Current Management of Male Chronic Pelvic Pain Syndromes

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The term prostatitis denotes a combination of infectious conditions (acute and chronic bacterial prostatitis), chronic pelvic pain syndrome (CPPS) and asymptomatic inflammation, of which most of them are CPPS. In spite of many years of investigation, the cause of CPPS remains elusive and can be multifactorial. Different factors have been proposed in the etiopathogenesis of CPPS, including viral infection, psychological stress effects, hormonal and neural factor, T-cell recognition of prostatic peptides, and possibly autoimmune diseases. However, a universally effective, reliable and lasting beneficial treatment of the CP/CPPS remains uncertain. A wide variety of treatments have been applied to CPPS patients, including alpha-blockers, antimicrobial therapy, nonsteroidal anti-inflammatory medicine, heat therapy and local infiltration therapies. Treatment is clinically based on optimal symptomatic relief and pain control. Psychological factors can also affect the development of chronic pain and treatment outcomes. Psychological distress comes from both persistent pelvic pain and worrying about tissue damage or malignancy development. It is important to inform patients about the variety of potential therapies and to develop a trusting relationship with them. Additional studies in the understanding of the etiologies of CP/CPPS and the establishment of treatment strategies are urgently needed.

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1. Introduction

The term prostatitis denotes a combination of infectious conditions (acute and chronic bacterial prostatitis), chronic pelvic pain syndrome (CPPS) and asymptomatic inflammation. The classification of prostatitis, as best defined by the National Institute of Diabetes and Digestive and Kidney Disease of the U.S. National Institutes of Health (NIH), includes all these four syndromes. Category III chronic prostatitis (CP) or CPPS is typically characterized by reported genital or pelvic pain (in or around the prostate, penis, rectum, perineum and scrotum), that lasts for more than 3 months. Its symptoms are also often associated with variable degrees of voiding pain or
ejaculation disturbances in the absence of urinary tract infection. There are two types of CPPS as categorized by the NIH: inflammatory (type IIIa) and non-inflammatory (type IIIb) CPPS. The distinction between inflammatory and non-inflammatory CPPS is based on the finding of white blood cells in the semen, expressed prostatic secretions, or urine after prostatic massage.

Prostatitis syndrome is not an uncommon disorder. The prevalence of prostatitis syndromes in the general population ranges from 2.2% to 13.8%,1–3 of which most of them are CP/CPPS. The frequency of bacterial prostatitis only accounts for 5–10%.4 CP/CPPS is a frustrating challenge for both physician and patient. Currently, there are no gold-standard and widely acceptable diagnostic tests or biomarkers available for CP/CPPS. The diagnosis of CP/CPPS only depends on the presence of classic symptoms of chronic pelvic pain and possibly of lower urinary tract symptoms on voiding. Serum white blood cell count and prostate-specific antigen level are not helpful in the diagnosis of CP/CPPS.

The Meares-Stamey four-glass test or two-glass test may provide information to rule out bacterial infection. The Meares-Stamey four-glass test5 involves the collection of sequential specimens of urine before and after prostatic massage and prostatic fluid during prostatic massage. The simpler two-glass test,6 which involves the collection of midstream and initial urine samples after prostatic massage, has been shown to be well correlated with the four-glass test. However, these findings are not helpful in the diagnosis or management of CP/CPPS. The symptoms should be validated with the standard questionnaire of the National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI), especially before treatment is initiated.7 This questionnaire has become the established international standard for symptom evaluation of prostatitis. However, despite its important role in evaluating the severity of symptoms, it has not been proved to be a valuable diagnostic tool.

Despite many years of investigation, the cause of CPPS remains elusive and can be multifactorial. Different factors have been proposed in the etiopathogenesis of CP/CPPS, including viral infection,8,9 psychological stress effects,10 hormonal and neural factors,11,12 T-cell recognition of prostatic peptides,13 and possibly autoimmune diseases.13–16 Psychological stress and panic are common findings in men with CP/CPPS. There is also growing evidence that inflammation plays a significant role in CP/CPPS. Elevated levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α, have been reported to be associated with the severity and diagnosis of CP/CPPS.17

Furthermore, a universally effective, reliable and lasting beneficial treatment of CP/CPPS remains uncertain. The aim of the present review is to provide an evidence-based evaluation of the current treatments for CP/CPPS.

2. Alpha-Blockers

The original rationale for alpha-blocker treatment was based on clinical and urodynamic observations. Some patients with CP/CPPS were found to suffer from bladder outflow obstruction, and alpha-blockers have been proven effective for patients with bladder outflow obstruction and voiding dysfunction. The identification of alpha receptors in the urinary tract raises the possibility that patients with prostatitis symptoms related to dysfunctional voiding might benefit from alpha-blocker therapy. Urodynamic evaluations have also revealed an increased maximal urethral closure pressure and a diminished urinary flow rate in patients with CP/CPPS.18 In addition to urodynamic parameters, Mehik et al.19 compared chronic nonbacterial prostatitis patients with normal controls. The intraprostatic tissue pressure was found to be higher in the prostatitis patients, reflecting an increase in interstitial resistance or poor tissue microcirculation. Alpha-blockers might improve such pathophysiological processes without affecting voiding.

The findings of randomized, placebo-controlled trials showed a clinically significant therapeutic effect with these alpha-blockers.12,20–22 Nickel et al.22 completed a multicenter study comparing CP/CPPS participants who received 6 weeks of tamsulosin (0.4 mg/day) or placebo. Assessments were performed on days 15 and 45 using the NIH-CPSI scores. Tamsulosin was found to be more effective than placebo for participants with higher total NIH-CPSI scores at baseline, higher pain scores, higher voiding scores, and worse quality of life (QoL) scores. Although the patients did not benefit significantly after 2 weeks of therapy, there was a significant improvement after 6 weeks of therapy.

In a randomized controlled trial to test the efficacy of alfuzosin, Nickel et al.23 randomized 272 CP/CPPS patients to alfuzosin 10 mg/day or placebo for 12 weeks. Based on NIH-CPSI scores, both study groups were found to have a decrease of at least 4 points in their total NIH-CPSI scores, but there was no significant difference between the two study groups. In addition, a global response assessment showed similar response rates at 12 weeks. This trial does not support the use of alfuzosin to reduce CP/CPPS symptoms in patients who have not received prior treatment with an alpha-blocker. In another prospective, randomized, placebo-controlled trial comparing alfuzosin 5 mg twice daily with placebo for a longer period of 6 months, it was found that at the end of 6 months of active therapy, the alfuzosin group had a statistically significant decrease in total NIH-CPSI score and pain domain score, but not in the voiding or QoL scores. At the 12-month follow-up (i.e. 6 months after the treatment was discontinued), the symptom scores in all domains of the NIH-CPSI showed deterioration, as compared with the original baseline scores. Treatment with alpha-blockers may be effective for reducing symptoms in men with CP/CPPS, especially in those who have not previously been treated.
with these drugs and who have had symptoms for a relatively short time (<1 year).

3. Antimicrobial Therapy

One of the pathogenic hypotheses for CP/CPPS is that chronic infection with bacteria is difficult to detect and cannot be cultured. Therefore, it is reasonable to treat CP/CPPS patients with fluoroquinolones if they have not previously been exposed to antibiotics. However, the effectiveness of antimicrobial agents in men with CPPS is controversial. Trials comparing levofloxacin (500 mg/day) with placebo for 6 weeks showed that treatment with 6 weeks of levofloxacin in CP/CPPS men had no statistically or clinically significant difference from that with placebo at the end of treatment (6 weeks) or at follow-up visits (12 weeks). Based on a decrease of 6 points in NIH-CPSI scores compared to placebo, more patients responded in the levofloxacin group; the difference was statistically significant only at 3 weeks. Another trial comparing with ciprofloxacin 500 mg twice daily (196 patients) for 6 weeks revealed no significant benefit from active therapy in terms of a reduction in total NIH-CPSI scores.

Nanobacteria are implicated in stone formation in the kidney, blood vessels and prostate. Recently, nanobacterial infection has been detected from expressed prostatic secretions and urine samples in CP/CPPS patients. A non-randomized trial was performed to evaluate the effect of anti-nanobacterial therapy (comET), which consisted of 500 mg tetracycline and ethylene-diaminetetraacetic acid (EDTA) in 16 CP/CPPS patients. A non-randomized trial was performed to evaluate the effect of anti-nanobacterial therapy (comET), which consisted of 500 mg tetracycline and ethylene-diaminetetraacetic acid (EDTA) in 16 CP/CPPS patients. Mean NIH-CPSI total scores were found to decrease from 25.7 to 13.7, and a total of 12 patients (80%) had at least 25% improvement on NIH-CPSI and 8 (53%) had at least 50% improvement. Therapy designed to eliminate nanobacteria resulted in significant improvement in CPPS symptoms in the majority of men. Whether the effect was due to treatment for stone-producing nanobacteria or through some other mechanisms remains unclear. Despite a lack of strong supporting evidence from clinical trials, antimicrobial and anti-inflammatory agents are often considered the mainstay of drug therapy for CP/CPPS, especially for newly diagnosed, antimicrobial-naive patients.

4. Nonsteroidal Anti-inflammatory Medicine and Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) can inhibit the cyclooxygenase enzyme, decrease prostaglandin production, and decrease local prostate inflammation. However, there are very few studies on the use of NSAIDs for CP/CPPS patients. A randomized, placebo-controlled trial was tested to compare 6 weeks of 25 mg and 50 mg rofecoxib in the treatment of CP/CPPS with placebo. For the higher-dose rofecoxib group (50 mg), there was a significant difference (25% decrease or 6-point improvement) in total NIH-CPSI scores, pain and QoL ($p<0.005$) compared with placebo. Generally, nonselective, low-potency NSAIDs should be used first and are most likely to be helpful when the pain has an inflammatory component. The opioids have well-established roles in the management of chronic pain syndrome or non-malignant neuropathic pain. However, the potential therapeutic benefit and risk of drug addiction should be carefully weighed. The use of opioids should be carefully reserved for treatment-refractory CP/CPPS patients.

5. Heat Therapy

Heat therapy has been delivered with interstitial heat and microwaves, transrectally or transurethrally, against symptoms of benign prostate enlargement. The mechanism underlying the efficacy of hyperthermia in treating prostatitis is unclear. One hypothesis proposes that thermotherapy accelerates the resolution of the inflammatory process, and alters the sensory nerves in the prostatic stroma that transmit pain sensations and alpha-adrenergic neuron modulation. Transurethral microwave thermotherapy procedures have been reported to achieve intraprostatic temperatures of 55–70°C, and transurethral needle ablation uses radiofrequency to heat intraprostatic tissue to 90–100°C. However, the results on heat therapy for the treatment of CP/CPPS patients are inconsistent. In a small, uncontrolled trial, a total of 35 patients completed transurethral microwave thermotherapy treatment and were followed-up for 12 months. There were significant improvements in NIH-CPSI pain, voiding and QoL subscores from the baseline versus 12-month follow-up. Treatment discomfort and side effects were minimal and transient, resolved spontaneously or with medication. One uncontrolled trial (32 patients) showed that transurethral needle ablation significantly decreased Prostate Symptom Severity Index (PSSI) score and leukocyte counts in the expressed prostate secretions at 3 and 6 months compared with baseline, without major complications on sexual dysfunction or retrograde ejaculation. However, another randomized, single-blind controlled trial demonstrated that there were no statistically significant differences between the treatment and control groups in PSSI, International Prostate Symptom Score, QoL and pain domains. A larger, well-designed, multicenter trial is necessary to elucidate the effect of heat therapy.

6. Local Infiltration Therapy

The characteristic and dominant symptom of CP/CPPS is chronic prostatic or pelvic pain. The clinical observations suggest that a significant proportion of pain is of pelvic musculoskeletal origin. Faced with the obscure nature of CP/CPPS and the poor response to oral medication,
physicians have considered alternative routes of drug administration. Local infiltration injections have several advantages over oral drugs and surgical therapies: systemic pharmacologic effects are rare; there is no permanent destruction of tissue; and graded degrees of actions may be achieved by varying the dose injected.

Botulinum (BoNT), a potent neurotoxin, has been used in the management of prostate enlargement-induced lower urinary tract symptoms. The mechanisms of BoNT involve a direct inhibition of motor neurons, an inhibition of the release of local neuropeptides (acetylcholine and norepinephrine) via vesicle-dependent exocytosis, alterations within the autonomic nervous system resulting in changes in regional perfusion, and an inhibition of afferent neurotransmitter leading to local analgesic properties. In Zermann et al.’s study, a transurethral perinephritic injection of 200 units of BoNT-A in 11 CP/CPPS patients was followed by 2–4 weeks of follow-up. Basic parameters of bladder function (capacity, sensitivity, compliance) were normal. The BoNT injection was followed by a pelvic floor muscle weakening and a relief of prostatic pain and urethral hypersensitivity. A BoNT-related decrease in functional urethral length and postvoid residual volume and an increase in peak urinary flow were also observed. Using a capsacin-induced prostatitis rat model, Chuang et al. demonstrated that intraprostatic pretreatment with BoNT-A can significantly decrease inflammatory cell accumulation and cyclooxygenase-2 expression in the prostate, ventral horn and dorsal horn of the L6 spinal cord. These results suggest a therapeutic potential of BoNT-A for the treatment of nonbacterial prostatitis.

7. Other Therapies

An important factor for the development of CP may be sex hormone. This proposition has been examined in the following studies. Treating rats with estrogen induced prostatic inflammation, while co-administration with testosterone limited prostatic inflammation. In an autoimmune prostatitis rat model, inflammation impaired $5\alpha$-reductase activity and lowered the intraprostatic level of dihydrotestosterone relative to testosterone. The $5\alpha$-reductase inhibitor, finasteride, can inhibit the conversion of testosterone to dihydrotestosterone, thus increasing local testosterone level. Finasteride 5 mg/day improved subjective overall assessment and NIH-CPSI scores compared to placebo over a 6-month period in 76 men with inflammatory CPPS. However, the researchers did not recommend finasteride as monotherapy for CP/CPPS, except for men who also have benign prostatic hyperplasia. In another trial, finasteride 5 mg/day over 12 months significantly improved PSS1 score in men with CP/CPPS, but no significant reduction in pain scores was achieved.

Given the lack of proven efficacy of conventional therapies, there are many patients who turn to phytotherapy or other alternative treatments. Pentosan polysulfate (PPS), a plant-derived mucopolysaccharide similar to glycosaminoglycans, can form a protective layer of the urinary tract epithelium. PPS has been used in patients with interstitial cystitis, another chronic pelvic pain condition that occurs more commonly in women. In a recent study, the potassium chloride (KCl) sensitivity test, especially the KCl voiding test, was shown to be useful in the diagnosis of CP/CPPS patients, showing that a defect in the bladder mucosa glycosaminoglycan layer is a possible etiology of CP/CPPS. Nickel et al. conducted a 16-week double-blind study of 100 CP/CPPS men who were randomized to receive 300 mg PPS or placebo three times daily. A significant number of patients receiving PPS experienced a moderate to marked improvement based on clinical global improvement assessment. The improvement in NIH-CPSI QoL domain score was notably different between the PPS and control groups. Another longer but smaller trial evaluated 28 CP/CPPS patients who received 100 mg PPS three times daily for 6 months. The decreases in frequency (Symptom Frequency Questionnaire), severity (PSS1), and total NIH-CPSI scores were significant when baseline was compared with 6 months.

The pollen extract cernilton contains defined pollen extract fractions: Cernitin T60 (water-soluble fraction) and Cernitin GBX (fat-soluble fraction), which have been used for the treatment of benign prostatic hyperplasia and CP in Europe. Experimental data in nonbacterial prostatitis in rats showed that cernilton has both anti-inflammatory and antioxidant effects. Recently, a double-blind, placebo-controlled study was carried out to investigate CP/CPPS (NIH IIIa) participants randomized to receive pollen extract or placebo for 12 weeks. The individual pain and QoL domains as well as the total NIH-CPSI score were significantly improved after 12 weeks of treatment with pollen extract compared to placebo.

Other therapies, such as tricyclic antidepressants, muscle relaxant agents, biofeedback, prostatic massage, low-energy extracorporeal shock wave therapy and neuromodulation, have been evaluated in some small uncontrolled studies, which show some improvement in NIH-CPSI scores. However, studies of larger and randomized placebo-controlled trials are warranted before any recommendations can be made.

8. Conclusion

The present review demonstrates that there are currently no universally effective treatments available that can provide significant lasting effects in CP/CPPS patients. There is also no evidence to suggest that treatment for inflammatory and non-inflammatory CP/CPPS should be different. Chronic pain is considered not only a primary symptom, but also the center of treatment focus. Treatment is clinically based on optimal symptomatic relief and pain control. Psychological factors can affect the development of chronic pain and treatment outcomes. Psychological distress
comes from both persistent pelvic pain and worrying about tissue damage or malignancy development. It is important to inform patients about the varieties of potential therapies and to develop a trusting relationship with them. Additional studies on the etiologies of CP/CPPS and the establishment of treatment strategies are urgently needed.

References


10. Mehik A, Hellstrom P, Sarpola A, Lukkarinen O. Fears, therapies and to develop a trusting relationship with them. Additional studies on the etiologies of CP/CPPS and the establishment of treatment strategies are urgently needed.


