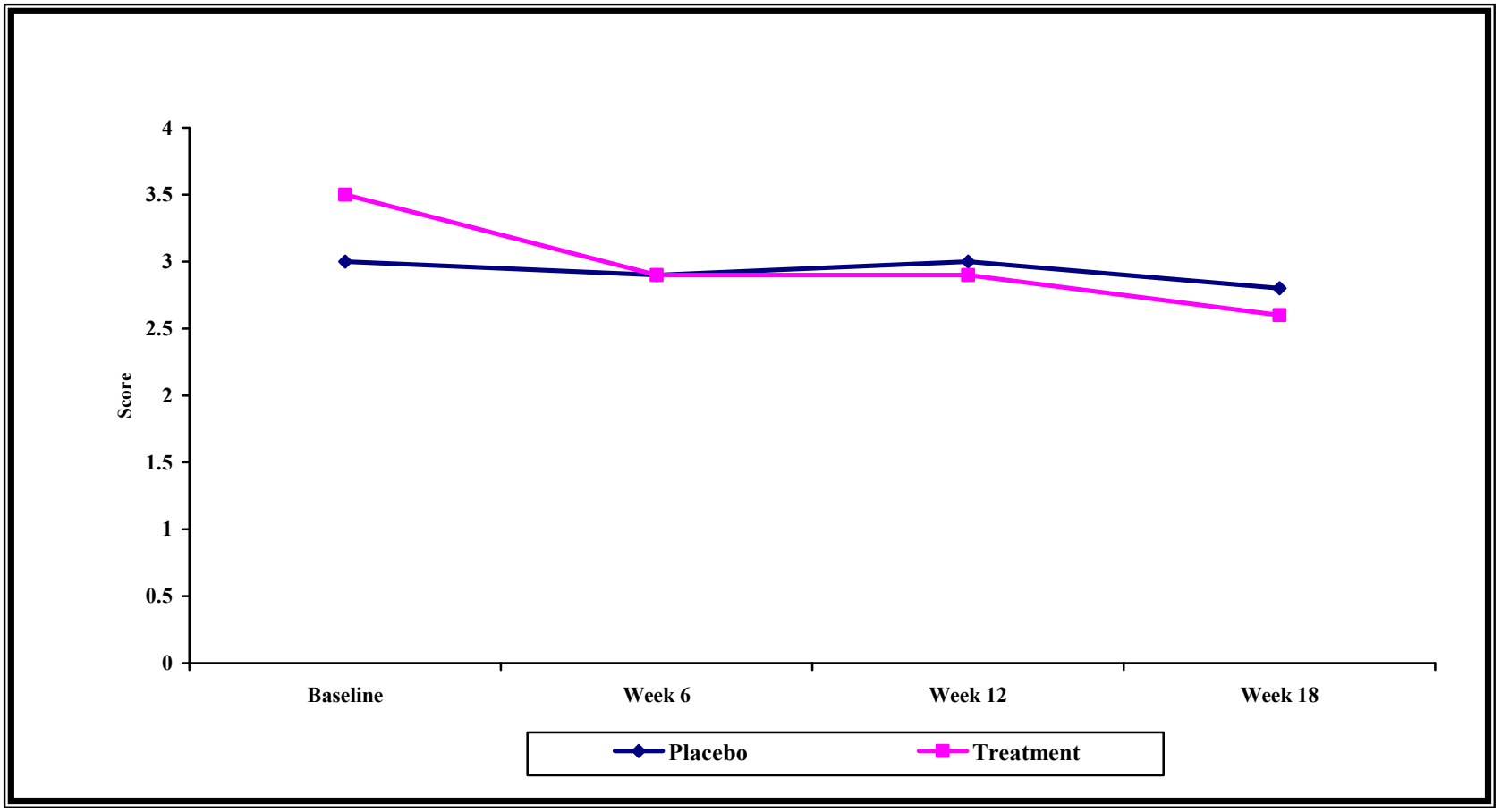
4.4.2.1 Changes in Each of the IC Symptoms Among Treatment and Placebo Groups Over the Study Period

Figures 4-4, 4-5, 4-6 and **4-7** show time plots of pain score, urgency score, number of voids during day time (urinary frequency) and number of voids during sleeping time (nocturia) for both study groups respectively. Interestingly, both treatment and placebo groups showed a decreasing trend in the scores of pain and of urgency as well as in the number of voids during daytime and during sleeping hours over the study period. Although the descriptive results by study group in **section (4.2.2.4)** showed that the two groups had comparable pain and urgency scores at baseline as well as comparable urinary frequency and nocturia, the treatment group showed more reduction (improvement) in each of IC symptoms over time compared to the placebo group.



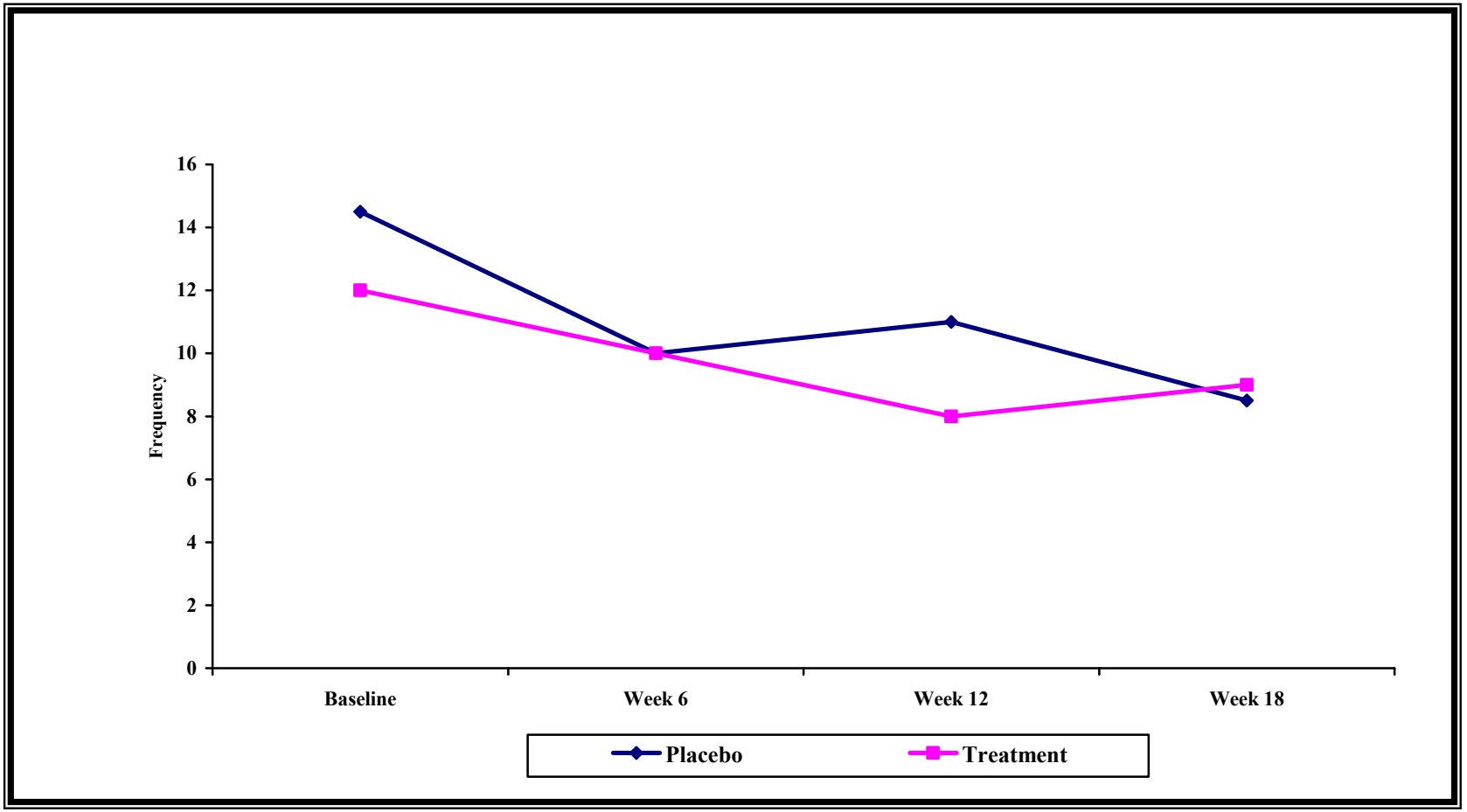
* Scores were presented as median

Figure 4-4: Time Plots of the Pain Score by Study Group



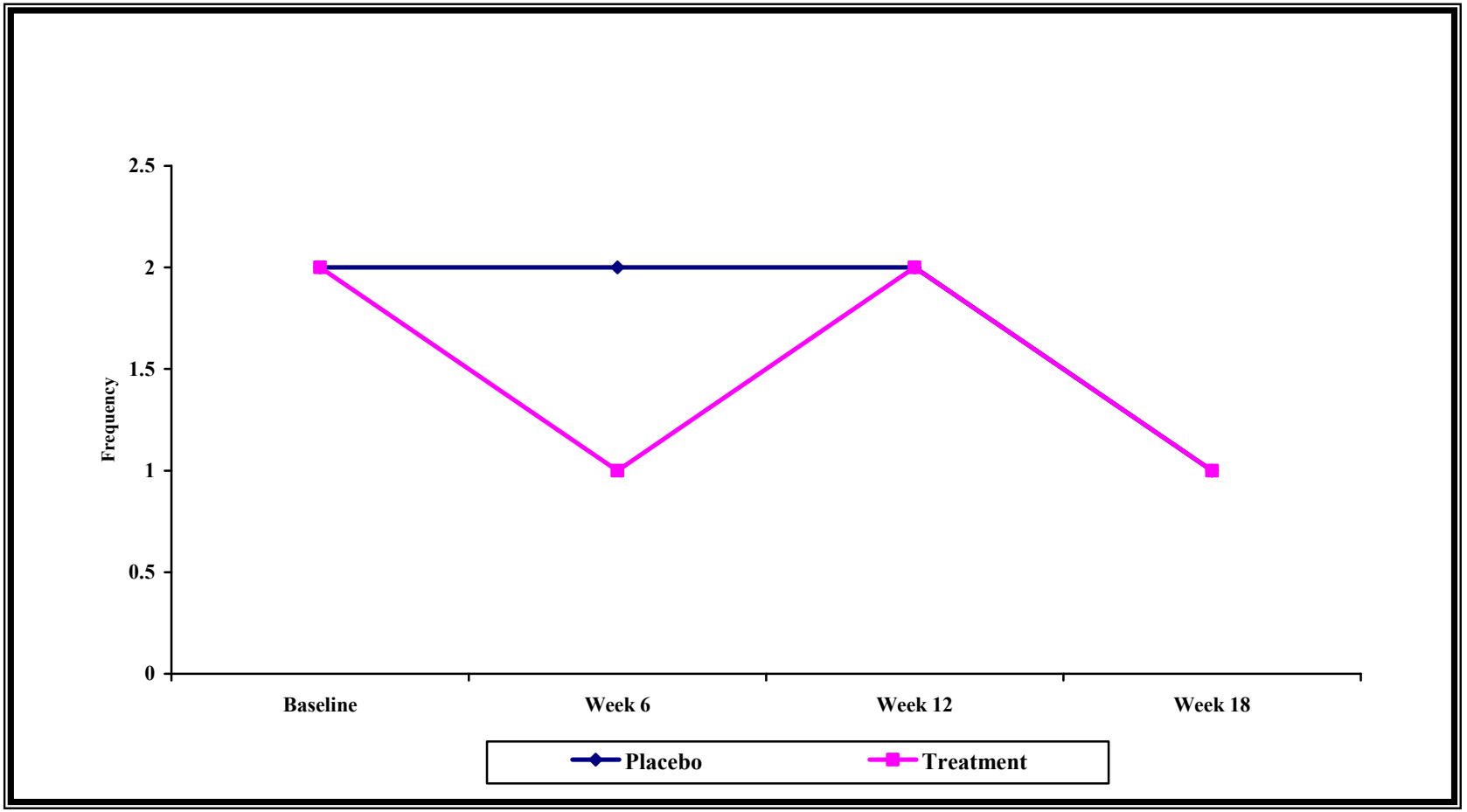
* Scores were presented as median

Figure 4-5: Time Plots of the Urgency Score by Study Group



* Data were presented as median

Figure 4-6: Time Plots of the Number of Voids During Day Time (Urinary Frequency) by Study Group



* Data were presented as median

Figure 4-7: Time Plots of the Number of Voids During Night Sleeping (Nocturia) by Study Group

4.4.2.2 Effect of Trial Treatment and Placebo on IC Symptoms

Table 4-37 shows the changes in IC symptoms from baseline to week 6, week 12 and week 18 in the treatment group. At each endpoint, the treatment group reported a highly statistically significant reduction (improvement) in both pain and urgency scores compared to the baseline. Moreover, by the end of the trial, treatment group showed ~50% reduction in pain score and ~17% reduction in urgency score compared to the baseline ($p<0.005$). Significant reduction in nocturia (number of voids during sleeping) was reported at the end of the trial in comparison to the baseline. (~50% reduction, $p=0.002$). No significant improvement was observed in urinary frequency (number of voids during daytime) at any endpoint in comparison to the baseline.

Table 4-38 presents the changes in IC symptoms from baseline to week 6, week 12 and week 18 in the placebo group. Interestingly, significant reduction (improvement) was observed in pain score as well as in urinary frequency at each endpoint in comparison to the baseline. Furthermore, at week 18, placebo group reported ~ 42% reduction in pain score and ~21% reduction in the number of voids during daytime (urinary frequency) compared to the baseline. Similar to the treatment group, placebo group showed significant reduction in the number of voids during sleeping time only at the end of the trial compared to the baseline (~50% reduction, $p=0.01$). Importantly, placebo group did not show significant improvement in urgency score at any endpoint in comparison to the baseline.

Table 4-39 shows the changes in IC symptoms from baseline to week 6, week 12 and week 18 between study groups. Interestingly, The placebo group reported significantly more reduction in the urinary frequency from baseline to week 6 compared to the treatment group, (changes in urinary frequency: -2.5 vs -1, p value =0.04, respectively). No significant differences were observed in pain score, urgency score and/or nocturia from baseline to any endpoint between the study groups.

Table 4-37: Changes in IC Symptoms from Baseline to Week 6, Week 12 and Week 18 in the Treatment Group*

OUTCOMES	TREATMENT GROUP (N=21)									
	Baseline	Week 6	Changes B-W6*	P [D]	Week 12	Change B-W12*	P [D]	Week 18	Change B-W18*	P [D]
Pain Scale (1-9) [A]	4 (4, 5)	2 (2, 4)	-1 (0, -2)	0.004	2 (1.5, 3.8)	-2 (-0.5, -3)	0.001	2 (1, 3)	-2 (-1, -3)	0.001
Urgency Scale (1-5) [B]	3.5 (2.6, 3.6)	2.9 (2, 3.4)	-0.4 (0.1, -1)	0.008	2.9 (2, 3.4)	-0.6 (-0.1, -1)	0.007	2.6 (2, 3)	-0.6 (0, -1.2)	0.007
Voiding Frequency [C]	12 (9, 16)	10 (7, 15)	-1 (3, -2.5)	0.8	8 (7, 15.5)	-2 (1.5, -3.5)	0.1	9 (7, 16.5)	-1 (0, -3)	0.1
Nocturia [C]	2 (1, 4)	1 (1, 3)	0 (0, -1)	0.08	2 (1, 3)	0 (1. 5, -1)	0.8	1 (0, 2)	-1 (-0.5, -2)	0.002

* Data were presented as median (25^{th}, 75^{th} percentiles) , negative sign was inserted to indicate a reduction from baseline (equates improvement)

[A] A score of 1 indicates no pain; a score of 9 indicates severe pain

[B] A score of 1 indicates no urgency; a score of 5 indicates severe urgency

[C] Voiding frequency: number of voids during day time, Nocturia: number of voids during night sleeping

[D] Wilcoxon Sign Rank test

Table 4-38: Changes in IC Symptoms from Baseline to Week 6, Week 12 and Week 18 in the Placebo Group*

OUTCOMES	PLACEBO GROUP (N=20)									
	Baseline	Week 6	Change B-W6*	P [D]	Week 12	Change B-W12*	P [D]	Week 18	Change B-W18*	P [D]
Pain Scale (1-9) [A]	4.8 (4, 5.8)	2.5 (2, 5)	-1.5 (-0.3, -3)	0.007	3 (1.3, 5)	-1.5 (0, -3)	0.001	2.5 (1.3, 4)	-2 (0, -3)	0.001
Urgency Scale (1-5) [B]	3 (2.5, 3.2)	2.9 (2, 3.5)	-0.2 (0.5, -0.8)	0.4	3 (1.9, 3.4)	-0.2 (0.4, -1.1)	0.3	2.8 (2, 3.4)	-0.4 (0.2, -0.9)	0.09
Voiding Frequency [C]	14.5 (10, 18.8)	10 (8, 14.5)	-2.5 (-1, -4.8)	0.001	11 (8, 14.5)	-2 (-0.3, -4.8)	0.003	9 (7, 15)	-3 (-1, -7)	0.001
Nocturia [C]	2 (1, 4)	2 (1, 3.8)	-0.5 (0.8, -2)	0.4	2 (0, 2)	-0.5 (0, -2.8)	0.09	1 (0, 2)	-1 (0.8, -2)	0.01

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates improvement)

[A] A score of 1 indicates no pain; a score of 9 indicates severe pain

[B] A score of 1 indicates no urgency; a score of 5 indicates severe urgency

[C] Voiding frequency: number of voids during day time, Nocturia: number of voids during night sleeping

[D] Wilcoxon Sign Rank test

Table 4-39: Changes in IC Symptoms from Baseline to Week 6, Week 12 and Week 18 Between Study Groups*[189]

OUTCOMES	BASELINE TO WEEK 6*			BASELINE TO WEEK 12*			BASELINE TO WEEK 18*		
	Treatment	Placebo	P [D]	Treatment	Placebo	P [D]	Treatment	Placebo	P [D]
Pain Scale (1-9) [A]	-1 (0, -2)	-1.5 (-0.3, -3)	0.5	-2 (-0.5, -3)	-1.5 (0, -3)	0.7	-2 (-1, -3)	-2 (0, -3)	0.7
Urgency Scale (1-5) [B]	-0.4 (0.1, -1)	-0.2 (0.5, -0.8)	0.3	-0.6 (-0.1, -1)	-0.2 (0.4, -1.1)	0.4	-0.6 (0, -1.2)	-0.4 (0.2, -0.9)	0.3
Voiding Frequency [C]	-1 (3, -2.5)	-2.5 (-1, -4.8)	0.04	-2 (1.5, -3.5)	-2 (-0.3, -4.8)	0.4	-1 (0, -3)	-3 (-1, -7)	0.05
Nocturia [C]	0 (0, -1)	-0.5 (0.8, -2)	0.9	0 (1. 5, -1)	-0.5 (0, -2.8)	0.3	-1 (-0.5, -2)	-1 (0.8, -2)	0.8

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates improvement)

[A] A score of 1 indicates no pain; a score of 9 indicates severe pain

[B] A score of 1 indicates no urgency; a score of 5 indicates severe urgency

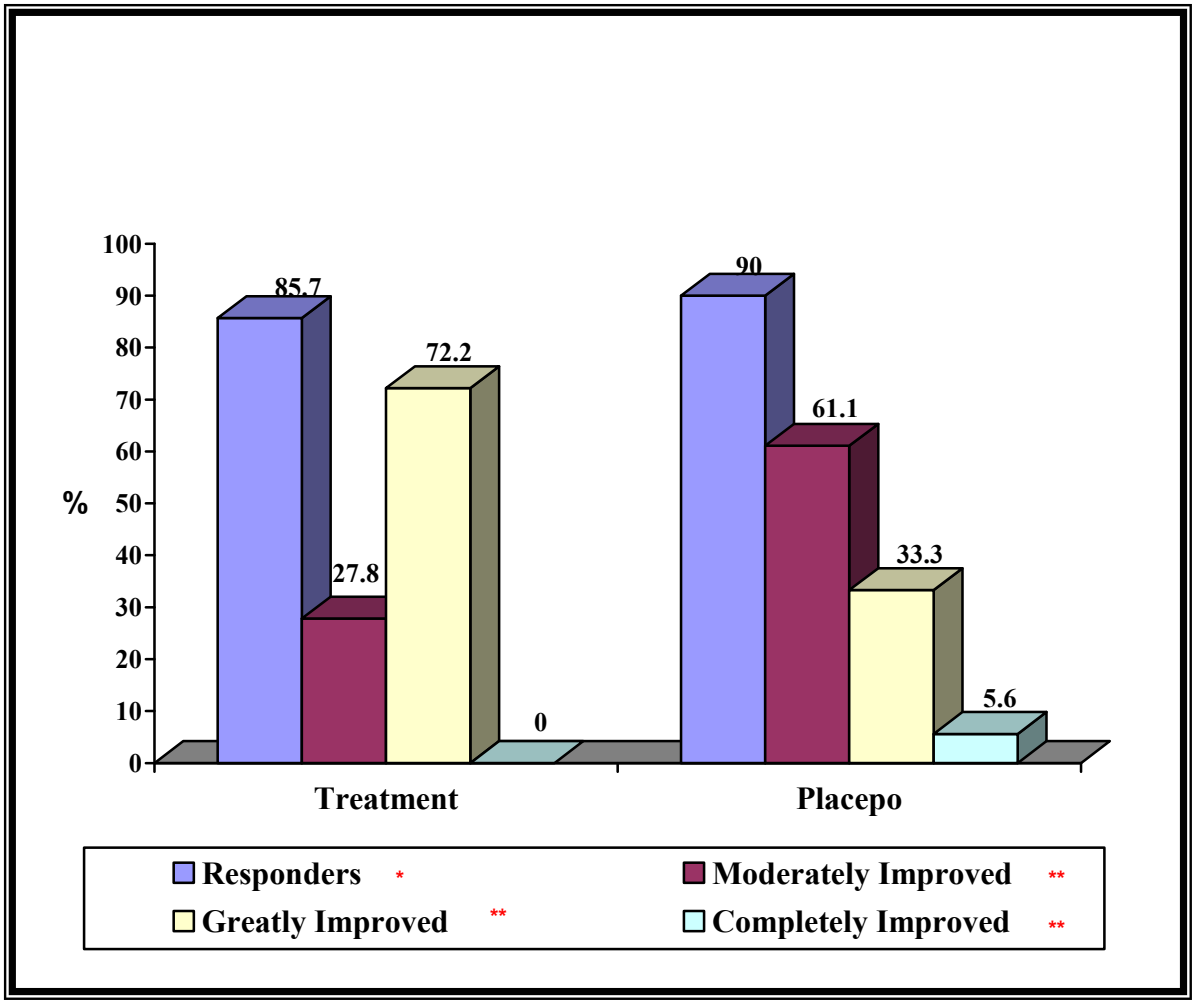
[C] Voiding frequency: number of voids during day time, Nocturia: number of voids during night sleeping

[D] Mann-Whitney test

4.4.3 Proportion of Responders and Level of Improvement Among Responders in Both Study Groups at the End of the Trial (Week 18)

As it was mentioned previously in chapter three of this dissertation, responders to trial interventions were defined as those who reported any level of improvement in their overall condition, urinary frequency or in their urgency at the end of the trial (After 18 weeks).

Figure 4-8 shows the proportion distribution of responders who reported any level of improvement in their overall condition by study group at week 18. It also shows the proportion distribution of the level of improvement among responders in each group. The proportion of subjects who reported any level of improvement in their overall condition were comparable among the two study groups (treatment: 85.7%, placebo: 90%, p>0.9). [189] Interestingly, 72.2% of the responders in the treatment group reported that their overall condition was greatly improved at week 18 compared to 33.3% of the responders in the placebo group (p value: 0.04). [189]

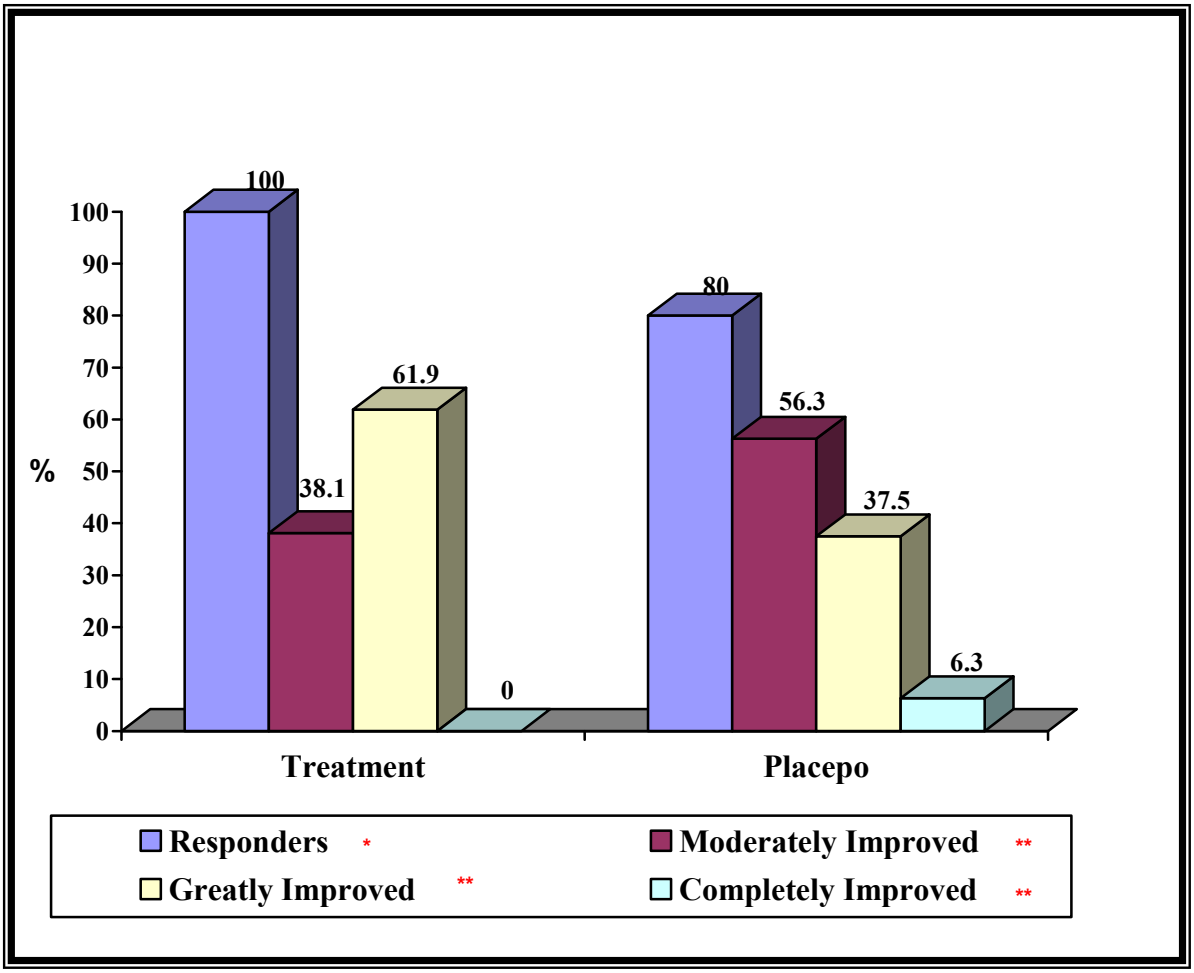


* Responders were defined as those who reported any level of improvement in their overall condition at the end of the trial. Fisher's exact p value >0.9

** Levels of Improvement in overall condition among responders were moderately improved, greatly improved and/ or completely improved. Fisher's exact p value was 0.04

Figure 4-8: Proportion Distribution of Responders and Level of Improvement in Overall Condition in Both Study Groups at the End of the Trial

According to **Figure 4-9**, all subjects of the treatment group reported improvement in their urgency (considered responders) in comparison to 80% of the placebo group, p=0.04. [189] Moreover, reporting urgency as greatly improved was more among responders in the treatment group compared to that among responders in the placebo group (61.9% vs. 37.5%, p=0.2). [189]



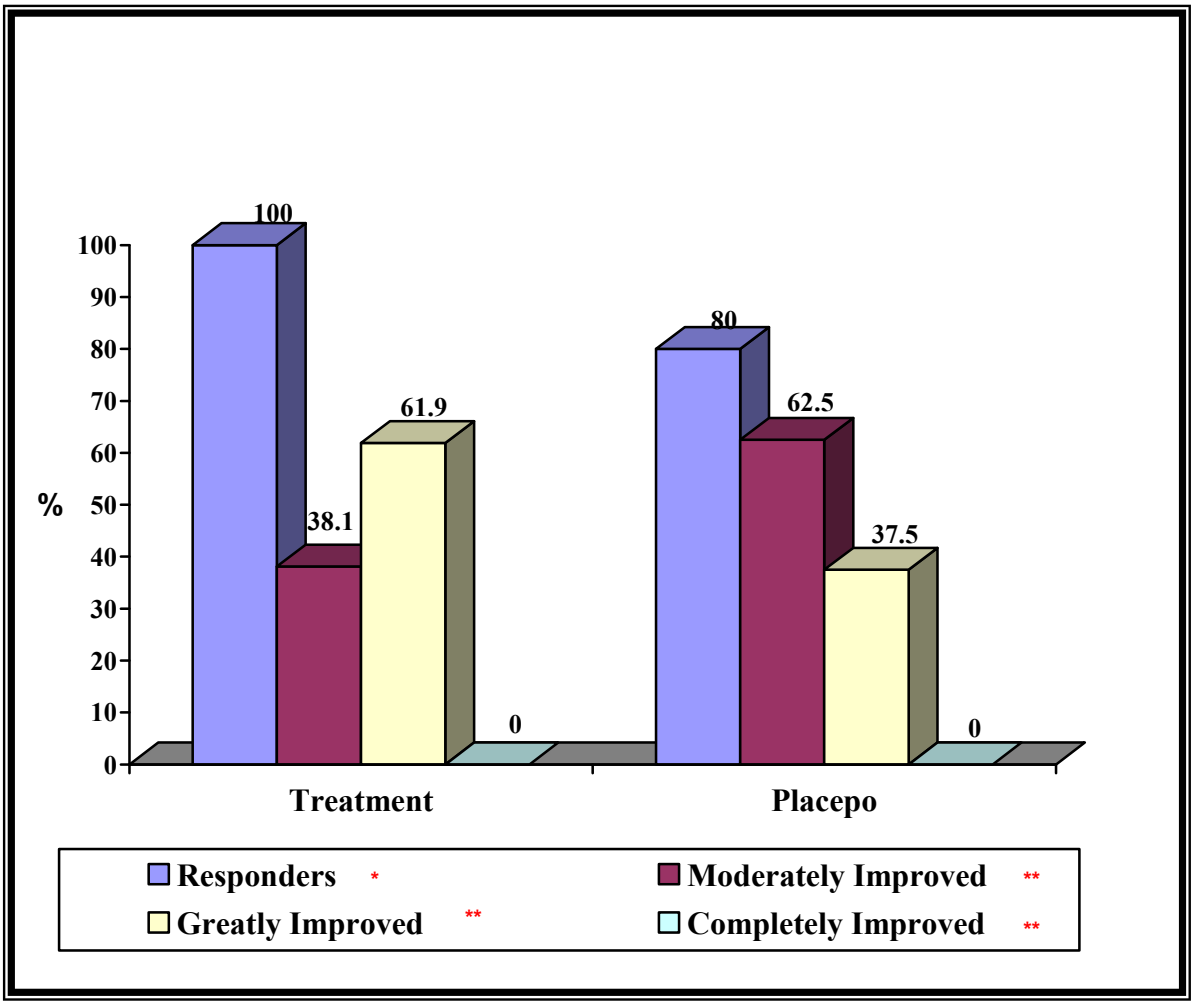
* Responders were defined as those who reported any level of improvement in their urgency at the end of the trial. Fisher's exact p value 0.04

** Levels of Improvement in urgency among responders were moderately improved, greatly improved and/ or completely improved. Fisher's exact p value was 0.2

Figure 4-9: Proportion Distribution of Responders and Level of Improvement in Urgency in Both Study Groups at the End of the Trial

Similar results were found when we asked the study subjects to report if they had any improvement in their urinary frequency after 18 weeks of the study, **Figure 4-10**. Interestingly, all subjects in the treatment group reported improvement in their urinary frequency (considered responders) after 18 weeks of the beginning of the study in comparison to 80% in the placebo group, p=0.04. [189]

Moreover, about 61.9% of the responders in the treatment group reported that their urinary frequency symptom was greatly improved since baseline in comparison to 37.5% of the responders in the placebo group, p=0.2. [189]



* Responders were defined as those who reported any level of improvement in their urinary frequency at the end of the trial. Fisher's exact p value 0.04

** Levels of Improvement in urinary frequency among responders were moderately improved, greatly improved and/ or completely improved. Fisher's exact p value was 0.2

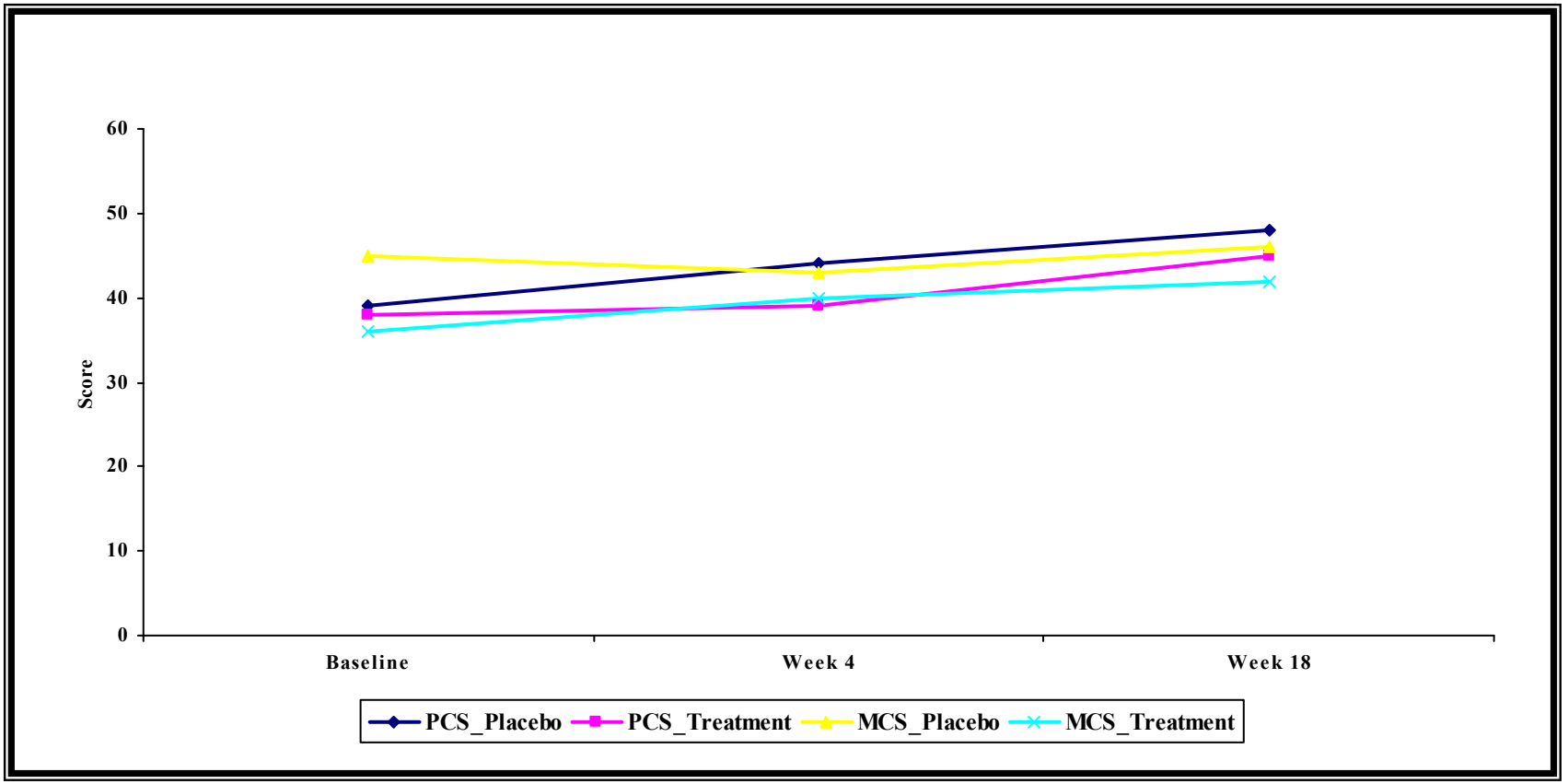
Figure 4-10: Proportion Distribution of Responders and Level of Improvement in Urinary Frequency in Both Study Groups at the End of the Trial

4.4.4 Health Related Quality of Life (HRQL)

SF-36 was used to assess the effect of the trial interventions on HRQL. The efficacy of the combination of intravesical and oral PPS was assessed using each of the component summary scales (PCS and MCS) as well as each domain of the SF-36 (physical functioning, role-physical, bodily pain and general health (physical component domains), vitality, social functioning, role-emotion and mental health (mental component domains)) as an outcome. The scores of either the two component summary scales or the domains of the SF-36 were calculated in the norm-based score format. Therefore, all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation.

4.4.4.1 Changes in HRQL Scores Among Treatment and Placebo Groups Over the Study Period

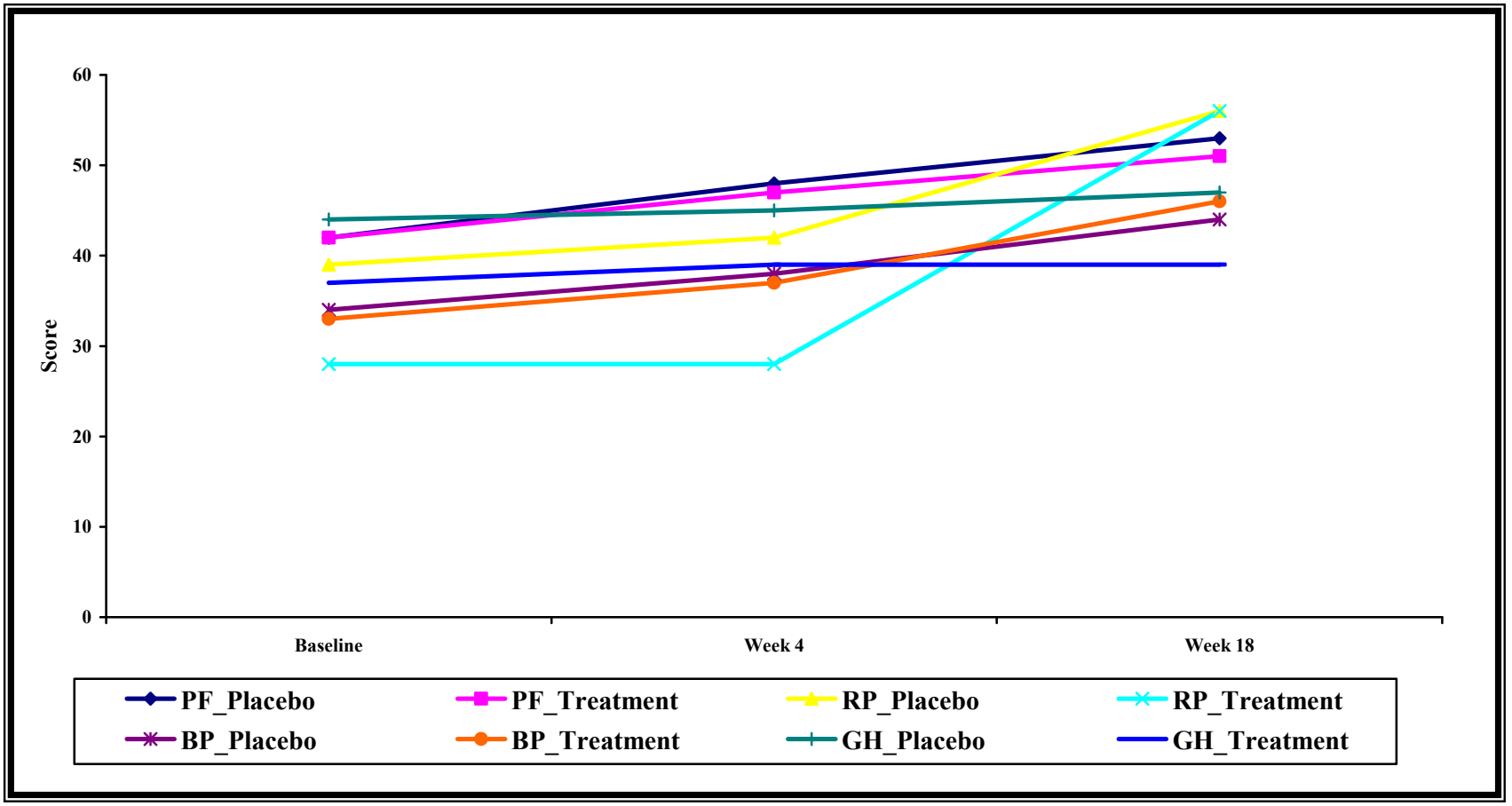
Figures 4-11 presents the time plots of PCS and MCS for both study groups. Both treatment and placebo groups showed an increasing trend in their PCS and/or MCS over the study period. In terms of the component domains of each summary scale, **Figures 4-12** and **4-13** show similar pattern of change in the scores of either the physical component domains (physical functioning, role-physical, bodily pain and general health) or the mental component domains (Vitality, social functioning, role-emotion and mental health), respectively, among both the study groups. In general increasing trends in each domain were observed among both study groups.



* Scores were presented as median.

* PCS_Placebo: physical component summary score for placebo, PCS_Treatment: physical component summary score for treatment, MCS_Placebo: mental component summary score for placebo, MCS_Treatment: mental component summary score for treatment.

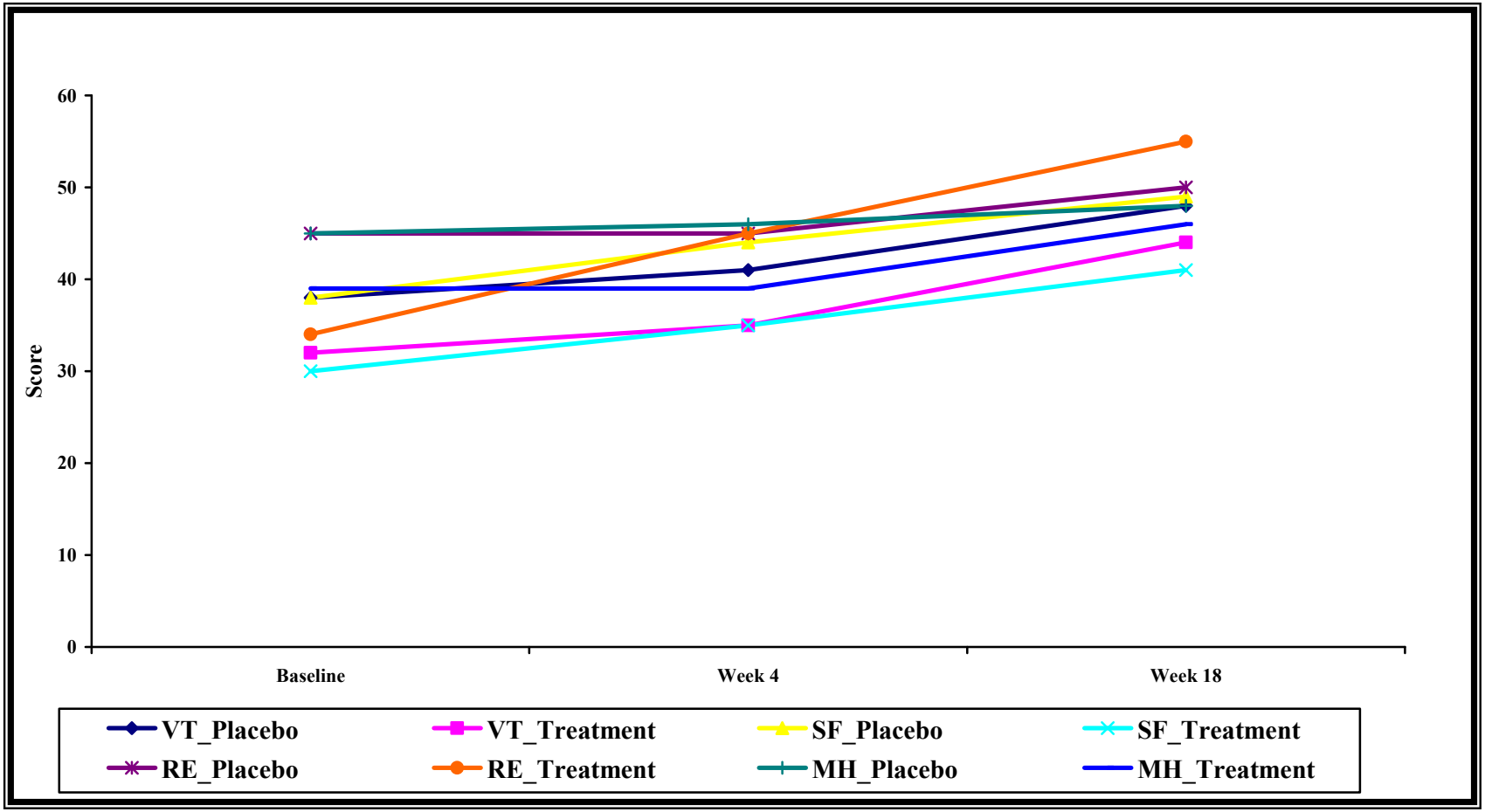
Figure 4-11: Time Plots of the PCS and MCS Norm-based Scores by Study Group



* Scores were presented as median.

* PF_Placebo: physical functioning score for placebo, PF_Treatment: physical functioning score for treatment, RF_Placebo: role-physical score for placebo, RF_Treatment: role-physical score for treatment, BP_Placebo: bodily pain score for placebo, BP_Treatment: bodily pain score for treatment, GH_Placebo: general health score for placebo, GH_Treatment: general health score for treatment.

Figure 4-12: Time Plots of the SF-36 Physical Component Domain Norm-based Scores by Study Group



* Scores were presented as median.

* VT_Placebo: vitality score for placebo, VT_Treatment: vitality score for treatment, SF_Placebo: social functioning score for placebo, SF_Treatment: social functioning score for treatment, RE_Placebo: role-emotional score for placebo, RE_Treatment: role-emotional score for treatment, MH_Placebo: mental health score for placebo, MH_Treatment: mental health scores for treatment.

Figure 4-13: Time Plots of the SF-36 Mental Component Domain Norm-based Scores by Study Group

4.4.4.2 Effect of Trial Treatment and Placebo on HRQL in IC Patients

4.4.4.2.1 PCS and MCS Scores

Table 4-40 shows the changes in each of the PCS scale and MCS scale from baseline to week 4 and week 18 in the treatment group. Interestingly, only at the end of the study (after 18 weeks) treatment group reported a highly statistically significant increase (improvement) in both component summary scales compared to the baseline. Moreover, by the end of the trial, treatment group showed ~17.9% increase in PCS score and ~21.8% increase in MCS score compared to the baseline ($p<0.0001$).

Table 4-41 presents the changes in each of the PCS scale and MCS scale from baseline to week 4 and week 18 in the placebo group. Significant improvement (increase) was reported in PCS score at week 4 (median change = 4, $p=0.002$) and at week 18 (median change = 7.5, $p=0.001$) compared to the baseline. On the other hand, no significant improvement was observed in MCS score either at week 4 or at week 18 compared to the baseline.

Table 4-42 shows the changes in PCS and MCS scores from baseline to week 4 and week 18 between the study groups. No significant differences were observed in PCS score from baseline to any endpoint between the study groups. On the other hand, treatment group reported significantly more increase in MCS score from baseline to week 4 compared to the placebo group (2 vs -0.6, p value =0.04, respectively).

Because the treatment group reported significantly lower MCS score (median=35.7) compared to the placebo group (median=44.5) at baseline, $p=0.03$ **(Table 4-13)**, it was very important to repeat the previous test, however, after adjusting for baseline score. Importantly,

after adjusting for baseline score, no significant differences were observed in the change in MCS score from baseline to any endpoint between the treatment and the placebo groups ($p>0.05$).

Table 4-40: Changes in PCS and MCS Scores from Baseline to Week 4 and Week 18 in the Treatment Group*

OUTCOMES	TREATMENT GROUP (N=21)						
	Baseline	Week 4	Change B-W4*	P [C]	Week 18	Change B-W18*	P [C]
PCS [A]	38 (32.6, 44.9)	38.5 (30.6, 48.7)	0 (-2.4, 5.9)	0.5	45.3 (38.1, 57.2)	6.8 (2.8, 13.1)	<0.0001
MCS [B]	35.7 (25.3, 43.7)	40.4 (30.6, 51)	2 (-1.9, 12.1)	0.06	42.5 (34.8, 54.8)	7.8 (1.7, 14.7)	<0.0001

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates impairment)

A PCS = physical component summary scale. Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

B MCS = mental component summary scale. Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

C Wilcoxon Sign Rank test

Table 4-41: Changes in PCS and MCS Scores from Baseline to Week 4 and Week 18 in the Placebo Group*

OUTCOMES	PLACEBO GROUP (N=20)						
	Baseline	Week 4	Change B-W4*	P [C]	Week 18	Change B-W18*	P [C]
PCS [A]	38.6 (31.9, 48.3)	43.7 (35.2, 52.1)	4 (0.9, 7.9)	0.002	48.2 (35.3, 54.8)	7.8 (0.8, 14.4)	0.001
MCS [B]	44.5 (37.2, 51.9)	42.9 (33.2, 52.9)	-0.6 (-6.5, 3.4)	0.3	46.5 (38.5, 53.7)	1.8 (-2.5, 9.5)	0.2

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates impairment)

A PCS = physical component summary scale. Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

B MCS = mental component summary scale. Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

C Wilcoxon Sign Rank test

Table 4-42: Changes in PCS and MCS Scores from Baseline to Week 6 and Week 18 Between Study Groups*

OUTCOMES	BASELINE TO WEEK 4*			BASELINE TO WEEK 18*		
	Treatment	Placebo	P [C]	Treatment	Placebo	P [C]
PCS [A]	0 (-2.4, 5.9)	4 (0.9, 7.9)	0.08	6.8 (2.8, 13.1)	7.8 (0.8, 14.4)	0.9
MCS [B]	2 (-1.9, 12.1)	-0.6 (-6.5, 3.4)	0.04	7.8 (1.7, 14.7)	1.8 (-2.5, 9.5)	0.1

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates impairment)

A PCS = physical component summary scale. Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

B MCS = mental component summary scale. Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation.

C Mann-Whitney test

4.4.4.2.2 SF-36 Domains

Table 4-43 shows the changes in each of the SF-36' domains from baseline to week 4 and week 18 in the treatment group. After 4 weeks of the study, treatment group reported significant improvement (increase) in bodily pain score (median change=3.9, p=0.03) and vitality score (median change=2.4, p=0.02) compared to the baseline. Moreover, after 18 weeks of the study, the treatment group reported significant improvement (increase) in all the SF-36 domains in comparison to the baseline ($p<0.05$).

Table 4-44 presents the changes in each of the SF-36' domains from baseline to week 4 and week 18 in the placebo group. Significant improvement (increase) was reported in bodily pain score at week 4 (median change = 4.7, p=0.01) compared to the baseline. Marginal significant improvement (increase) was also reported in each of the physical functioning score (median change = 3.1, p=0.07) and the role-physical score (median change = 3.5, p=0.05) compared to baseline. At the end of the trial, the placebo group showed significant improvement (increase) in only three domains of the SF-36 compared to the baseline (role-physical: median

change = 14.1, p=0.004; bodily pain: median change = 8.9, p= 8.9; vitality: median change = 5.9, p= 0.01).

Table 4-45 shows the changes in each of the SF-36' domains from baseline to week 4 and week 18 between the study groups. The treatment group reported greater change (improvement) from baseline to week 18 in both general health domain and mental health domain compared to the placebo group, however, the differences were marginally significant (general health: median change in treatment =3.7 vs. 0 in placebo, p=0.06; mental health: median change in treatment=6.8 vs. 1.1 in placebo, p =0.06).

Because the treatment group reported marginal significant lower vitality score (median=32.5) compared to the placebo group (median=38.4) at baseline, p=0.06, and marginal significant lower mental health score (median=39.1) compared to the placebo group (median=44.8) at baseline, p=0.08 **(Table 4-13)**, it was very important to repeat the previous test, however, after adjusting for baseline scores. Importantly, after adjusting for vitality baseline score, no significant differences were observed in the change in the vitality score from baseline to any endpoint between the study groups. On the other hand, after adjusting for baseline mental health score, treatment group continued to show greater marginal significant change (increase) in mental health score from baseline to week 18 compared to the placebo group, p=0.05.

Table 4-43: Changes in SF-36 Domain Norm-based Scores from Baseline to Week 4 and Week 18 in the Treatment Group*

OUTCOMES [A]	TREATMENT GROUP (N=21)						
	Baseline	Week 4	Change B-W4*	P [B]	Week 18	Change B-W18*	P [B]
Physical Functioning	42.5 (34.1, 50.9)	46.7 (34.1, 50.9)	0 (-2.1, 6.2)	0.3	50.9 (39.3, 57.1)	6.3 (1, 10.1)	0.01
Role-Physical	28 (28, 42.1)	28 (28, 56.2)	0 (0, 7.1)	0.2	56.2 (31.5, 56.2)	14.1 (0, 21.2)	0.005
Bodily Pain	33.2 (26.8, 37.5)	37.5 (29.3, 46)	3.9 (0, 6.9)	0.03	46.5 (37.5, 55.9)	12 (6.6, 17.8)	<0.0001
General Health	36.8 (30.1, 48.5)	39.2 (32.4, 50.9)	1.4 (-1.6, 5.2)	0.2	39.2 (32.9, 57.9)	3.7 (1, 9.4)	0.002
Vitality	32.5 (27.8, 36)	34.9 (30.1, 43.1)	2.4 (-1.2, 7.1)	0.02	44.3 (37.2, 56.2)	9.5 (4.7, 16.6)	<0.0001
Social Functioning	30 (24.6, 40.9)	35.4 (24.6, 51.7)	0 (0, 5.4)	0.2	40.9 (30, 57.1)	10.9 (0, 19)	0.003
Role-Emotional	34.3 (23.7, 55.3)	44.8 (29, 55.3)	0 (0, 10.5)	0.09	55.3 (34.3, 55.3)	5.3 (0, 21.1)	0.01
Mental Health	39.1 (25.5, 45.9)	39.1 (33.4, 47)	6.8 (-5.7, 10.2)	0.1	45.9 (31.1, 56.1)	6.8 (2.3, 10.2)	<0.0001

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates impairment)

[A] Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] Wilcoxon Sign Rank test

Table 4-44: Changes in SF-36 Domain Norm-based Scores from Baseline to Week 4 and Week 18 in the Placebo Group*

OUTCOMES [A]	PLACEBO GROUP (N=20)						
	Baseline	Week 4	Changes B-W4*	P [B]	Week 18	Change B-W18*	P [B]
Physical Functioning	42.5 (30.4, 52.8)	47.7 (35.1, 56.6)	3.1 (-2.1, 7.9)	0.07	52.9 (32.5, 56.6)	2.1 (0, 10.5)	0.06
Role-Physical	38.6 (28, 47.4)	42.1 (29.7, 56.2)	3.5 (0, 12.4)	0.05	56.2 (36.8, 56.2)	14.1 (0, 19.4)	0.004
Bodily Pain	33.6 (29.3, 40.7)	37.7 (30.3, 46.4)	4.7 (0, 8.6)	0.01	44.3 (33.6, 54.8)	8.9 (4.4, 17.9)	0.002
General Health	44 (36.1, 55)	44.6 (33.6, 52.6)	-0.5 (-2.3, 2.3)	0.6	46.9 (33.3, 50.9)	0 (-4.7, 4.3)	0.9
Vitality	38 (32.4, 50.2)	40.8 (31.3, 48.5)	0 (-4.1, 7.1)	0.8	47.9 (37.8, 53.2)	5.9 (-2.4, 13.6)	0.01
Social Functioning	38.1 (25.9, 55.8)	43.6 (30, 55.8)	0 (0, 5.4)	0.1	49 (32.7, 57.1)	0 (0, 16.3)	0.05
Role-Emotional	44.8 (34.3, 55.3)	44.8 (23.7, 55.3)	0 (0, 0)	0.6	50.1 (34.3, 55.3)	0 (-7.9, 18.4)	0.4
Mental Health	44.8 (39.1, 49.9)	45.9 (37.9, 52.7)	2.3 (-2.3, 6.2)	0.3	48.2 (39.7, 52.7)	1.1 (0, 8.5)	0.1

* Data were presented as median (25^{th}, 75^{th} percentiles), negative sign was inserted to indicate a reduction from baseline (equates impairment)

[A] Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] Wilcoxon Sign Rank test

Table 4-45: Changes in SF-36 Domain Norm-based Scores from Baseline to Week 4 and Week 18 Between Study Groups*

OUTCOMES [A]	BASELINE TO WEEK 4*			BASELINE TO WEEK 18*		
	Treatment	Placebo	P [B]	Treatment	Placebo	P [B]
Physical Functioning	0 (-2.1, 6.2)	3.1 (-2.1, 7.9)	0.5	6.3 (1, 10.1)	2.1 (0, 10.5)	0.6
Role-Physical	0 (0, 7.1)	3.5 (0, 12.4)	0.4	14.1 (0, 21.2)	14.1 (0, 19.4)	0.6
Bodily Pain	3.9 (0, 6.9)	4.7 (0, 8.6)	0.5	12 (6.6, 17.8)	8.9 (4.4, 17.9)	0.5
General Health	1.4 (-1.6, 5.2)	-0.5 (-2.3, 2.3)	0.1	3.7 (1, 9.4)	0 (-4.7, 4.3)	0.06
Vitality	2.4 (-1.2, 7.1)	0 (-4.1, 7.1)	0.3	9.5 (4.7, 16.6)	5.9 (-2.4, 13.6)	0.1
Social Functioning	0 (0, 5.4)	0 (0, 5.4)	0.9	10.9 (0, 19)	0 (0, 16.3)	0.4
Role-Emotional	0 (0, 10.5)	0 (0, 0)	0.2	5.3 (0, 21.1)	0 (-7.9, 18.4)	0.3
Mental Health	6.8 (-5.7, 10.2)	2.3 (-2.3, 6.2)	0.2	6.8 (2.3, 10.2)	1.1 (0, 8.5)	0.06

* Data were presented as median (25^{th}, 75^{th} percentiles) , negative sign was inserted to indicate a reduction from baseline (equates impairment)

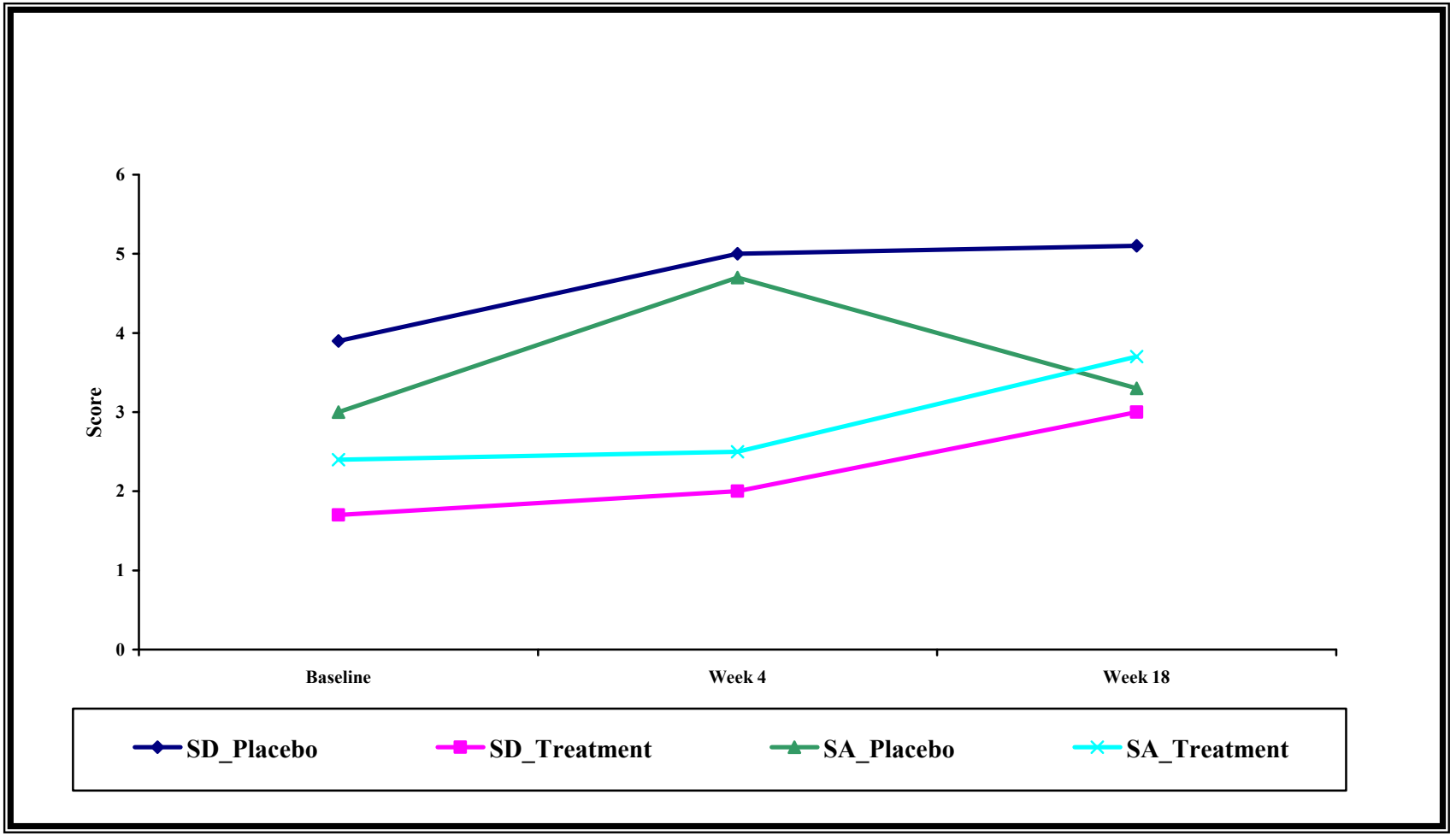
[A] Norm-based score: all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population. Each one difference in score is one tenth of a standard deviation

[B] Mann-Whitney test

4.4.5 Sexual Function

4.4.5.1 Changes in Sexual Function Domain Score Among Treatment and Placebo Groups Over the Study Period

Figures 4-14 presents the time plots of sexual desire and sexual arousal domains for both study groups. Interestingly, only the treatment group showed continuous increasing trend in both sexual desire and sexual arousal domains over the study period. On the other hand, the placebo group showed increasing trend in both dominos only between baseline and week 4, however, after that a decreasing trend was reported in sexual arousal domain in particular.



* Scores were presented as median.
* SD_Placebo: sexual desire scores for placebo, SD_Treatment: sexual desires scores for treatment, SA_Placebo: sexual arousal scores for placebo, SA_Treatment: sexual arousal scores for treatment.

Figure 4-14: Time Plots of the Sexual Function Domain Scores by Study Group

4.4.5.2 Effect of Trial Treatment and Placebo on Sexual function Domain Scores of IC Patients

Table 4-46 shows the changes in each of the sexual function domains from baseline to week 4 and week 18 in the treatment group. Marginal significant improvement (increase) in sexual desire was observed at the end of the trial compared to the baseline (median change=0.7, p=0.05). No significant improvement was observed in any of the sexual desire or sexual arousal domains after 4 weeks of the study compared to the baseline.

Table 4-47 presents the changes in each of the sexual function domains from baseline to week 4 and week 18 in the placebo group. No significant improvement was observed in any of the sexual desire or sexual arousal domains at any endpoint compared to the baseline, $p>0.05$.

Table 4-48 shows the changes in each of the sexual function domains from baseline to week 4 and week 18 between the study groups. No significant differences were observed in the change in any of the two sexual domains from baseline to any endpoint between the two groups.

Table 4-46: Changes in Sexual Function Domain Scores from Baseline to Week 4 and Week 18 in the Treatment Group*

OUTCOMES [A]	TREATMENT GROUP (N=21)						
	Baseline	Week 4	Change B-W4*	P [B]	Week 18	Change B-W18*	P [B]
Sexual Desire Score	1.7 (0.5, 4.5)	2 (0.7, 6.5)	0.2 (-0.1, 1.8)	0.1	3 (0.7, 5.7)	0.7 (-0.05, 3.2)	0.05
Sexual Arousal Score	2.4 (0.7, 4.9)	2.5 (0.6, 6.8)	0 (-0.3, 2.3)	0.5	3.7 (0.7, 7.8)	0.2 (-0.8, 3.6)	0.1

* Data were presented as median (25th, 75th percentiles) , negative sign was inserted to indicate a reduction from baseline (equates impairment)

[A] All sexual assessments were assessed for previous month period. Sexual desire and sexual arousal were based on visual analog scale (0-10cm): 0 indicates none, while 10 indicates high.

[B] Wilcoxon Sign Rank test

Table 4-47: Changes in Sexual Function Domain Scores from Baseline to Week 4 and Week 18 in the Placebo Group*

OUTCOMES [A]	PLACEBO GROUP (N=20)						
	Baseline	Week 4	Change B-W4*	P [B]	Week 18	Change B-W18*	P [B]
Sexual Desire Score	3.9 (2.2, 5.5)	5 (2.7, 6.8)	0.4 (-0.6, 1.4)	0.2	5.1 (1.1, 6.9)	0.7 (-1.5, 1.5)	0.5
Sexual Arousal Score	3 (1.2, 5.8)	4.7 (0.9, 7.2)	0.5 (-1.1, 3.2)	0.2	3.3 (1.2, 7)	0.6 (-1, 3.5)	0.2

* Data were presented as median (25th, 75th percentiles) , negative sign was inserted to indicate a reduction from baseline (equates impairment)

[A] One was missing at baseline. All sexual assessments were assessed for previous month period. Sexual desire and sexual arousal were based on visual analog scale (0-10cm): 0 indicates none, while 10 indicates high.

[B] Wilcoxon Sign Rank test

Table 4-48: Changes in Sexual Function Domain Scores from Baseline to Week 4 and Week 18 Between Study Groups*[189]

OUTCOMES[A]	BASELINE TO WEEK 4*			BASELINE TO WEEK 18*		
	Treatment	Placebo	P [B]	Treatment	Placebo	P [B]
Sexual Desire Score	0.2 (-0.1, 1.8)	0.4 (-0.6, 1.4)	0.9	0.7 (-0.05, 3.2)	0.7 (-1.5, 1.5)	0.4
Sexual Arousal Score	0 (-0.3, 2.3)	0.5 (-1.1, 3.2)	0.6	0.2 (-0.8, 3.6)	0.6 (-1, 3.5)	0.6

* Data were presented as median (25^{th}, 75^{th} percentiles) , negative sign was inserted to indicate a reduction from baseline (equates impairment)

[A] One was missing at baseline. All sexual assessments were assessed for previous month period. Sexual desire and sexual arousal were based on visual analog scale (0-10cm): 0 indicates none, while 10 indicates high.

[B] Mann-Whitney U test

5.0 DISCUSSION

Despite the small sample size, the current study was able to contribute significantly to the literature of interstitial cystitis. It provided important information about the quality of life (QOL) of IC patients and supported the efficacy of a new therapeutic option for this devastating condition. This study attempted to determine to what extent socio-demographic, lifestyle, reproductive and clinical history factors as well as sexual function domains affect the severity of IC symptoms and the HRQL in IC patients comprehensively. Moreover, the current study examined the association between the severity of IC symptoms and the QOL extensively, and determined the effect of each IC symptom on the physical component as well as on the mental component of the QOL. This study is unique in examining the efficacy of the only approved oral therapy for IC in USA applied intravesically on several outcomes.

The discussion will focus on our primary findings. This will include: the representation of our study population compared to other studies, a discussion of the main results from both the cross-sectional and the clinical trial parts and finally, directions for future research.

5.1 COMPARISON BETWEEN THE CURRENT STUDY POPULATION AND OTHER STUDY POPULATIONS

Our study population is a convenience sample from clinical patients seen in a very large urological practice in Southern California. One can argue that they may not be similar to the entire IC patients in the community. Assessing how our sample representative to the IC patients in the community is not applicable, as there is no specific diagnostic criterion for IC. However, we can compare the characteristics of our sample with that from other similar studies. Unfortunately, very few studies presented the characteristics of their populations. The Interstitial Cystitis Data Base (ICDB) study, sponsored by the NIDDK, is one of the few studies that described its population clearly. [17, 194] It is a multicenter, longitudinal, observational study designed to determine the treated history of IC and identify common patient characteristics. It comprised of 5 clinical centers including multiple hospital in 6 cities in USA (Detroit, Chicago, Madison, Oklahoma city, Philadelphia and San Diego). Participants were recruited primarily from the available patient pool of each principal investigator in each center. In comparison to the ICDB study, our study population was younger (mean: 38.3 vs. 44.3 years old), [17] included less Caucasian (70.7% vs. 91%, respectively), no men (0% vs. 8.8%), were more highly educated (68.3% post secondary vs. 57.3% college or advanced) and more of our participants were currently employed (78% vs. 61.2%). [194] Approximately 80% of the current study population were women of perimenopausal age (<49 years old). This is not surprising as the prevalence of the disease appears to be increasing among young and middle aged women with a median age of 43. [96, 140] Only female patients were included in the current study. It has been reported that the prevalence of IC is more common among women. Approximately 90% of IC patients are females. [137]

About 36.6% (15/41) of our study population were menopausal, and more than 50% (9/15) of them reached menopause surgically (21.9% of the total study population). Previous studies reported high proportion of hysterectomies among IC patients (range: 25.3% - 44.4%). [18, 61, 205] The present study as well as the previous investigations applied the NIDDK criteria in order to enroll IC patients. We therefore, would not expect to detect an extreme discrepancy in the clinical profile between our study population and other study populations. According to O'Leary-Sant IC Symptom Index (ICSI), the current study population classified mainly as either having moderate IC (46.3%, ICSI score: 7-13) or severe IC (51.2%, ICSI score: 14-20); the median score is 14. This was approximately similar to the study population of Payne et al., which tested the efficacy of intravesical Resiniferatoxin for the treatment of IC (mean ICSI score: 14 among treatment groups and 13 among the placebo), [206] and the study of Sant et al., which tested the efficacy of oral PPS and oral Hydroxyzine in IC patients (mean ICSI score: 13.3). [32] Applying NIDDK criteria ensures homogeneity and similarity between study populations; however, it also leads to misdiagnosing more than 60 percent of patients who were defined by researchers as definitely having or likely to have interstitial cystitis. [96] NIDDK criteria only define moderate and severe IC cases. About 14.6% (6/41) of our study population had Hunner's ulcers; this is higher than what is expected, it has been reported that approximately 10% of IC patients showed Hunner's ulceration, [94] and less than what was reported in Rothrock et al.'s study, which assessed the extent of depressive symptoms and impaired quality of life in a sample of female patients with IC compared to healthy controls (19% of IC patients had Hunner's ulcers). [22] Voiding frequency during waking hours among the participants in the current study (median 12) was approximately similar to what was reported by Payne et al. (mean range between 12.7-14.8 among placebo and treatment groups) [206] and by Nickel et al. (mean: 13.2)

who compared the ordinary dose of PPS with doses two to three times higher in a randomized clinical trial. [33] Importantly, further comparison about other medical profile parameters was not applicable as the methods used to collect and measure these data were different in each study.

In summary, our IC cases were representative of other IC intervention studies; applied a consistent set of criteria and therefore with some reservations the results can be considered to be applicable to the universe of moderate and severe IC patients.

5.2 CROSS-SECTIONAL'S RESULTS (AIMS 1, 2 AND 3)

The cross-sectional part of the current study determined the main socio-demographic, reproductive, lifestyle and/or clinical factors that significantly associated with the severity of IC symptoms and the impairment in each domain of the HRQL. It also determined if the severity of IC symptoms affects each domain of HRQL, and if each IC symptom is associated with either of the two major component of HRQL; physical component and mental component summary scales. Interestingly, ***being currently not married*** was found to be significantly associated with the increase in the severity of IC symptoms after adjusting for age, co-morbidity and menopausal status. Furthermore, being ***unemployed, obese, currently not married, and never being pregnant*** were found to be associated with impaired HRQL in at least one SF-36 subscale after adjusting for age, co-morbidity and the main study covariates. Not surprisingly, the severity of IC symptoms was an independent predictor of the impairments in ***physical functioning, bodily pain, general health and mental health domains***. Finally, ***pain during urination and nocturia*** were the only symptoms that were found to be associated with the impairment in the physical

component of the HRQL after adjusting for age, co-morbidity and marital status. Interestingly, none of the IC symptoms was found to be significantly associated with the impairment in mental component of HRQL.

Interstitial cystitis remains an idiopathic illness characterized by pelvic pain, urinary frequency and urgency with substantial morbidity in those affected. Previous researchers have studied risk factors for IC, but few have focused on the predictors of symptom severity. [6, 17, 152] Symptom severity has been associated with higher medical cost. [207] Identifying factors associated with increased symptom severity may provide insight into the etiology and/or treatment of this difficult condition and decrease health care costs. We investigated the effect of socio-demographic, reproductive, lifestyle, clinical factors as well as sexual functioning domains on the severity of symptoms among a clinical sample of females with IC. In contrast to other researchers, [17] we found that ***marital status*** is significantly associated with severity of IC symptoms in the univariate analyses. Married patients reported a lower ICSI score compared to currently not married. This association remained highly significant, even after adjusting for age, co-morbidity and menopausal status. Married patients may have more social support from their husbands and families, which increase their ability to accommodate the devastating symptoms of IC and thus reduce their stress. It has been suggested that stress may play a role in autoimmune and neuroinflammatory syndromes in which the nervous system interacts with the immune system. [88, 89] Stress is also known to worsen conditions involving mast cells such as interstitial cystitis. [57] The possible role of stress as an etiological factor of IC is thought to be related to its ability to activate mast cells through activating the bladder nerve endings, which in turn leads to release of Substance P (SP) and neuropeptide that activate local mast cells to secrete vasoactive, proinflammatory and nociceptive mediators. [90, 92] The effect of these, in turn, could explain most

of the clinical symptoms of IC. However, again were the IC patients who were married experiencing fewer symptoms or is it that the worsening of symptoms is related to not being currently married, it is difficult relationship to study in a cross-sectional vein, a prospective study is necessary to confirm what we found.

As the severity of symptoms increases, there appears to be a slight trend toward greater age. [17] In univariate analyses, Temml et al. reported that the prevalence of moderate/severe IC symptoms (using ICSI score: 7-20) was highest (18.8%) in the oldest age group (>=60yr), followed by middle-aged women (40-59 yr); (16.7%) and then the youngest (20-39yr) women; 12.8%. [6] However, age was not significant in the multivariate analyses. This was consistent with Clemens et al. [152] who assessed the same association among women diagnosed with IC and men diagnosed with chronic prostatitis recruited from an academic urology practice at a tertiary care facility in Chicago. We failed to find any trend or possible association between age and severity of IC symptoms in both univariate and multivariate analyses. The slight trend which was observed by both Simon et al. [17] and Temml et al. [6] was confounded by co-morbidities such as bowel disorder, hypertension...etc; it disappeared once both studies adjusted for these covariates. It is worthy of note that each of these studies used different methods to identify IC cases as well as different criteria to categorize patients according to their symptom severity. For example in Temml et al.'s study, [6] women were not diagnosed as IC cases using the NIDDK (cystoscopic and urine analysis), however, based on their total score of O'Leary-Sant IC Symptom and Problem Index as follows: 0-6 no risk for IC, 7-13 minimal risk, 14-23 moderate risk and 24-36 high risk for IC. Temml et al.'s study was a questionnaire-based analysis and no individual underwent a thorough urologic evaluation. Also the study population was not generated by standard epidemiologic sampling and might therefore be biased.

We did not find any association between educational level and severity of IC symptoms. These findings are similar to those reported by Temml et al.; [6] and against the significant inverse association that was observed by both Clemens et al. [152] and Simon et al. [17]. Both studies reported that women with lower educational level were more likely to report severe symptoms. A possible explanation for this inverse association is that less educated individuals may not seek treatment at tertiary care centers unless symptoms are quite severe. Another reason could be the lack resources for treatment and support, so that more severe symptoms tend to develop with time. [152] Our failure to detect this association could be due to the small sample size and to the fact that approximately 70% (28/41) of our study population were post secondary educated, thus we may have not enough power to find such this association.

In terms of reproductive history factors, we reported a significant association between menopausal status and severity of IC symptoms in the univariate analyses. Menopausal women reported significantly higher score of symptom severity compared to currently not menopause. After adjusting for age, co-morbidity and martial status, being menopausal was no longer associated with more severe IC symptoms. Similar to our univariate analyses, Clemens et al. also reported that postmenopausal status is associated with worsening symptoms; however, in contrast to our findings from the multivariate analyses, this association remained significant after adjusting for educational level, depression, frequency and urgency. [152] After menopause the pH of the vagina rises and therefore promotes an alteration in the normal vaginal flora, with decreased lactobacilli leading to increased colonization by pathogenic faecal flora. [208] This increases the incidence of Urinary Tract Infection (UTI). Furthermore, estrogen deficiency after menopause results in generalized urogenital atrophy, therefore, postmenopausal women are at increased risk not only of recurrent UTI but also of dyspareunia, vaginal irritation, pruritus, pain,

and symptoms of urgency, frequency, dysuria, and urinary incontinence. [208] While it seems probable that the postmenopausal decline in estrogen levels has a major impact on lower urinary tract, it is possible that the increase in urinary symptoms at this time is simply due to the aging process**.** [209] Previous studies in women have reported an increased incidence of urinary symptoms starting as early as 10 years before the menopause. Importantly, urinary symptoms can have a systemic cause and not only as a result of aging. For example, diabetic patients may be receiving diuretic therapy for cardiovascular disease, or may be taking other medications that affect the bladder. [209] Thus, IC among postmenopausal most likely has a multifactorial etiology. Further studies of this issue are required before any meaningful conclusion can be drawn.

It was surprising that neither severity of glomerulations nor the presence of Hunner's ulcer was significantly associated with severity of IC symptoms. In fact, there is no clear correlation between cystoscopic appearance and IC symptom severity. [210] The presence of Hunner's ulcer varies between 6 and 50% in different series of IC patients, [211, 212] which may reflect a discrepancy in diagnostic procedures. Interestingly, a positive correlation was reported between the ICDB summary severity score and increasingly severe physiological markers, such as scar tissue, Hunner's ulcer and decreased bladder capacity. [17] On the other hand, it has been reported that glomerulations are not specific to IC, and they are most likely a reflection of a chronically under distended bladder; not all patients with symptoms of IC have glomerulations, and not all patients with glomerulations have symptoms of IC. [96] Our failure to report any association between the presence of Hunner's ulcer and severity of IC symptoms could be related to our study design, as we only included moderate and severe IC cases. May be there is no extensive difference between moderate and severe cases regarding to the presence of Hunner's ulceration. The real differences could be between severe and mild cases or moderate and mild

cases. Further studies are needed to investigate this relationship; because the very narrow range of our cases (lack of a full spectrum of disease) may have precluded this finding.

We observed a significant association between being sexually active during the month previous to baseline visit and severity of IC symptoms. Women who had sexual intercourse during the month previous to baseline visit reported significantly lower ICSI score. This can be explained by two different ways; either being sexually active is a significant predictor of reduction of severity of IC symptoms or severe IC symptoms associated with avoiding sexual intercourse. Importantly, because of the cross-sectional analysis limitation, we are not able to tell which one of these two explanations is the correct. Prospective studies are required to address this association comprehensively.

IC is physically debilitating as well as emotionally distressing for many patients who suffer from it. The quality of life for many IC patients has been shown to be worse than that of patients undergoing dialysis for end-stage renal disease. [2] In severe cases, patient may have voiding frequency up to 60 times a day and nocturia every 20 minutes. As a result of that, patient with IC suffers from subsequent sleep deprivation that affects on his/her well-being. IC patient is often unable to work and perform daily activities; sometimes he/she is unable to leave home. [2] More than 94% of IC patients indicated that travel was impossible or difficult, and 69.7% reported disruption in family relationships and responsibility. [18]

Previous research showed that patients with interstitial cystitis reported significantly poorer QOL than controls across all SF-36 domains including: physical functioning, bodily pain, vitality, general health, social functioning, role limitations due to physical and emotional problems and mental health ($p<0.01$). [22] Although we did not have a control group, the negative impact on QOL was also demonstrated in our sample of IC patients when we compared their

HRQL scores in the original format **(Table 4-5)** and in the norm-based format **(Table 4-6)** with those from a normative sample of the US females from the 1990 and the 1998 general surveys, within the same age group, respectively. In both tables, the scores of the eight domains were extremely lower than those of the normative sample. Ware et al. suggested that a 5-point difference on an SF-36 subscale is indicative of a clinically meaningful decrease in QOL. [177] We reported subscale difference score between 16 and 46.5 point in the original scales. Clearly the degree of impairment experienced by patients with IC is substantial.

The reader may observe that most of the QOL's results in the current study were presented in the norm-based format. Using norm-based format has many advantages; when interpreting the scores the reader will no longer have to remember the norms for 8 scales because the general population norm is built into the scoring algorithm that all scores above or below 50 can be interpreted as above or below the general population norm. Furthermore, the standard deviation for each scale is equalized at 10. Therefore, it's easier to see exactly how far above (or below) the mean the score is in standard deviation units. Moreover, because all 8 scales are scored to have the same standard deviation, comparisons in scores across scales and summary measures can be made directly. [184]

Limited studies addressed how socio-demographic, reproductive, lifestyle, clinical history factors and/or sexual function domains affect on the HRQL in IC patients. Although of a cross-sectional nature, our study is the first to assess the impact of each of these factors on each of the eight domains of SF-36. We investigated the above mentioned associations first, without including symptom severity to regression models, so we can determine the main covariates of the association between symptom severity and QOL. Secondly, we tested the effect of symptom severity on each HRQL domain adjusting for all the significant covariates we identified from the

univariate analyses. Therefore, we were able to answer if symptom severity confounds any of the previous identified relationships and vise versa. As it was expected, we reported a significant association between employment status and physical functioning domain. ***Being currently not employed*** was significantly associated with impairment in physical functioning in the univariate analyses and after adjusting for age, co-morbidity and had sexual intercourse during the month previous to the baseline visit. This was consistent with researches applied to other diseases; Papadopoulos et al. who studies predictors of HRQL in type II diabetic patients (52.8% females), [203] and with Riazi et al. among multiple sclerosis patients (65.3% females). [213] Interestingly, employment status was no longer significantly associated with the impairment in physical functioning after adjusting for ICSI, age and co-morbidity. This demonstrates the importance of severity of IC symptoms over employment status in predicting impairment in physical functioning of IC patients. Therefore, it is really the severity of IC symptoms that reduces IC patient's ability to work and thus impairs their physical functioning.

As social support is an important predictor of QOL, [214] marital status might be expected to be significantly associated with impairment of different domains of QOL. This was supported in our univariate analyses and some of the multivariate models. In a consistent manner, we observed significant associations between ***being currently unmarried*** and ***impairment in each of role-physical, bodily pain, general health, vitality and social functioning domains*** in the univariate analyses. However, after adjusting for age, co-morbidity and certain study covariates, marital status remained a significant predictor of only social functioning. Interestingly, ***marital status*** was found to be significantly associated with even more domains (***role-emotional, bodily pain and vitality***) after including ICSI to the models. Similar to what we observed, however among type II diabetic patients, Papadopoulos et al. found that being unmarried was a significant

predictor of impairment in vitality domain after adjusting for age, gender and diabetic covariates. [203] Our finding supported with that of Papadopoulos et al. indicates that lack of social support and family relationships have a profound impact on the HRQL in IC patients exactly like the impact of the severity of IC symptoms. However, because of the limitations of the cross-sectional design of our study, a prospective study is required to determine if IC patients never get married because of their pain our was their pain ameliorated because they got married.

Assessing how reproductive history factors affect on QOL domains reveals some interesting findings. We were unable to see if our findings match other's because we are the first to assess these factors. ***Being sexually active*** during the month previous to baseline interview was found to be significantly associated with ***better score of physical functioning and vitality*** in the univariate analyses. We were not able to test if these associations were confounded by severity of IC symptoms in particular and age, co-morbidity and other study covariates in general because of the limitation of the small sample size, which restricted the number of covariates that we can adjust for.

A noteworthy association was that between ***ever using OC*** and the ***impairment in role-physical domain***. Although this association was marginally significant in the univariate analyses, once we adjusted for ICSI, age, co-morbidity and marital status it became highly significant. This finding supports the previous suggestion about the importance of considering a hormonal effect on IC. Given that the majority of IC patients are females and the clinical literature suggests a flare in IC symptoms during premenstrual period, [64, 147, 148] a direct influence of gonadal hormones and estrogen may be considered. It is possible that the increase of estrogen level among those patients who ever used OC increases their symptom severity which in turn impairs their role-physical functioning. Theoharides et al. showed that estradiol may influence

pathophysiological responses via bladder mast cells expressing high affinity estrogen receptors. [147] ***Clarifying this topic is important because the most notable application of that will be the use of hormone to selectively modulate pain sensation and improve quality of life. Reporting ever pregnant*** was found to be significantly associated with ***better mental health score*** in both univariate analyses and after adjusting for ICSI, age, co-morbidity. This can be explained by the importance of motherhood on the mentality of those patients. It also supports the significant impact that family relationships might play in improving the quality of life in IC patients.

Several previous studies in general population and/ or among obese participants reported a significant impact of BMI on HRQL. [215, 216] Our results correspond well to these previous findings. We observed a marginal significant negative correlation between ***BMI and general health domain***. This marginal association became highly significant after including ICSI, age, co-morbidity and marital status to the model. IC patients with greater BMI reported worse general health score compared to those with lower BMI. This finding supports the substantial independent effect of BMI on general health of IC patients and not on physical functioning, like one might expect. It is important to mention that BMI in the current study was based on self-reported heights and weights at week 18 of the study and not at the baseline. However, we didn't notice or record any extreme increase in weight in any of the study participants since baseline. Further studies with more accurate measures are required to confirm what we found.

The extent to which quality of life is consequence of disease severity in patients with IC is unclear. Very few studies attempted to investigate that. [17, 22] Our observations about the impact of severity of IC symptoms on the different domains of HRQL were semi-consistent with that of Rothrock et al. [22] Rothrock et al. reported that greater IC severity was associated with greater compromise in physical, social functioning and mental health but not in other quality of life

domains. Importantly, Rothrock et al. didn't adjust for age or co-morbidity or any other covariates. In the current study we demonstrated that severity of IC symptoms even associated with impairment in domains other than those noticed by Rothrock et al. After adjusting for age, co-morbidity and certain study covariates for each domain based on our results from the first aim, ***symptom severity was significantly associated with impairment not only in physical functioning and mental health domains but also in bodily pain and general health domains***. These findings suggest that severity of IC symptoms has profound impact on physical component of QOL more than on mental component of QOL. Ware et al. reported strong and significant correlations between each of the physical functioning, bodily pain and general health and the physical component summary of QOL. [177]

Most IC patients suffer from urgency and frequency in the early stages of the disease. As the disease progresses, pain increases in severity and becomes the most dominating and debilitating symptom. For many, the pain becomes so severe it significantly impacts their personal and professional life. We investigated which of the IC symptoms is associated with the impairment in physical component summary (**PCS**) and/or mental component summary (**MCS**) of QOL. In the univariate analyses, we reported negative significant correlations between each of IC symptoms (pain, urinary frequency, nocturia and urgency) and the PCS. On the other hand, a marginally significant negative correlation was observed between pain and MCS. Because we found significant correlations between pain and urgency and between frequency and nocturia we were unable to include any of these together in one model. Therefore, we tested if the significant associations between each of the IC symptoms and PCS were independent after adjusting for age, co-morbidity and marital status. ***Pain during voiding and nocturia were found to be significantly associated with impairment in the final models*** (adjusting for age, co-morbidity

and marital status). This coincident with Nickel et al. who studied predictors of PCS and MCS in a similar study population. [185] Nickel et al. found significant effect of pain on PCS but not MCS. They investigated the effect of frequency and urgency but not nocturia, and none of these impair either PCS or MCS. These results highlight the importance of managing pain and nocturia over frequency and urgency to improve physical component of IC patients' QOL.

5.3 CLINICAL TRIAL'S RESULTS (AIMS 4, 5, 6, 7, 8 AND 9)

The clinical trial part of the current study investigated for the first time ever in USA, if the intravesical use of pentosan polysulfate sodium (PPS) accompanied with oral PPS, the only approved oral therapy for IC by FDA, is better than using oral PPS only. Several outcomes were assessed and included the changes in O'Leary-Sant IC Symptom and Problem Index, PUF instrument, pain and urgency scales, frequency and nocturia from 24 hours voiding log, patient global assessment, sexual functioning domains and HRQL. Our findings demonstrated that using intravesical PPS simultaneously with oral PPS is an effective therapeutic option. In particular, ***females with IC who received a regimen of intravesical and oral PPS showed a twofold reduction in the severity of IC symptoms compared to those who received the oral regimen of PPS alone (p=0.04).*** Furthermore, at the end of the trial, ***remarkable significant improvements in all health related quality of life domains have been reported in the treatment group compared to their baseline self evaluation***.

Because of the biochemical nature of PPS (semi-synthetic sulfate polysaccharide) that chemically and structurally resembles glycosaminoglycan (GAG), the protective layer of the bladder, PPS is considered as a treatment option for IC. When GAG layer is damaged, it allows

many harmful solutes in the urine to leak across the transitional cells to initiate IC symptoms. [217] PPS is thought to augment the GAG layer of the bladder and repair deficiencies, and thus relieve symptoms. Its strong hydrophilic properties attract water molecules to bind tightly to its sulfated portion is thought to produce an insulator layer of water between the transitional cells and the urine in the bladder that can block highly charged compounds and reduce electrochemical interactions. [29] Because only 1-3% of oral PPS reaches the bladder, [34] the therapeutic efficacy of PPS should be greater when applied intravesically. Furthermore, using both intravesical and oral PPS simultaneously for a specific period of time followed by sustained use of oral PPS may empower the therapeutic effect of oral PPS and enhance the proliferation of the GAG layer, to produce greater relief and return to normal protective coating faster.

As we mentioned previously in chapter 2, only one small clinical trial attempted to test the efficacy of intravesical PPS in the Netherlands, 1997. [37] It was not applicable to make an extensive comparison between the results from our study and the results from the Netherlands' study because of the difference in the study design and the outcomes that were used in each study to assess the efficacy of intravesical PPS. In particular, our study used oral PPS plus intravesical placebo as a control compared to only placebo in the Netherlands' study. Furthermore, the main outcomes in the Netherlands' study were urodynamic capacity, cystometric volume and mean volume from a 24 hours voiding log. Our study in general was consistent with the Netherlands' study in that instilling intravesical PPS is an effective therapeutic option for IC patients. The Netherlands' study reported significant increase in the urodynamic capacity after 3 months among the treatment group. ($p=0.04$). We did not assess that, however we were able to report remarkable significant improvements in other several

outcomes among those who received both intravesical and oral PPS compared to those who received only oral PPS.

In terms of severity of IC symptoms, we used two well-known and validated instruments (O'Leary-Sant IC Symptom and Problem Index and PUF instrument) to measure the change in the severity of IC symptoms within each group and between the two groups at each study endpoint. [23, 24] Interestingly, we reported ***significant improvement in the severity of IC symptoms*** in both groups from baseline to each endpoint using both instruments. However, we only reported statistically significant differences in the improvement in the severity of IC symptoms between the two groups using O'Leary-Sant IC Symptom and Problem Index, but not the PUF instrument, at week 12 and marginally significant at week 18. It is worthy to mention that although both instruments were designed to identify IC cases, O'Leary-Sant instrument mainly measures the frequency and the problematic of the four symptoms of IC (voiding frequency, urgency, nocturia and pain mainly in the bladder). [23] On the other hand, PUF instrument not only measures the frequency and bothersomeness of the four IC symptoms, but also the sexual activity and the impact of IC symptoms on it. It also measures the frequency of any pain in the pelvis and not only in the bladder. [24] This may explain why we reported significant difference in the change of symptom severity using O'Leary-Sant but not PUF. Another explanation is related to the design of the O'Leary-Sant instrument; we noticed that our study participants completed O'Leary-Sant instrument without any problem compared to PUF. The way the questions were presented in the PUF instrument were somewhat confusing for some participants and need more explanation. It is important to conduct a study to measure the consistency between the two instruments and to correlate the objective measures of IC symptoms (cystoscopy and urodynamics) to the subjective measures from each of the two instruments. Our

findings of a significant difference between the two groups at week 12 but not week 6 suggests that using both intravesical PPS and oral PPS together for the first 6 weeks enhances the proliferation of the protective layer of the bladder, to produce greater relief and return to normal protective coating when maintained with oral PPS alone after that.

As we expected, ***pain was the only IC symptom that improved in both groups*** at each endpoint. Moreover, nocturia showed significant improvement in both groups only at week 18. A noteworthy ***significant improvement in urgency score*** was reported among treatment group, but not placebo group at each endpoint compared to the baseline. On the other hand, the same was reported about ***urinary frequency***, however, among the placebo group. The latter finding may surprise the reader. One suggested explanation for this unexpected result is that urine frequency can be a misleading symptom as it may affect by other uncontrolled factors. Patients tend to restrict their fluid intake during painful periods and increase their fluid intake when pain is relieved. [28] Furthermore, a decrease in urinary frequency was found to be accompanied by an increase in pain, likely due to higher concentration of irritating agents in the urine. [218] Therefore, it is expected that patients who experienced greater improvement in their pain as a result of the treatment will increase their fluid intake and thus will have an increase in their urinary frequency in comparison to those who experienced less improvement (placebo group). We failed to report any significant difference in the changes in individual IC symptoms as measured by pain assessment, urgency scale, urinary frequency, and/ or nocturia between the two groups at any endpoint. The multifactorial complex nature of IC condition and the wide variation of individual IC symptoms within and between patients suggest that the significant improvement in IC is the result of improvement in overall condition rather than in a specific symptom. Importantly, our study proved the superiority of the combination of intravesical and oral PPS over only oral PPS

using measurers that provide a cumulative picture of the disease such as the O'Leary-Sant IC Symptom and Problem Index. Sharp focusing on each symptom may dilute the expected effect that we were able to determine using measures that reflect the cumulative picture of IC. Another possible reason for not being able to report any significant differences between groups using individual IC symptoms measures could be lack of power because of our small sample size. More studies with larger sample size are required to clarify that.

In terms of proportion of responders (defined as participants who reported any level of improvement in their overall condition, urgency or urinary frequency after 18 weeks of the trial), ***significant differences were reported for responders in urgency and urinary frequency but not in overall condition between the two groups***. All participants in the treatment group reported improvement in either their urgency or urinary frequency at week18 of the trial compared to only 80% of the placebo group. Moreover, responders in the treatment group were significantly more likely to report "great level of improvement" in their overall condition compared to responders in the placebo group. These findings may be biased because of the unbalanced scale of level of improvement in the patient global assessment instrument that we used. We were forced to consider responders as those who reported any level of improvement because of the design of the patient global assessment. There was no "Slightly improved" option available for the question "how do you evaluate your level of improvement?" Therefore, those who evaluated their improvement as slightly will be obligated to consider themselves as improved moderately (50% improvement), which in turn will introduce miss classification bias to the moderate improvement level category in particular. It was expected that those who received both intravesical and oral PPS will experience moderate to great improvement (50%-75% improvement) while those who received only oral PPS will distributed between slightly improved and moderately improved

(25%-50% improvement). For that reason, we observed greater proportion of responders with moderate level of improvement among placebo group compared to treatment group and greater proportion of responders with great level of improvement among treatment group compared to the placebo group in all the three sections of patient global assessment. Another study with well balanced version of patient global assessment is required to confirm what we found.

Although IC has a severe impact on patient quality of life, very few trials which assessed the efficacy of oral PPS used HRQL as an outcome. Our study investigated the effect of a combination of intravesical and oral PPS on HRQL in IC patients comprehensively. We assessed that on both the two component summary scales to identify which of them will be improved (the physical or the mental component of QOL). We also assessed the effect of the trial intervention on each domain of HRQL to determine which domain in particular will get benefit from the trial intervention. Our findings demonstrated the importance of using HRQL as a sensitive measure of efficacy. At the end of the trial, the ***treatment group showed ~ 17.9% increase in PCS score*** and ***21.8% increase in MCS score compared to the baseline.*** Moreover, placebo group reported significant improvement in the PCS score but not MCS score compared to the baseline. Furthermore, the treatment group reported significantly more increase in MCS score from baseline to week 4 in comparison to the placebo group. The significant difference in the MCS which we observed between the two groups was confounded by the baseline score of the MCS. The treatment group reported significantly worse MCS score at baseline compared to the placebo group. Interestingly, once we adjusted for MCS baseline score, no significant difference was found between the two groups.

When we examined the effect of the trial treatment on each domain extensively, after week 18, ***the treatment group showed significantly greater improvement in all HROL domains***

compared to the baseline while the placebo group reported that in only three domains. Moreover, although the treatment group showed better score in each of the eight domains of the SF-36, marginally significant greater improvements were only reported in general health and mental health domains compared to the placebo. The ***marginal significant difference in mental health score*** remained even after adjusting for baseline score. These findings suggested that the combination of intravesical and oral PPS may improve mental health domain of the HRQL in IC patient better than using only oral PPS. Other study with larger sample size is needed to confirm what we found.

With regard to sexual functions, recent study by Nickel et al. [219] that included 128 IC patients who were treated with 300 mg/day oral PPS for 32 weeks reported statistically significant improvement in sexual function scores at weeks 8, 16, 24, and 32 of the study. The authors observed moderately positive significant correlation between reduction in symptom index score and sexual function score at the end of study ($r = -0.35$, $P = 0.0002$). The results from the current study did not support any superiority of using a combination of oral and intravesical PPS over using only oral PPS in improving sexual function. Although the present study reported marginal significant improvement in sexual desire at week 18 compared to the baseline among the treatment group, it failed to show significant differences between the two groups. This could be related to the small sample size that we have. Further studies with larger sample size and more comprehensive measures of sexual function are required to clarify this effect.

Our findings cannot be explained by other factors such as the use of concurrent medications as well as the compliance with oral PPS. Both groups showed comparable use of antihistamines, antispasmodics, antidepressants and analgesics during the entire study period (p

> 0.05). Furthermore, both groups administered more than 95% of the oral PPS during either the entire study period or the first, second or third six weeks of the trial. It is also unlikely that our results were biased as we adhered to the LOCF method to handle missing data. The same results were found when all the statistical analyses were performed with and without including the drop out subject in the treatment group or applying the LOCF method.

5.4 STRENGTHS AND LIMITATIONS

The current study had several strengths and limitations. The main strengths were: 1) The present study is the first among IC patients that comprehensively assessed the extent to which socio-demographic, reproductive, lifestyle, clinical history factors and sexual function domains affect both the severity of IC symptoms and the HRQL. 2) It is the first to examine the association between severity of IC symptom and HRQL extensively after adjusting for important covariates. 3) It is the first in USA to test the efficacy of intravesical PPS using a powerful study design (randomized double blind clinical trial). 4) The current study used several well-known standardized instruments to collect baseline data and data about the main clinical trial outcomes. 4) The intravesical instillation of PPS in the clinical trial part of the current study was done by the principal investigator or a well trained nurse which ensure both the validity and reliability of the data.

On the other hand, the major limitations of the present study were: 1) the cross-sectional nature of the measurement of socio-demographic and reproductive factors makes impossible to assess these measures as risk factors but as being related or not related to the severity of IC symptoms and/ or the impairment in HRQL. Therefore, the direction of causality was not be

inferred from our analyses. 2) The small sample size which may reduce the study power to detect significant associations between study main outcomes and different covariates. It also limited the regression analyses and the number of covariates to be included in multivariate models. 3) Study participants of the present study were generally highly educated, females and white, reflecting the demographic of the facility population. Therefore, the results may not be generalized to less educated patients, men with IC and those of different racial or ethnic groups. 4) The current study only included moderate to severe cases. Therefore, the results may not be generalized to mild cases, although one can argue that mild cases would not necessarily be bad enough to seek care or to show improvement results. 5) Using unbalanced version of patient global assessment to define responders may introduce misclassification bias to the results about the efficacy of intravesical and oral PPS on patient global assessment, although we tried to reduce that effect by defining our responders as those who reported any level of improvement. However, using this wide definition for the responders may prevent us from detecting significant differences between the responders in the two groups related to the improvement in the overall condition.

5.5 CONCLUSIONS AND FUTURE RESEARCHES

The findings from the current study will have significant implications on both IC research and well-being of IC patients. ***The cross-sectional part highlights the substantial impact of family relationships and social life on both the severity of IC symptoms and the quality of life in IC patients.*** Married patients who have permanent families and therefore more social activities reported less severity of IC symptoms and much better QOL compared to unmarried patients. Furthermore, being unemployed, obese, and never being pregnant associated with impaired

HRQL in at least one SF-36 subscale after adjusting for age, co-morbidity and the main study covariates. Moreover, severity of IC symptoms compromises mainly the physical component of HRQL rather than the mental component. ***After adjusting for age, co-morbidity and important study covariate, severity of IC symptoms was significantly impaired three domains of the physical component (physical functioning, bodily pain, general health) and only one domain of the mental component of the HRQL (mental health)***. Noteworthy, only pain and nocturia were the main IC symptoms that impair the physical component of HRQL in the patients. These findings have important public health significance because they emphasize on the substantial role of family relationship in improving patient severity of symptoms and quality of life. They also direct the health care providers to focus more on managing pain and nocturia, in particular, as urinary frequency and urgency can be controlled by patients through restricting their fluid intake. Improving pain and reducing nocturia will have a great impact on the physical functioning of IC patients and will improve their well-being.

On the other hand, the ***double blind placebo controlled trial part demonstrated the efficacy of the use of a multimodal therapy of intravesical and oral PPS for the treatment of moderate and severe IC cases***. The findings suggests that using both intravesical PPS and oral PPS together may enhance the proliferation of the protective layer of the bladder, to produce greater relief and return to normal protective coating when maintained with oral PPS alone. These findings of great public health evidence as they will open a new option for IC patients to reduce their severely devastating symptoms and to improve their quality of life and well-being.

The results from the two parts of the present study call for several future studies. It is very important to conduct a prospective study with larger sample size that include men and different racial ethnic groups with mild, moderate and severe IC condition to confirm what we

found from the cross-sectional part and to assess extensively the marginally significant associations that could be under power because of our small sample size. Because the current study showed significant association between menopausal status and the severity of IC symptoms, and a highly significant association between ever used OC and impairment in role-physical domain, it is crucial to assess the role of gonadotropin hormones as well as estrogen on the severity of IC symptoms among menopause and perimenopause in a large prospective study. It seems that estrogen has different roles on IC based on the menopausal status of the patient. The current study showed in the univariate analysis significant impact of sexual function on QOL. It will be of great interest to assess this association, however, in prospective study with larger and more representative study population. The next step after our randomized trial is to test the efficacy of intravesical PPS, however, compared to another intravesical option (such as heparin or DMSO).

APPENDIX A: INFORMED CONSENT

INFORMED CONSENT

STUDY DRUG: ELMIRON® (Pentosan Polysulfate Sodium)

PROTOCOL TITLE: Intravesical Elmiron® Administration(CAPSS-245)

SPONSOR-INVESTIGATOR: Edward L. Davis, M.D

TELEPHONE: (626) 914-3921 (24 hour number)

You are being asked if you want to take part in a research study of an investigational medication called pentosan polysulfate sodium (Elmiron®). The word investigational means this drug is being tested and is not approved in the United States by the U.S. Food and Drug Administration (FDA) for intravesical instillation in the treatment of interstitial cystitis(IC). Elmiron® has been approved by the Food and Drug Administration (FDA) for the oral use for the diagnosis of interstitial cystitis (IC).

Before agreeing to participate in this research study, it is important that you read and understand the following explanation of the proposed procedures. This statement describes the purpose, procedures, benefits, risks discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. No guarantees or assurances can be made as to the results of the study. If you are not completely truthful with your study doctor regarding your health history, you may harm yourself by participating in this study.

CONTACT INFORMATION

The study doctor or study staff will answer any questions you have about this research study or your participation in the study. You can ask questions about this research study or your participation in the study. Please call if you have any questions about the study or your experience in the study. Please call right away if you have an injury, illness or side effect.

Study doctor: Edward L. Davis, M.D. Telephone number: (626) 914-3921

This study was reviewed by Foothill Presbyterian Hospital (FPH) Institutional Review Board (IRB), and ethics committee that is independent of the doctor-sponsor. The purpose of the IRB is to protect the rights and safety of people who volunteer to take part in research studies. You may call if you have questions about your rights as a research participant or a complaint or concern about participating in this study.

FPH IRB is located at 220 South Grand Avenue, Glendora, CA 91741.

c/oMr. Larry Fetters, COO, (626)963-8411.

PURPOSE OF THE STUDY

The purpose of this study is to test the theory that the intravesical administration of pentosan polysulfate sodium, hereafter identified as Elmiron®, will accelerate the relief of the symptoms of interstitial cystitis (IC). This study is based on data collected from Citrus Valley Medical Research, Inc. This is a double blind, randomized, and placebo controlled study designed to assess the safety and efficacy of intravesical instillation of Elmiron®, in addition to

orally administered Elmiron®. A placebo contains no active ingredient. This combination of intravesical instillation and oral Elmiron® will be compared to oral administration of Elmiron® and the intravesical administration of placebo (sterile buffered normal saline) in the treatment of IC.

DESCRIPTION OF THE STUDY

You have been invited to participate in this study because you have been diagnosed with interstitial cystitis and are over the age of 18.

The symptoms of IC are characterized by suprapubic, pelvic, low back, inguinal, and flank pain, irritative voiding symptoms of frequency, urgency, urination at night and negative urine culture. The theory is that the cellular lining of the bladder (the glycosaminoglycan or GAG layer) is defective in IC patients, thus allowing caustic agents in the urine to irritate the bladder. Elmiron® is used orally to replace the GAG layer. Once this layer is replaced the bladder lining may be protected from the caustic effects in urine, and the symptoms of IC may be reduced or even disappear. However, one drawback to the oral treatment is the low amount of active drug reaching the bladder (1-3% of the oral dose is excreted into the urine) resulting in a long lag time before improvement is expected.

All patients who receive oral treatment with Elmiron® will receive bladder instillations. Twenty (20) subjects will receive Elmiron® through a catheter into the bladder, and twenty (20) subjects will receive placebo through a catheter into the bladder .

STUDY PROCEDURES

A total of forty (40) subjects, female, diagnosed with interstitial cystitis and previously untreated with Elmiron® will be randomized according to the study protocol and enter into this study. Twenty (20) subjects, randomized according to the study protocol, will receive intravesical instillation of Elmiron® and oral Elmiron®. Twenty (20) subjects, randomized according to the study protocol, will receive intravesical instillation of placebo (sterile buffered normal saline) and oral Elmiron®.

Patients, eighteen (18) years or older and diagnosed with interstitial cystitis within one year are eligible for inclusion in this study. A cystoscopic examination under anesthesia with hydrodistension and photo documentation will be performed within one (1) year of entry into this study. Bladder biopsies will be performed only if carcinoma is suspected. Eligible patients will have sterile urine culture-documented as per study protocol. Patients will require baseline symptom scores according to the study protocol.

The subjects who meet the inclusion and exclusion criteria for IC will follow this protocol: All forty (40) subjects will be administered Elmiron® 200mg orally, taken one (1) hour prior to meals or two (2) hours after meals, twice (2x) per day (a total of 400mg per day) for eighteen (18) weeks of the study. All forty (40) of the subjects will have intravesical instillations twice (2x) a week for six (6) weeks for a total of twelve (12) instillations.

Baseline (Screening visit – up to 30 days before first instillation visit)

The following tests and procedures will be completed at your first visit to determine if you qualify to participate:

- You will be asked to read and sign this informed consent if you wish to participate in this study
- Review your medical history
- A Physical examination (if one has not been done in the last 30 days)
- A clean-catch urine will be collected. Your urine will be tested to check the functioning of your kidneys and check for any urinary tract infection, pregnancy test (if applicable), for possible future biomarker study and hormonal levels.
- A blood sample will be collected (approximately two (2) tablespoons) to assess complete blood count, kidney function, liver function, future biomarker study and hormonal levels.
- You should inform the study doctor of all medications that you use, this includes medication prescribed by a doctor or any medication you buy over the counter without a prescription.
- You will be asked to complete questionnaires that relate to your pain and bladder symptoms (urgency, frequency), health related quality of life, and sexual function.
- If you have not previously been examined by a urologist you may have one (1) or two (2) extra tests: an ultrasound to measure how much urine is in your bladder after you have been to the bathroom and/or a test where you pass urine into a machine that measures the flow, and/or a test to measure how much urine your bladder will hold.

If the study doctor determines that you are eligible for this study you will be scheduled to return to this office to begin intravesical (bladder) instillations. You will be given a voiding log to keep track of the number of times you urinate within a 24 hour period before returning to this office for your first bladder instillation visit.

INSTILLATION WEEKS

A total of Six (6) weeks x 2 Bladder Instillations per week = 12 Visits The following tests and procedures will be completed at each instillation visit. If you qualify to continue you will be asked to return to this office two times (2x) per week for instillation of the study medication.

If you continue to qualify to participate you will be randomly assigned by chance (like the toss of a coin) to receive as part of your instillation Elmiron® or placebo (inactive ingredient). This study is double-blind which means that neither you nor the study doctor will know which study treatment you are receiving. However, this information will be available in case of emergency.

- You should inform the study doctor of all medications that you use, this includes medication prescribed by a doctor or any medication you buy over the counter without a prescription
- At weeks one (1) through six (6) (visit one (1) and visit two (2) each week), before each intravesical instillation a clean-catch urine will be collected. Your urine will be tested to check the functioning of your kidneys and check for any urinary tract infection, at visit one (1) of each week your urine will be sent to a laboratory for a urine culture and

sensitivity test, which will document the absence or presence of any bacteria in your urine.

- You will be asked to complete questionnaires that relate to your pain and bladder symptoms (urgency, frequency), health related quality of life, and sexual function.
- The study doctor will ask you questions about your health.
- You will have a bladder instillation that includes the following.
    1. A self-lubricating catheter of the LoFric® brand will be inserted into your bladder. This is a small diameter tube that is inserted into the opening you usually urinate from.
    2. Any urine that is present will be removed through the catheter.
    3. All forty (40) subjects will be administered, as part of the instillation procedure, at each visit, a topical application of Lidocaine Hydrochloride Jelly USP 2%, to the perineal area and to the tip of the catheter. The reason for the lidocaine jelly is to prevent perineal sensitivity and to prevent urethral spasms.
    4. All subjects will be administered as part of the instillation procedure at each visit intravesical instillation of 8ml of 1% lidocaine and 3ml of 8.4% sodium bicarbonate, before intravesical instillation of Elimiron® or placebo (sterile buffered normal saline). The 1% lidocaine is a short acting and topical anesthetic. The purpose for the instillation of 8ml of 1% lidocaine as part of the instillation procedure, is to provide a topical and short acting anesthetic to the bladder membrane. This topical and short acting anesthetic will prevent bladder and urethral spasms and the possible uncontrolled expulsion of the study medication or placebo from the bladder. The duration of the anesthetic effect of 1% lidocaine

is sixty (60) to ninety (90) minutes. The instillation of 3ml of 8.4% sodium bicarbonate as part of the instillation procedure, is to prepare the bladder membrane for the absorption of the 1% lidocaine by alkalizes the acids in any residual urine.

5. You will then be administered ELMIRON® or placebo. This instillation should be retained in the bladder for a minimum of thirty (30) minutes and a maximum of sixty (60) minutes.
6. A blood sample will be collected (approximately two (2) tablespoons) to assess blood coagulation (clotting) time and future biomarker study . The blood sample will be collected one (1) hour after the bladder instillation.
7. You can leave the study center in one (1) hour after you have voided and a blood sample has been collected If you are unable to void at the required time, catheterization will be performed to remove the solution from your bladder.

- You will be given a voiding log at visit two (2) each instillation week to record your voiding pattern a 24 hour period of your choice before returning to this office for visit one (1) of the next instillation week.

If you develop a urinary tract infection during this study, an appropriate antibiotic will be prescribed.

FOLLOW-UP VISITS

You will return to this office for two (2) visits following your last study instillation. For the week (twelve) 12 visit (will occur six weeks after you have finished your last study instillation) the following assessments will be done.

- You should inform the study doctor of all medications that you use, this includes medication prescribed by a doctor or any medication you buy over the counter without a prescription.
- You will have these tests performed: a test where you pass urine into a machine that measures the flow and an ultrasound to measure how much urine is in your bladder after your flow has been measured by a machine.
- A clean-catch urine specimen will be collected. Your urine will be tested to check the functioning of your kidneys and check for any urinary tract infection, and for possible future biomarker study.
- A blood sample will be collected **(**approximately two (2) tablespoons) to assess blood coagulation (clotting) time, and future biomarker study.
- You will be asked to complete questionnaires that relate to your pain and bladder symptoms (urgency, frequency), health related quality of life, and sexual function.
- The study doctor will ask you questions about your health.
- You will be given a voiding log to keep track of the number of times you urinate within a 24 hour period before returning to this office for visit week eighteen (18) in six (6) weeks.

For the week eighteen (18) follow-up visit the following assessments will be done

- You should inform the study doctor of all medications that you use, this includes medication prescribed by a doctor or any medication you buy over the counter without a prescription.
- A physical examination will be performed
- You will have these tests performed: a test where you pass urine into a machine (Uroflow) that measures the flow, and an ultrasound to measure how much urine is in your bladder after your flow has been measured by a machine.
- A clean-catch urine specimen will be collected. Your urine will be tested to check the functioning of your kidneys and check for any urinary tract infection, and a pregnancy test (if applicable).
- You will be asked to complete questionnaires that relate to your pain and bladder symptoms (urgency, frequency), health related quality of life, and sexual function.
- The study doctor will ask you questions about your health.
- This will be your last study visit.

Some of these procedures might be done as part of your standard of care even if you do not take part in the research study. The study doctor or a member of the study staff can answer any questions you may have about the procedures that are not part of your standard of care.

See the Flow Chart on the next page that further outlines the visit procedures.

Your Responsibilities

If you decide to be in this study, you will have to:

- Keep all scheduled appointments
- Complete the voiding logs as instructed.
- Tell your study doctor about any other medicines that you take, even if it is medicine you buy without a prescription.
- Tell your study doctor about any medical problems that you have.
- Avoid becoming pregnant while on the study and for 30 days after you leave the study by using an effective method of birth control.

If you do not follow the items listed above, you may be removed from the study.

Study Flow Chart*

	Baseline Screening	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Follow-up Wk12 Wk 18	
Visits		V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	Wk 12	Wk 18
Informed Consent	X														
Medical History	X														
Physical Examination	X														X
Cystoscopy/ Hydrodistentiom	X														
Uroflow	X													X	X
Cystometrogram	X														
Ultrasound to measure Post Void Residual	X													X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Culture & Sensitivity	X	X		X		X		X		X		X		X	X
Complete Blood Count	X													X	
BUN,Serum Creatinine Electrolytes	X													X	
Pregnancy Test (if applicable)	X														X
HepaticPanel, APTT, Platelet count, Prothrombin time	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine/Blood Biomarker, Hormone level	X													X	
Quality of Life Questionnaire (SF-36)	X							X							X
Voiding Log	X		X		X		X		X		X		X	X	
Pain Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Parson's Patient Symptom Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
O'Leary –Sant Symptom/Problem Index	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sexual Function Assessment	X							X				X		X	X
Patient Global Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Elmiron/Placebo Instillation		X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* All assessments must be done within time frame allowed in protocol;

OTHER TREATMENTS

Participation in this study is not a substitute for your usual ongoing medical care by your regular doctor or specialist. You do not have to participate in this study to receive treatment for your condition. There may be other ways to treat your condition. Your study doctor can tell you more about these other treatments and their side effects.

You are strongly encouraged to ask the study doctor about the results of your lab tests and other diagnostic procedures. At your request you will be provided with copies of the results to review with your regular doctor or specialist.

BENEFITS

If you are in this study, you will get medical examinations and laboratory tests at no extra cost to you. You will not have to pay for the medicine. Your Interstitial Cystitis might improve, but there is no guarantee.

RISKS

You will have blood taken from one of your veins. The risks of having blood taken from your vein include pain, bruising, or infection at the site where blood was taken, and fainting.

There will be twelve (12) bladder instillations. Blood samples will be taken (1) hour after each bladder instillation. These blood samples are to assess complete blood count, kidney function, liver function, and blood coagulation (clotting) time.

Elmiron® taken orally can cause some side effects. They include: a weak anticoagulant effect (this effect may increase bleeding times, possibility of rectal bleeding and blood in your urine), nausea, diarrhea, liver function abnormalities, and mild hair loss. These are all possible side effects of this medicine. You may or may not have any of these side effects. A severe allergic reaction could be life-threatening. If researchers learn important new information that could change your decision to continue to take part in this study, your study doctor will tell you in a timely manner.

You may experience discomforts associated with catheterization. These include burning when passing urine, blood-tinged urine or urinary frequency following the procedure.

The cystometrogram which evaluates bladder capacity and urination rate, involves filling the bladder with liquid and measuring the bladder's response. Catheterization is done for this procedure. You may experience discomfort and a feeling of fullness. There is also a risk of infection and a small amount of bleeding.

As a part of this study you may be randomized to receive placebo(an instillation without study medication). In this case your symptoms may not improve or may get worse.

In rare cases the use of local anesthesia (topical lidocaine) may cause and allergic reaction, difficulty in breathing, low blood pressure, seizures or death.

The other risk is that Elmiron® might not work for you.

PREGNANCY

This study may involve unknown risks to a pregnant woman, embryo or fetus. Therefore if you are pregnant or breast feeding you may not participate in this study.

Subjects of child-bearing potential must test negative for pregnancy prior to randomization or provide documentation for having undergone the following: hysterectomy or tubal ligation. Patients who are physiologically capable of becoming pregnant must be on reliable birth control while participating in this study and must remain on reliable birth control while in the study.

Reliable birth control would be intrauterine device (IUD), birth control pills of combination type, hormonal implants, injectable contraceptives, surgical sterilization or double barrier method. Please discuss this with your study doctor.

If a subject or a female partner of a randomized subject becomes pregnant during the course of this study, the subject will inform the Principal Investigator within one (1) working day of learning of the pregnancy.

UNFORSEEN RISKS

There may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening.

ALTERNATIVE THERAPIES

You do not have to participate in this study to receive treatment for your condition. You may decide to receive no treatment for your disease or other approved therapeutic treatments. Your study doctor will discuss with you the risks and benefits of other treatments.

NEW FINDINGS

Any new findings, which may affect your safety or your willingness to continue in the study, that become available during your participation in the study will be given to you in a timely manner.

COSTS

All study subjects will receive oral Elmiron® at no cost. The Elmiron® or placebo for instillation will be supplied at no cost. Blood and urine that is collected for possible future biomarker study will be done at no cost.

The tests (culture and sensitivity, routine blood analysis, bladder scan, uroflow, and cystometrogram) and clinic visits are considered standard of care and will be billed to your insurance company.

If you develop a documented urinary tract infection during the study and an antibiotic is prescribed the sponsor will reimburse the costs of the antibiotic.

You will still be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications, that your study doctor or regular doctor requires during this study, as part of your usual medical care. If you have any questions, please ask the study doctor or a member of the study staff.

VOLUNTARY PARTICIPATION

Your decision to take part in the research study is voluntary at all times. If you decide not to participate in the study, or if you decide to withdraw from the study before it is complete, your routine medical care at this site will not be affected in any way. There will be no penalty to you, and you will not lose any benefits that you are entitled to that are unrelated to the research study.

You may decide to leave the study at any time. Your study doctor may also decide to remove you from the study if you fail to follow instructions, for medical reasons, or for other reasons. There is also the possibility that the study could be stopped before your participation is complete. If you leave the study for any reason please notify the study doctor or a member of the study staff. You will be asked to return to the study doctor to complete the final study activities.

COMPENSATION FOR PARTICIPATION

You will not receive any monetary compensation for participating in this study.

CONFIDENTIALITY

Records of your participation in this study will remain confidential to the extent allowed by law. No material which could personally identify you will be used in any reports on this study.

Permission to Release Personal Health Information

This section explains how personal health information collected about you for the study may be used. Your personal health information includes, but is not limited to, information that was collected for your entry into the study and information that is collected during the study. The purpose of collecting this information is to allow the study staff and the study doctor to conduct the study, to evaluate the study:

Intravesical ELMIRON administration – CAPSS-245, and to analyze the study results.

You may decide not to give permission for the release of your personal health information for the study. In that case, you will not be able to participate in the study. This is because the study staff and/or the study doctor would not be able to collect the information needed to evaluate the study: Intravesical ELMIRON administration - CAPSS-245

The information the study doctor sends to Ortho-McNeil Pharmaceutical, Inc. (hereinafter OMP)) does not include your name, address, or social security number. Instead, the study doctor will use your initials and assign a code number to the information that is sent to OMP.

The study doctor may disclose your personal health information to the Institutional Review Board (IRB) and to OMP, including people who work with OMP. The people who work with OMP may include data monitoring committees, contract research organizations, and consultants who have contracts with the company to do the study and review the study results.

Your study records and also your entire medical record may be inspected at the study doctor's office by OMP and/or people who work with OMP and by regulatory authorities in the United States, such as the Food and Drug Administration (FDA), or regulatory agencies from other countries. These reviews are done to check on the quality of the study.

The results of the study may be published in a medical book or journal, or presented at meetings for educational purposes. Neither your name, nor any other personal health information that specifically identifies you, will be used in those materials or presentations.

You may ask the study doctor to see and copy your personal health information related to the study. You may also ask the study doctor to correct any study related information about you that is wrong. You may have to wait until the end of the study to see your study records, so that the study can be organized properly.

This permission to share your personal health information for this study does not have an expiration date. If you no longer want to share your personal health information, you may cancel your permission at any time by writing to the study staff and/or the study doctor at the address below:

Edward L. Davis, M.D.

C/O Citrus Valley Medical Research, Inc.

412 West Carroll Glendora, CA 91741

If you cancel your permission after you have started in the study, the study staff and the study doctor will stop collecting your personal health information. Although they will stop collecting new information about you, they will need to use the information they have already collected to evaluate the study results. If you start the study and then cancel your permission, you will not be able to continue to participate in the study. This is because the study staff and/or the study doctor would not be able to collect the information needed to evaluate the study drug..

Ortho-McNeil Pharmaceutical, Inc. will make every effort to keep your personal health information private. But after the study staff or the study doctor share your personal health information from the study, federal privacy laws may not keep it private. There might be laws in your state or other federal laws that would protect the privacy of this information.

STUDY FUNDING

Ortho-McNeil Pharmaceutical is paying your study doctor and/or your study doctor's institution to conduct this study. The amount of this payment is sufficient to cover the study doctor's and/or institution's expenses to perform the study, but provides no personal financial benefit to your study doctor and/or his institution.

CONSENT STATEMENT

- ✓ I voluntarily agree to participate in this study.

- ✓ I understand that the study may be stopped at any time. If this happens I will no longer receive the study medication and planned evaluations.

- ✓ I have read and understand the information describing this medical research study in this information and consent form

- ✓ I authorize the release of my medical records related to this study, including my signed consent form.

- ✓ I understand that I will receive a singed and dated copy of this consent form.

- ✓ I understand that I may withdraw my consent at any time.

- ✓ I have had a chance to ask questions and understand the answers given to all my questions.

- ✓ I have read and received a copy of the California Experimental Subjects Bill of Rights which is attached to this consent form.

✓ I have read and understand the pregnancy waiver included in this consent form

---

_____

Printed Name of Participant

_____ _____

Signature of Participant **Date**

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent **Date**

APPENDIX B: O'LERAY-SANT IC SYMPTOM AND PROBLEM INDEX

Interstitial Cystitis (I.C) Symptom and Problem Questionnaire (Treatment)

Subject number_____

Subject Initials_____

Date Completed_____

IC Symptom index

Since your last visit:

Q1. How often have you felt the strong need to urinate with little or no warning?

0. __ Not at all
1. __ Less than 1 time in 5
2. __ Less than half the time
3. __ About half the time
4. __ More than half the time
5. __ Almost always

Q2. Have you had to urinate less than 2 hours after you finished urinating?

0. __ Not at all
1. __ Less than 1 time in 5
2. __ Less than half the time
3. __ About half the time
4. __ More than half the time
5. __ Almost always

Q3. How often did you most typically get up at night to urinate?

0. __ None
1. __ Once
2. __ 2 times
3. __ 3 times
4. __ 4 times
5. __ 5 or more times

Q4. Have you experienced pain or burning in your bladder?

0. __ Not at all
2. __ A few times
3. __ Almost always
4. __ Fairly often
5. __ Usually

Add the numerical values of the checked entries; total score: _____ .

IC Problem Index

Since your last visit how much has each of the following been a Problem for you?

Q1. Frequent urination during the day?

0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Q2. Getting up at night to urinate?

0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Q3. Need to urinate with little warning?

0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Q4. Burning, pain, discomfort, or pressure in your bladder?

0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Add the numerical values of the checked entries; total score: _____ .

APPENDIX C: PELVIC PAIN AND URGENCY/ FREQUENCY (PUF) QUESTIONNAIRE

Patient Symptom Scale Assessment Questionnaire

Subject number_____

Subject Initials_____

Date Completed_____

For each question below, please circle the answer that best describes how you feel.

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you void during the waking hours?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you void at night?	0	1	2	3	4+		
	b. If you get up at night to void, to what extent does it usually bother you?	None	Mild	Moderate	Severe			
3	Are you currently sexually active. YES ____ NO____							
4	a. IF YOU ARE SEXUALLY ACTIVE, do you now or have you ever had pain or urgency to urinate during or after sexual intercourse?	Never	Occasionally	Usually	Always			
	b. Has pain or urgency ever made you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6	Do you still have urgency shortly after urinating?	Never	Occasionally	Usually	Always			
7	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. How often does your pain bother you?	Never	Occasionally	Usually	Always			
8	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. How often does your urgency bother you?	Never	Occasionally	Usually	Always			

SYMPTOM SCORE (1, 2a, 4a, 5, 6, 7a, 8a)	
BOTHER SCORE (2b, 4b, 7b, 8b)	
TOTAL SCORE (Symptom Score + Bother Score) =	

APPENDIX D: PAIN ASSESSMENT

Pain Assessment

Subject number_____

Subject Initials_____

Date Completed_____

Please assign a number based on the scale below as to how you feel.

Level 1: I feel no symptoms of IC. I can do anything.

Level 2: I feel slight discomfort, possibly the beginning of a flare. But it doesn't stop me from my life. I can drive, work, shop etc.

Level 3: I feel mild symptoms of IC. I can still do anything, but I'll be looking for restrooms more frequently.

Level 4: I feel moderate symptoms of IC. I have a moderate need to urinate, moderate level of pain. It's starting to limit my activities, and I make the decision to head home and rest. Driving and sitting is uncomfortable.

Level 5: I'm hurting now, biting my lip and/or holding my abdomen. At this point, I am more comfortable laying in bed now with a heating pad. Walking is more painful now as my IC throbs. It has stopped me for the moment from doing my daily functions; I am utilizing my pain management tool kit fully at this point.

Level 6: I have constant gnawing deep severe pelvic pain, constant feeling to urinate, and body fatigue. I'm using all of my pain strategies here: self-help, medication, relaxation, and tens.

Level 7: I'm in bed in severe pain. I'm using all of my pain tool kit, but I may need help at this point. I'm considering calling my doctor or going to the emergency room.

Level 8: I need help. The pain isn't responding to my strategies. I am calling my medical care provider and/or on the way to the emergency room.

Level 9-10: I'm in the hospital.

Pain # for this visit_____

APPENDIX E: VOIDING LOG

DATE_____SUBJECT INITIALS_____RANDOM #_____

Subject Voiding Log

Please record each time you urinate for a 24 hour period. Your 24 hour Time period will begin when you wake up and will continue until the same time the next day. (Example if you wake up at 8:00 a.m. on the day you should start your voiding log you would end at 8:00 a.m. the next day) Place a star next to the times you record that are when you wake up in the middle of your sleep period to urinate. You will also record a pain number that reflects your pain level at the time of urination based on pain scale attached. You will also assign a *urgency score for each urination based on the 1-5 scale at the bottom of this page.

Time of Void	Pain	Urgency	Time of Void	Pain	Urgency	Time of Void	Pain	Urgency
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		
:			:			:		

*Please assess each urination you record and assign a "Urgency score" to be placed in the "urgency" column of the above table based on the following:

Score Definition

1. No Urgency, I felt I had no need to empty my bladder, but did so for other reasons

2. Mild Urgency, I could wait to void as long as necessary without fear of wetting myself.

3. Moderate Urgency, I could wait to void for a short time without fear of wetting myself.

4. Severe Urgency, I could not wait to void – I had to rush to the restroom/toilet in order not to wet myself.

5. Urge Incontinence, I leaked either a small or large amount before reaching the restroom/toilet.

APPENDIX F: PATIENT GLOBAL ASSESSMENT

Subject Initials_____ Subject #_____

Date of Visit_____

Labs Reviewed? Yes No

Any clinically significant finding by P.I.? Yes No

(If yes, P.I. to explain below reason for continuing or termination)

_____
_____
_____
_____
_____

Patient Global Assessment:

1. Evaluate ***the overall change in your condition*** since your enrollment in the study that you believe is due to the study:

A. Worse B. No change C. Improved

If overall condition improved indicate change as:

A. Moderately B. Greatly C. Completely (no symptoms)

2. Evaluate any change in ***urgency*** since your enrollment in the study:

A. Worse B. No change C. Improved

If urgency improved indicate change as:

A. Moderately B. Greatly C. Completely (no symptoms)

3. Evaluate any change in ***frequency*** since your enrollment in the study:

A. Worse B. No change C. Improved

If frequency improved indicate change as:

A. Moderately B. Greatly C. Completely (no symptoms)

4. Evaluate nocturia. How many times are you up at night to void? _____

5. Evaluate oral medication (Elmiron) taking on schedule? Any problems?

6. Adverse event reviewed? Yes No
7. Con-meds reviewed? Yes No
8. Inclusion, exclusion reviewed? Yes No
9. Pain reviewed? Yes No

Subject completed study per protocol? Yes No

Overall assessment of health status:

_____
_____
_____

APPENDIX G: MEDICAL OUTCOME STUDY SHORT FORM-36 (SF-36)

The SF-36 Health Survey

Subject number_____

Subject Initials_____

Date Completed_____

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

For each question you will be asked to fill in a bubble in each line:

1. How strongly do you agree or disagree with each of the following statements?

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

Your Health in General

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. **Compared to one year ago**, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

Please turn the page and continue.

The SF-36 Health Survey

3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, Limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c) Lifting or carrying groceries	○	○	○
d) Climbing **several** flights of stairs	○	○	○
e) Climbing **one** flight of stairs	○	○	○
f) Bending, kneeling, or stooping	○	○	○
g) Walking **more than a mile**	○	○	○
h) Walking **several blocks**	○	○	○
i) Walking **one block**	○	○	○
j) Bathing or dressing yourself	○	○	○

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	○	○
b) **Accomplished less** than you would like	○	○
c) Were limited in the **kind** of work or other activities	○	○
d) Had **difficulty** performing the work or other activities (for example, it took extra time)	○	○

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	○	○
b) **Accomplished less** than you would like	○	○
c) Didn't do work or other activities as **carefully** as usual	○	○

Please turn the page to continue.

The SF-36 Health Survey

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. How much bodily pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
○	○	○	○	○	○

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) did you feel full of pep?	○	○	○	○	○	○
b) have you been a very nervous person?	○	○	○	○	○	○
c) have you felt so down in the dumps nothing could cheer you up?	○	○	○	○	○	○
d) have you felt calm and peaceful?	○	○	○	○	○	○
e) did you have a lot of energy?	○	○	○	○	○	○
f) have you felt downhearted and blue?	○	○	○	○	○	○
g) did you feel worn out?	○	○	○	○	○	○
h) have you been a happy person?	○	○	○	○	○	○
i) did you feel tired?	○	○	○	○	○	○

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	○	○	○	○	○
b) I am as healthy as anybody I know	○	○	○	○	○
c) I expect my health to get worse	○	○	○	○	○
d) My health is excellent	○	○	○	○	○

***THANK YOU* FOR COMPLETING THIS QUESTIONNAIRE!**

APPENDIX H: SEXUAL FUNCTION ASSESSMENT

Date Completed:

Day Month Year

Subject number_____

Subject Initials_____

SEXUAL FUNCTION ASSESSMENT

Sexual Desire

This scale consists of a line that is 10 cm in length and the line is anchored by two extremes of **sexual desire**. The extremes are "none" and "high". Please put a vertical stroke on the line that best represents how much sexual desire you have felt during the past month.

1. The Visual Analog Scale (VAS 0-10 cm)

None ——————————————— High

Sexual Arousal

This scale consists of a line that is 10 cm in length and the line is anchored by two extremes of **sexual arousal**. The extremes are "none" and "high". Please put a vertical stroke on the line that best represents how much sexual arousal you have felt during the past month.

2. The Visual Analog Scale (VAS 0-10 cm)

None ——————————————— High

3. During the past month, have you had sexual intercourse? 1 ☐ Yes 2☐ No

If Yes, how frequently have you experienced painful intercourse? Please check (✓) the statement that best describes your experience. Please select only one.

0☐ Not at all

1☐ Sometimes, less than 25% of the time

2☐ Sometimes, about 50% of the time

3☐ Usually, about 75% of the time

4☐ Always

APPENDIX I: STUDY FLOW CHART

Study Flow Chart*

Visits	Baseline Screening	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Follow-up Wk12 Wk 18	
		V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	Wk 12	Wk 18
Informed Consent	X														
Medical History	X														
Physical Examination	X														X
Cystoscopy/ Hydrodistentiom	X														
Uroflow	X													X	X
Cystometrogram	X														
Ultrasound to measure Post Void Residual	X													X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Culture & Sensitivity	X	X		X		X		X		X		X		X	X
Complete Blood Count	X													X	
BUN,Serum Creatinine Electrolytes	X													X	
Pregnancy Test (if applicable)	X														X
HepaticPanel, APTT, Platelet count, Prothrombin time	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine/Blood Biomarker, Hormone level	X													X	
Quality of Life Questionnaire (SF-36)	X							X							X
Voiding Log	X		X		X		X		X		X		X	X	
Pain Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Parson's Patient Symptom Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
O'Leary –Sant Symptom/Problem Index	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sexual Function Assessment	X							X				X		X	X
Patient Global Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Elmiron/Placebo Instillation		X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* All assessments must be done within time frame allowed in protocol;

APPENDIX J: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology

APPENDIX K: IRB APPROVAL

University of Pittsburgh
Institutional Review Board

Exempt and Expedited Reviews

University of Pittsburgh FWA: 00006790
University of Pittsburgh Medical Center: FWA 00006735
Children's Hospital of Pittsburgh: FWA 00000600

3500 Fifth Avenue
Suite 100
Pittsburgh, PA 15213
Phone: 412.383.1480
Fax: 412.383.1508

TO: Samar El Khoudary

FROM: Christopher M. Ryan, Ph.D., Vice Chair

DATE: October 12, 2006

PROJECT: Effect of Intravesical Installation of Pentosan Polysulfate Sodium on the Quality of Life of Interstitial Cystitis Patients: A Double Blind Randomized Placebo Controlled Clinical Trial

IRB Number: 0609086

The above-referenced protocol has been reviewed by the University of Pittsburgh Institutional Review Board. Based on the information provided to the IRB, this project includes no involvement of human subjects, according to the federal regulations [§46.102(f)]. That is, the investigator conducting research will not obtain data through intervention or interaction with the individual, or will not obtain identifiable private information. Should that situation change, the investigator must notify the IRB immediately.

Given this determination, you may now begin your project.

CR:kh

BIBLIOGRAPHY

1. Hanno PM, Levin RM, Monson FC, et al. Diagnosis of interstitial cystitis. *J Urol*.1990;143(2):278-81.

2. Held PJ, Hanno PM, Wein AJ, Pauly MV, Cann MA. Epidemiology of interstitial Cystitis 2. In: Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds. *Interstitial Cystitis*. New York: Springer-Verlag;1990:29-48.

3. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. *Female Urology*. 1999;161(2):549-52.

4. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. *J Urol*. 2005;174(6):2231-4.

5. Leppilahti M, Sairanen J, Tammela TLJ, Aaltomaa S, Lethtoranta K, Auvinen A. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finaland. *J Urol*. 2005;174(2):581-3.

6. Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in health screening project. *European Urology*. 2006, doi:10.1016/j.euro.2006.08.028.

7. Oravisto KJ. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn*. 1975; 64(2):75-7.

8. Forrest JB, Vo Q. Observations on the presentation, diagnosis, and treatment of interstitial cystitis in men. *Urology*. 2001;57(6 Suppl 1):26-9.

9. Nigro DA, Wein AJ, Foy M, et al. Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. *Urology*. 1997;49(5A Suppl): 86–92.

10. NIDDK National Kidney and Urology Diseases Information clearinghouse. Interstitial cystitis. Available at: http://www.niddk.nih.gov/health/urolog/pubs/cystitis/cystitis.htm. Accessed October 10, 2006.

11. Jones CA, Harris M, Nyberg L. Prevalence of interstitial cystitis in the United States (abst 781). Presentation at the American urologic association annual meeting, May 1994, San Francisco, CA. *J Urol*. 1994;151:423A.

12. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. *J Urol*. 2005;173(1):98-102.

13. Forrest JB. Epidemiology and quality of life. *J Reprod Med*. 2006;51(3 Suppl):227-33.

14. Ratner V, Slade D, Greene G. Interstitial cystitis: a patient's perspective. *Urol Clin North Am*. 1994;21(1):1-5.

15. Webster DC, Brennan T. Use and effectiveness of psychological self care strategies for interstitial cystitis. *Health Care Women Int*. 1995;16(5):463-75.

16. Ratner V, Slade D. Interstitail cystitis: A women's health perspective. In: Sant GR, eds. *Interstitial Cystitis*. Philadelphia: Lippincott-Raven; 1997:257-60.

17. Simon LJ, Landis JR, Erickson DR, Nyberg LM, and the ICDB Study group. The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. *Urology*. 1997;49(5A Suppl): 64-75.

18. Koziol JA, Clark, DC, Gittes RF, Tan EM. The natural history of interstitial cystitis: a survey of 374 patients. *J Urol*. 1993;149(3):465–9.

19. Henderson LJ. Diagnosis, treatment, and lifestyle changes of interstitial cystitis. *AORN J*. 2000;71(3):525-38.

20. Koziol JA. Epidemiology of interstitial cystitis. *Urol Clin North Am*. 1994;21(1):7-20.

21. Michael YL, Kawachi I, Stampfer MJ, Colditz GA, Curhan GC. Quality of life among women with interstitial cystitis. *J Urol*. 2000;164(2):423-7.

22. Rothrock NE, Lutgendorf SK, Hoffman A, Kreder KJ. Depressive symptoms and quality of life in patients with interstitial cystitis. *J Urol*. 2002;167(4):1763-7.

23. O'Leary MP, Sant GR, Fowler FJ JR, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology*. 1997;49(5A Suppl):58-63.

24. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases using a new symptom questionnaire and intravesical potassium sensitivity. *Urology*. 2002;60(4):573-8.

25. Rovner E, Propert KJ, Brensinger C, et al. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. *Urology*. 2000;56(6):940-5.

26. Parsons CL. Bladder surface glycosaminoglycans: efficient mechanism of environmental adaption. *Urology*. 1986;27(2 Suppl):9-14.

27. Hom-Bentzen M, Jacobsen F, Nerstrøm B, et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. *J Urol*. 1987;138(3):503-7.

28. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. *Urology*. 1990; 35(6):552-8.

29. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate sodium. *J Urol*. 1987;138(3):513-6.

30. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. *J Urol*. 1993; 150(3):845-8.

31. Waters MG, Suleskey JF, Finkelstein LJ, Van Overbeke ME, Zizza VJ, Stommel M. Interstitial cystitis: a retrospective analysis of treatment with pentosan polysulfate and follow-up patient survey. *J Am Osteopath Assoc*. 2000;100(3 Suppl):S13-8.

32. Sant GR, Propert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol*. 2003;170(3):810-5.

33. Nickel JC, Barkin J, Forrest J, et al. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology*. 2005;65(4):654-8.

34. Ortho-McNeil Pharmaceutical I. Elmiron® 100 mg (pentosan polysulfate sodium) capsules. Available at: http://www.orthoelmiron.com. Accessed November 5, 2006.

35. La Rock DR, Sant GR. Intravesical Therapies for Interstitial cystitis. In: Sant GR, ed. *Interstitial Cystitis*. Philadelphia: Lippincott-Raven; 1997: 247-255.

36. Parsons CL. Interstitial Cystitis: epidemiology and clinical presentation. *Clin Obstet Gynecol*. 2002;45(1):242-9.

37. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosan polysulphate for the treatment of interstitial cystitis. *Br J Urol*. 1997 ;79(2):168-71.

38. Davis EL, Davis J, Regan L, Talbott EO, Zborowski JV. A prospective evaluation of intravesical instillation of pentosan polysulfate sodium (PPS; Elmiron®, [Ortho-McNeil] in patients with interstitial cystitis: the association of clinical outcomes and symptom triad. Research insights into interstitial cystitis: a basic and clinical science symposium, presented by national institute of diabetes and digestive and kidney diseases and interstitial cystitis association. Radisson hotel Alexandria, Virginia. October 30-November 1, 2003.

39. Teichman JM, Thompson IM, Taichman NS. Joseph Parrish, tic doloureux of the bladder and interstitial cystitis. *J Urol*. 2000;164(5):1473-5.

40. Skene AJC. *Diseases of Bladder and Urethra in Women*. New York: Wm Wood; 1887,167.

41. Christmas TJ. Historical aspects of interstitial cystitis. In: Sant GR, ed. *Interstitial Cystitis*. New York: Lippincott-Raven; 1997: 1.

42. Hunner GL. A rare type of bladder ulcer in women. Report of cases. *Trans South Surg Gynecol Assoc*. 1914;27:257.

43. Walsh A. Historical Perspectives. In: Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds. *Interstitial Cystitis*. London: Springer-Verlag; 1990:17-21.

44. Parsons CL. Diagnosing chronic pelvic pain of bladder origin. *J Reprod Med*. 2004;49(3 Suppl):235-42.

45. National Kidney and Urologic Disease Information Clearinghouse. *Interstitial Cystitis*. NIH, Pub. N. 99-3220; Aug 1999.

46. Hanno P. Interstitial cystitis and related diseases. In: Walsh PC, Retik AB, Stamey TA, Vaughan ED, eds. *Campbell's Urology*. Philadelphia: W.B. Saunders-Company; 1998:631-62.

47. Powell TO. Studies on the etiology of Hunner's ulcer. *J Urol*. 1945;53:823.

48. Holm-Bentzen M, Nordling J, Hald T. Etiologic and pathogenetic theories in interstitial cystitis In: Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds. *Interstitial Cystitis*. London: Springer-Verlag;1990:64-77.

49. Ho N, Koziol JA, Parsons CL. Epidemiology of interstitial cystitis. In: Sant GR, ed. *Interstitial Cystitis*. Philadelphia: Lippincott-Raven; 1997:9-15.

50. Messing EM. Interstitial cystitis and related syndrome. Walsh PC, Retik AB, Stamey TA, Vaughan ED, eds. *Campbell's Urology*. Philadelphia: W.B. Saunders-Company, 4th edn.:1070.

51. Holm-Bentzen M, Sondergaard I, Hald T. Urinary excretion of a metabolite of histamine (1,4-methyl-imidazole-acetic-acid) in painful bladder disease. *Br J Urol*. 1987;59(3):230-3.

52. Parsons CL, Schmidt JD, Pollen JJ. Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. *J Urol*. 1983;130(1):51-3.

53. Lilly JD, Parsons CL. Bladder surface glycoseaminoglycans is a human epithelial permeability barrier. *Surg Gynecol Obstet*. 1990;171(6):493-6.

54. Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol*. 1998;159(6):1862-7.

55. Chelsky MJ, Rosen SI, Knight LC, Maurer AH, Hanno PM, Ruggieri MR. Bladder permeability in interstitial cystitis is similar to that of normal volunteers: direct measurement by transvesical absorption of 99mtechnetium-diethylenetriaminepentaacetic acid. *J Urol*. 1994; 151(2):346-9.

56. Parsons CL, Housley JD, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol*. 1994;73(5):504-7.

57. Sant GR, Theoharides TC. The role of the mast cell in interstitial cystitis. *Urol Clin North Am*. 1994;21(1):41-53.

58. Simmons JL, Bunce PL. On the use of an antihistamine in the treatment of interstitial cystitis. *Am Surg*. 1958;24(9):664-7.

59. Larsen S, Thompson SA, Hald T, et al. Mast cells in interstitial cystitis. *Br J Urol*. 1982;54(3):283-6.

60. Kastrup J, Hald T, Larsen S, Nielsen VG. Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. *Br J Urol*. 1983;55(5):495-500.

61. Holm-Bentzen M, Jacobsen F, Nerstrom B, et al. Painful bladder disease-clinical and pathoanatomical differences in 115 patients. *J Urol*. 1987;138(3):500-2.

62. Spanos C, el-Mansoury M, Letourneau R, et al. Carbachol-induced bladder mast cell activation: augmentation by estradiol and implications for interstitial cystitis. *Urology*. 1996;48(5):809-6.

63. Theorides TC, Pang X, Leourneau R, Sant GR. Interstitial cystitis: a neuroimmunoendocrine disorder. *Ann N Y Acad Sci*. 1998; 840:619-34.

64. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. *Urology*. 1997;49(5A Suppl):14-40.

65. Theoharides TC, Sant GR, el-Mansoury M, Letourneau R, Ucci AA Jr, Meares EM Jr. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. *J Urol*. 1995;153(3 Pt 1):629-36.

66. Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibers in interstitial cystitis. *Br J Urol*. 1995; 75(6):744-50.

67. Letourneau R, Pang X, Sant GR, Theoharides TC. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. *Br J Urol*. 1996;77(1):41-54.

68. Silk MR. Bladder antibodies in interstitial cystitis. *J Urol*. 1970;103(3):307-9.

69. Oravisto KJ, Alfthan OS, Jokinen EJ. Interstitial cystitis clinical and immunological findings. *Scand J Urol Nephrol*. 1970;4(1):37-42.

70. Jokinen EJ, Alfthan OS, Oravisto KJ. Anti-tissue antibodies in interstitial cystitis. *Clin Exp Immunol*. 1972;11(3):333-9.

71. Anderson JB, Parivar F, Lee G, et al. The enigma of interstitial cystitis an autoimmune disease. *Br J Urol*. 1989;63(1):58-63.

72. Ochs R L, Tan EM. Autoimmune and interstitial cystitis. In: Sant GR, ed. *Interstitial Cystitis*. New York: Lippincott-Raven; 1997:47-52.

73. Erickson DR, Belchis DA, Dabbs DJ. Inflammatory cell types and clinical features of interstitial cystitis. *J Urol*. 1997;158(3 Pt 1):790-3.

74. Zuraw BL, Sugimoto S, Parsons CL, Hugli T, Lotz M, Koziol J. Activation of urinary kallikrein in patients with interstitial cystitis. *J Urol*. 1994; 152(3):874-8.

75. Lotz M, Villiger P, Hugli T, Koziol J, Zuraw BL. Interleukin- 6 and interstitial cystitis. *J Urol*. 1994;152(3):869-73.

76. Fleischmann JD, Huntley HN, Shingleton WB, Wentworth DB. Clinical and immunological response to nifedipine for treatment of interstitial cystitis. *J Urol*. 1991;146(5):1235-9.

77. Elgebaly SA, Allam ME, Walzak MP, Oselinsky D, Gillies C, Yamase H. Urinary neutrophil chemotactic factors in interstitial cystitis patients and a rabbit model of bladder inflammation. *J Urol*. 1992;147(5):1382-7.

78. Erickson DR. Interstitial cystitis: update on etiologies and therapeutic options. *J Womens Health Gend Based Med*. 1999;8(6):745-58.

79. Ratliff TL, Klutke CG, McDougal EM. The etiology of interstitial cystitis. *Urol Clin North Am*. 1994;21(1):21-30.

80. Hanash KA, Pool TL. Interstitial and hemorrhagic cystitis: viral, bacterial and fungal studies. *J Urol*. 1970;104(5):705-6.

81. Wilkins EG, Payne SR, Pead PJ, Moss ST, Maskell RM. Interstitial cystitis and the urethral syndrome: a possible answer. *Br J Urol*. 1989;64(1):39-44.

82. Hampson SJ, Christmas TJ, Moss MT. Search for mycobacteria in interstitial cystitis using mycobacteria-specific DNA probes with signal amplification by polymerase chain reaction. *Br J Urology*. 1993;72(3):303-6.

83. Haarala M, Kiiholma P, Nurmi M, Uksila J, Alanen A. The role of Borrelia burgdorferi in interstitial cystitis. *Eur Urol*. 2000;37(4):395-9.

84. Warren JW, Horne LM, Hebel JR, Marvel RP, Keay SK, Chai TC. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. *J Urol*. 2000;163(6):1685-8.

85. Casey LC. Antibiotics: more than just "bug" killers. *Crit Care Med*. 1997;25(8):1270-1.

86. Ruggieri MR, Hanno PM, Whitmore KE, Balagani RK. Effect of repeated instillation of interstitial cystitis urine on the rabbit urinary bladder. *Urology*. 1993;42(6):646-52.

87. Keay S, Zhang CO, Hise MK, et al. A diagnostic in vitro urine assay for interstitial cystitis. *Urology*. 1998;52(6):974-8.

88. Sternberg E M, Chrousos GP, Wilder R L, Gold P W. The stress response and the regulation of inflammatory disease. *Ann Intern Med*. 1992;117(10):854-66.

89. Ader R, Cohen N, Felten, D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet*. 1995;345(8942):99-103.

90. Spanos C, Pang X, Ligris K, et al. Stress-induced bladder mast cell activation: implications for interstitial cystitis. *J Urol*. 1997;157(2):669-72.

91. Boucher WS, Letourneau R, Huang M, et al Intravesical sodium hyaluronate inhibits the rat urinary mast cell mediator increase triggered by acute immobilization stress. *J Urol*. 2002;167(1):380-4.

92. Alexacos N, Pang X, Boucher W, Cochrane DE, Sant GR, Theoharides TC. Neurotensin mediates rat bladder mast cell degranulation triggered by acute psychological stress. *Urology*. 1999;53(5):1035-40.

93. Krishnan R, Marson L, Khoury JM. Interstitial cystitis. In: *Pfizer Pharmaceuticals Mediguide to Urology*. New York: Lawrence DellaCorte; 1996,9:1-6.

94. Metts JF. Interstitial cystitis: urgency and frequency syndrome. *Am Fam Physician*. 2001;64(7):1199-206, 1212-4.

95. Nigro DA, Wein AJ. Interstitial cystitis: clinical and endoscopic features. In: Sant GR., ed. *Interstitial Cystitis*. Philadelphia: Lippincott-Raven; 1997:137-142.

96. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L. The diagnosis of interstitial cystitis revised: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol*. 1999;161(2):553-7.

97. Fall M, Johansson SL, Aldenborg F. Chronic interstitial cystitis: a heterogeneous syndrome. *J Urol*. 1987;137(1):35-8.

98. NIDDK National Kidney and Urology Diseases Information clearinghouse. Urodynamic Testing. Available at:http://kidney.niddk.nih.gov/kudiseases/pubs/urodynamic/index.htm. Accessed November 27, 2006.

99. Abrams P. Urodynamic techniques. In: Abrams P, ed. *Urodynamics*. London: Springer-Verlag; 2006:17-116.

100. Sand PK, Ostergard DR. Supine urethroscopic cystometry. In: Sand PK, Ostergard DR, eds. *Urodynamics and the Evaluation of Female Incontinence*. London: Springer-Verlag; 1995:29-30.

101. Sand PK, Ostergard DR. Uroflowmetry in the female. In: Sand PK, Ostergard DR, eds. *Urodynamics and the Evaluation of Female Incontinence*. London: Springer-Verlag; 1995:6-8.

102. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C. Psychometric validation of the O'Leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. *Urology*. 2001;57(6 Suppl 1):62-6.

103. Keay SK, Zhang CO, Shoenfelt J, et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. *Urology*. 2001;57(6 Suppl 1):9–14.

104. Erickson DR, Xie SX, Bhavanandan VP, et al. A comparison of multiple urine markers for interstitial cystitis. *J Urol*. 2002;167(6):2461–9.

105. Keay S, Takeda M,Tamaki M, Hanno P. Current and future directions in diagnostic markers in interstitial cystitis. *Int J Urol*. 2003;10(Suppl):S27–S30.

106. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol*.1998;160(5):1663–7.

107. Keay S, Warren JW. A hypothesis for the etiology of interstitial cystitis based upon inhibition of bladder epithelial repair. *Med Hypotheses*. 1998;51(1):79–83.

108. Rhee E, Santiago L, Park E, Lad P, Bellman GC. Urinary IL-6 is elevated in patients with urolithiasis. *J Urol*. 1998;160(6 Pt 1):2284-8.

109. Keay S, Zhang CO, Shoenfelt JL, Chai TC. Decreased in vitro proliferation of bladder epithelial cells from patients with interstitial cystitis. *Urology*. 2003;61(6):1278–84.

110. Keay S, Kleinberg M, Zhang CO, Hise MK, Warren JW. Bladder epithelial cells from interstitial cystitis patients produce an inhibitor of HBEGF production. *J Urol*. 2000;164(6):2112–8.

111. Phatak S, Foster HE. The management of interstitial cystitis: an update. *Nat Clin Pract Urol*. 2006;3(1):45-53.

112. Minogiannis P, El-Mansoury M, Betances JA, Sant GR, Theoharides TC. Hydroxyzine inhibits neurogenic bladder mast cell activation. *Int J Immunopharmacol*. 1998;20(10):553-63.

113. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of Amitriptyline for the treatment of interstitial cystitis. *J Urol*. 2004;172(2):533-6.

114. Soucy F, Gregoire M. Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. *J Urol*. 2005;173(3):841-3.

115. Sairanen J, Forsell T, Ruutu M. Long – term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. *J Urol*. 2004;171(6 Pt 1):2138-41.

116. Food and Drug Administration. Drug Approvals for September 1996. Available at: http://www.fda.gov/cder/da/da996.htm. Accessed September 10, 2006.

117. Ortho-McNeil Pharmaceutical I. Elmiron 100mg (pentosan polysulfate sodium) capsules: prescribing information. Available at: http://www.orthoelmiron.com/active/janus/en_US/assets/common/company/pi/elmiron.pdf. Accessed September 10, 2006.

118. Kalota SJ, Stein PC, Parsons CL. Prevention of acrolein-induced bladder injury by pentosanpolysulfate. *J Urol*. 1992;148 (1):163-6.

119. Parsons CL, Forrest J, Nickel JC, et al. Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. *Urology*. 2002;59(3):329-33.

120. Ortho-McNeil Pharmaceutical I. Product monograph: Elmiron (Pentosan polysulfate sodium capsules 100mg. Available at: http://www.janssen-ortho.com/JOI/pdf_files/**Elmiron**_E.pdf. Accessed September 10, 2006.

121. Chiang G, Patra P, Letourneau R, et al. Pentosanpolysulfate inhibits mast cell histamine secretion and intracellular calcium ion levels: an alternative explanation of its beneficial effect in interstitial cystitis. *J Urol*. 2000;164 (6):2119-25.

122. Chiang G, Patra P, Letourneau R, et al. Pentosanpolysulfate (Elmiron) is a potent inhibitor of mast cell histamine secretion. *Adv Exp Med Biol*. 2003;539 (Pt B):713-29.

123. Faaij RA, Srivastava N, van Griensven JM, et al. The oral bioavailability of pentosan polysulphate sodium in healthy volunteers. *Eur J Clin Pharmacol*. 1999;54(12):929-35.

124. Nyska A, Nold JB, Johnson JD, Abdo K. Lysosomal-storage disorder induced by elmiron following 90-days gavage administration in rats and mice. *Toxicol Pathol*. 2002;30(2):178-87.

125. Simon M, McClanahan RH, Shah JF, Repko T, Modi NB. Metabolism of [3H] pentosan polysulfate sodium (PPS) in healthy human volunteers. *Xenobiotica*. 2005;35(8):775-84.

126. Hanno PM, Wein AJ. Medical Treatment of interstitial cystitis other than Rimso-50, Elmiron. *Urology*. 1987;29(4:Suppl):22-6.

127. Sant GR, La Rock DR. Standard intravesical therapies for interstitial cystitis. *Urol Clin North Am*. 1994;21(1):73-83.

128. Turner KJ, Stewart LH. How do you stretch a bladder? A survey of UK practice, a literature review, and a recommendation of a standard approach. *Neurourol Urodyn*. 2005;24(1):74-6.

129. Perez-Marrero R, Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol*. 1988;140(1):36-9.

130. Rossberger J, Fall M, Peeker R. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol*. 2005;39(1):73-7.

131. Hwang P, Auclair B, Beechinor D, Diment M, Einarson TR. Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: A meta-Analysis. *Urology*. 1997;50(1):39-43.

132. Bade JJ, Mensink HJ, Laseur M. Intravesical treatment of interstitial cystitis with a heparin analogue. *Br J Urol*. 1995;75(2):260.

133. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in the Netherlands. Prevalence, diagnosis criteria and therapeutic preference. *J Urol*. 1995;154(6):2035-8.

134. Ito T, Miki M, Yamada T. Interstitial cystitis in Japan. *Br J Urol*. 2000;86(6):634-7.

135. Parsons CL, Tatsis V. Prevalence of interstitial cystitis in young women. *Urology*. 2004;64(5):866-70.

136. Roberts RO, Bergstralh EJ, Bass SE, Lightner DJ, Lieber MM, Jacobsen SJ. Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. *B J U Int*. 2003;91(3):181-5.

137. Parsons CL, Parsons JK. Interstitial cystitis. In: Raz S, ed. *Female Urology*. Philadelphia: Saunders; 1996:Chapter 15.

138. Novicki DE, Larson TR, Swanson SK. Interstitial cystitis in men. *Urology*. 1998;52(4):621-4.

139. Jensen H, Nielsen K, Frimodt-Moller C. Interstitial cystitis: review of the literature. *Urol Int*. 1989;44(4):189-93.

140. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. *Urology*. 1997;49(5A Suppl):2-9.

141. Close CE, Carr MC, Burns MW, et al. Interstitial cystitis in children. *J Urol*. 1996;156(2 Pt 2):860-2.

142. Sant GR. Interstitial cystitis in minority women. *J Assoc Acad Minor Phys*. 1993; 4(3):89-92.

143. Forrest JB, Schmidt S. Interstitial cystitis, chronic nonbacterial prostatitis and chronic pelvic pain syndrome in men: a common and frequently identical clinical entity. *J Urol*. 2004;172(6 Pt 2):2561-2.

144. Dimitrakov JD. A case of familial clustering of interstitial cystitis and chronic pelvic pain syndrome. *Urology*. 2001;58(2):281.

145. Warren JW, Jackson TL, Langenberg P, Meyers DJ, Xu J. Prevalence of interstitial cystitis in first degree relatives of patients with interstitial cystitis. *Urology*. 2004;63(1):17-21.

146. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. *Urology*. 2001;57(3):428-33.

147. Theoharides TC, Pang X, Letourneau R, Sant GR. Interstitial cystitis: a neuroimmunoendocrine disorder. *Ann N Y Acad Sci*. 1998;840:619-34.

148. Webster DC, Brennan T. Use and effectiveness of sexual self-care strategies for interstitial cystitis. *Urol Nurs*. 1995;15(1):14-22.

149. Bjorling DE, Wang ZY. Estrogen and neuron-inflammation. *Urology*. 2001;57(6 suppl 1):40-6.

150. Gillespie LM. Interstitial cystitis and diet. In: Sant GR, eds. *Interstitial Cystitis*. Philadelphia. Philadelphia: Lippincott-Raven; 1997:109-115.

151. Bade JJ, Peeters JM, Mensink HJ. Is the diet of patients with interstitial cystitis related to their disease? *Eur Urol*. 1997;32(2):179-83.

152. Clemens JQ, Brown SO, Kozloff L, Calhoun EA. Predictors of symptom severity in patients with chronic prostatitis and interstitial cystitis. *J Urol*. 2006;175(3 Pt 1):963-7.

153. Tu YK, Kellett M, Clerehugh V, Gilthorpe MS. Problems of correlations between explanatory variables in multiple regression analyses in the dental literature. *Br Dent J*. 2005;199(7):457-61.

154. World Health Organization (WHO), Constitution of the WHO. In : Basic documents (37th edn), Geneva: *WHO*, 1946.

155. Osoba D. The quality of life committee of the clinical trials group of the National Cancer Institute of Canada: Organization and functions. *Qual Life Res*. 1992;1(3):211-8.

156. US Department of Health and Human services, Public Health Services, National Institute of Health. Quality of Life assessment in cancer clinical trials. *Report of the Workshop on Quality of life Research*. 1990;1(2):107-117.

157. World Health Organization, Division of Menatl Health. WHO-QOL Study protocol: the development of the World Health Organization Quality of Life assessment instrument (MNG/PSF/93.9). Geneva: Switzerland,1993.

158. Beitz J, Gnecco C, Justice R. Quality of life endpoints in cancer clinical trials: the US Food and Drug Administration perspective. *J Natl Cancer Inst Monogr*. 1996;(20):7-9.

159. Eiser C, Mrse R. A review of measures of quality of Life for children with chronic illness. *Archives of Disease in Childhood*. 2001;84(3):205-11.

160. Mandelbatt JS, Eisenberg JM. Histrorical and methodological perspectives on cancer outcomes research. *Oncology (Williston Park)*. 1995;9(11 Suppl):23-32.

161. Grant MM, Dean GE. Evolution of quality of life in oncology and oncology nursing. In: King CR, Hinds PS, eds. *Quality of Life from Nursing and Patient Perspectives Theory Research Practice*. Massachusetts: Jones and Bartlett publishers; 2002: 4-6.

162. Hunt S, McKenna S. Do we need measures other than QALYs? In: Hopkins A, ed. *Measures of the Quality of Life and the Uses to Which Such Measures May be Put*. London: Royal College of Physicians; 1992.

163. Grant M, Padilla GV, Ferrell BR, Rhiner M. Assessment of quality of life with a single instrument. *Semin Oncol Nurs*. 1990;6(4):260-70.

164. Osoba D. Lessons learned from measuring health-related quality of life in oncology. *J Clin Oncol*. 1994;12(3):608-16.

165. Spilker B. Introduction. In: B. Spilker B, ed. *Quality of Life Assessments in Clinical Trials*. New York: Raven Press; 1990: 3-9.

166. Padilla GV, Ferrell B, Grant MM, Rhiner M. Defining the content domain of quality of life for cancer patients with pain. *Cancer Nurs*. 1990;13(2):108-15.

167. Schipper H. Guidelines and caveats for quality of life measurement in clinical practice and research. In: Tchekmedyian NS, Cella DF, eds. *Quality of Life in Oncology Practice and Research*. Williston Park, NY: Dominus Publishing Company; 1991:25-31.

168. Schipper H, Clinch J, Powell V. Definition and conceptual issues. In: B. Spilker B, ed. *Quality of Life Assessments in Clinical Trials*. New York: Raven Press; 1990:11-24.

169. Bowling A. Measuring health. *A Review of Quality of Life Measurement Scale*. Buckingham: Open University Press; 2005.

170. Stewart AL, Ware JE, eds. Measuring functioning and well-being. *The Medical Outcomes Study Approach*. Durham, NC: Duke University Press;1992.

171. Wilkin D, Hallam L, Doggett MA. *Measures of Need and Outcome for Primary Health Care*. Oxford: Oxford University Press;1992.

172. Ware JE. The status of health assessment 1994. *Annu Rev Public Health*. 1995;16:327-54.

173. Temkin NR, Dikmen S, Machamer J, McLean A. General versus disease-specific measures: further work on the sickness impact profile for head injury. *Med Care*. 1989;27(3 Suppl):S44-53.

174. de Jong Z, van der Heijde D, Mckenna SP, Whalley D. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. *Br J Rheumatol*. 1997;36(8):878-83.

175. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-76.

176. Ware JE. SF-36 Health Survey Update. *Spine*. 2000;25(24):3130–9.

177. Ware JE, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Lincoln, RI: QualityMetric Incorporated; 1993, 2000.

178. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care*. 1988;26(7)**:**724–735.

179. Tarlov AR, Ware JE Jr, Greenfield S, Nelson EC, Perrin E, Zubkoff M. The Medical Outcomes Study. An application of methods for monitoring the results of medical care. *JAMA*. 1989**;**262(7)**:**925–930.

180. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. 1999;53(1):46-50.

181. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305(6846):160-4.

182. Kurtin PS, Davies AR, Meyer KB, DeGiacomo JM, Kantz ME. Patient-based health status measures in outpatient dialysis. Early experiences in developing an outcomes assessment program. *Med Care*. 1992;30(5 Suppl):MS136-49.

183. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-83.

184. Ware JE, Kosinski M. *SF-36 Physical and mental health summary scales: A Manual for Users of Version 1, Second Edition*. Lincoln, RI: QualityMetric Incorporated; 2001.

185. Nickel JC, Tripp D, Teal V, et al. Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. *J Urol*. 2007;177(5):1832-6.

186. Peters K, Diokno A, Steinert B, et al. The efficacy of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. *J Urol*. 1997;157(6):2090-4.

187. Oyama IA, Rejba A, Lukban JC, et al. Modified Thiele massage as therapeutic intervention for female patients with interstitial cystitis and high-tone pelvic floor dysfunction. *Urology*. 2004;64(5):862-5.

188. Gordis L. Assessing the efficacy of preventive and therapeutic measures: randomized trials. In: *Epidemiology*. Philadelphia: Elsevier-Saunders; 2004:115-29.

189. Reprinted with permission from *Journal of Urology*, 2008; 179(1): 177-85, Edward L. Davis, Samar R. El Khoudary, Evelyn O. Talbott, Josephine Davis, Lisa J. Safety and Efficacy of the Use of Intravesical and Oral Pentosan Polysulfate Sodium for Interstitial Cystitis: A Randomized Double Blind Clinical Trial. Copyright©2008 Elsevier.

190. Gordis L. Case-control and cross-sectional studies. In: *Epidemiology*. Philadelphia: Elsevier-Saunders; 2004:173-4.

191. Clemons JL, Arya LA, Meyers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. *Ostet Gynecol*. 2002;100(2):337–341.

192. Acute pain management: operative or medical procedures and trauma, clinical practice guideline NO.1. AHCPR Publication No. 92-0032; February 1992. Agency for Healthcare Research and Quality, Rockville, MD; pages 7-14, 116-117.

193. Mayer R, Propert KJ, Peters KM, et al. A randomized controlled trial of intravesical bacillus Calmette-Guérin for treatment refractory interstitial cystitis. *J Urol*. 2005;173(4):1186–1191.

194. Propert KJ, Schaeffer AJ, Brensinger CM, Kusek JW, Nyberg LM, Landis JR. A prospective study of interstitial cystitis: results of longitudinal follow-up of the interstitial cystitis data base cohort. The Interstitial Cystitis Data Base Study Group. *J Urol*. 2000;163(5):1434-9.

195. Propert KJ, Mayer RD, Wang Y, et al. Responsiveness of symptom scales for interstitial cystitis. *Urology*. 2006;67(1):55-9.

196. Ito T, Tomoe H, Ueda T, Yoshimura N, Sant G, Hanno P. WORKSHOP 6 Clinical symptoms scale for interstitial cystitis for diagnosis and for following the course of the disease. *Int J Urol*. 2003;10 Suppl**:**S24–6.

197. Bioniche Life Sciences Inc.: Human Health News Release, Preliminary Results of North American Cystistat® Trial Announced. Available at: http://www.bioniche.com/news_item.cfm?id=2010. Accessed June 21, 2007.

198. SF-36 Organization. Frequently Asked Questions. Available at: http://www.sf-36.org/faq/generalinfo.aspx?id=4. Accessed November 27, 2006.

199. Haake P, Schedlowski M, Exton MS, et al. Acute neuroendocrine response to sexual stimulation in sexual offenders. *Can J Psychiatry*. 2003;48(4):265-71.

200. Wagner G, Rabkin J, Rabkin R. Effects of testosterone replacement therapy on sexual interest, function, and behavior in HIV positive men. *The Journal of Sex Research*. 1997;34:27-33.

201. Rosner B. Non-parametric methods. In: *Fundamentals of Biostatistics*. USA: Duxbury Thomson Learning; 2000:331.

202. Rosner B. Estimation. In: *Fundamentals of Biostatistics*. USA: Duxbury Thomson Learning; 2000:157.

203. Papadopoulos AA, Kontodimopoulos N, Frydas A, Ikonomakis E, Niakas D. Predictors of health-related quality of life in type II diabetic patients in Greece. *BMC Public Health*. 2007;7:186.

204. CDC Centers for Disease Control and Prevention. About BMI for adults. Available at: http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/about_adult_BMI.htm. Accessed July 7, 2007.

205. DeJuana CP, Everett JC JR. Interstitial cystitis: experience and review of recent literature. *Urology*. 1977;10(4):325-9.

206. Payne CK, Mosbaugh PG, Forrest JB, et al. Intravesical Resiniferatoxin for the treatment of interstitial cystitis: a randomize, double-blind, placebo controlled trial. *J Urol*. 2005;173(5):1590-4.

207. Calhoun EA, McNaughton Collins M, Pontari MA, et al. The economic impact of chronic prostatitis. *Arch Intern Med*. 2004;164(11):1231-6.

208. Bachmann GA. Vulvovaginal complaints. In: Lobo RA, ed. *Treatment of Postmenopausal Women: Basic and Clinical Aspects*. New York: Raven Press; 1994:137-42.

209. Hextall A, Cardozol L. Managing postmenopausal cystitis. *Hosp Pract (Minneap)*. 1997;32(6):191-8.

210. Rosamilia A. Painful bladder syndrome/interstitial cystitis. *Best Pract Res Clin Obstet Gynaecol*. 2005;19(6):843-59.

211. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol*. 1990;143(6):1118-24.

212. Tomaszewski JE, Landis JR, Russack V, et al. Biopsy features are associated with primary symptoms in interstitial cystitis: results from the interstitial cystitis database study. *Urology*. 2001;57(6 Suppl 1):67-81.

213. Riazi A, Hobart JC, Fitzpatrick R, Freeman JA, Thompson AJ. Socio-demographic variables are limited predictors of health status in multiple sclerosis. *J Neurol*. 2003;250(9):1088-93.

214. Bosworth HB, Siegler IC, Olsen MK, et al. Social support and quality of life in patients with coronary artery disease. *Qual Life Res*. 2000;9(7):829-39.

215. Larsson U, Karlsson J, Sullivan M. Impact of overweight and obesity on health-related quality of life—A Swedish population study. *Int J Obes Relat Metab Disord*. 2002;26(3):417-24..

216. Le Pen C, Levy E, Loos F, Banzet MN, Basdevant A. ‘‘Specific’’ scale compared with ‘‘generic’’ scale: A double measurement of the quality of life in a French community sample of obese subjects. *J Epidemiol Community Health*. 1998;52(7):445-50.

217. Parsons, C. L. and Lilly, J. D. and Stein, P.: Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol*. 1991;145(4):732-5.

218. Marshall K. Interstitial cystitis: understanding the syndrome. *Altern Med Rev*. 2003;8(4):426-37. Review.

219. Nickel JC, Parsons CL, Forrest J, Kaufman D, Evans R, Chen A, Wan G, Xiao X. Improvement in Sexual Functioning in Patients with Interstitial Cystitis/Painful Bladder Syndrome. *J Sex Med*. 2008;5(2):394-9.