PTNS

a new treatment option for lower urinary tract dysfunction

Vera Vandoninck

POSTERIOR TIBIAL NERVE STIMULATION

a new treatment option for lower urinary tract dysfunction

V. Vandoninck
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UMC St Radboud, Nijmegen, the Netherlands

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POSTERIOR TIBIAL NERVE STIMULATION
A NEW TREATMENT OPTION FOR LOWER URINARY TRACT DYSFUNCTION

NERVUS TIBIALIS STIMULATIE
EEN NIEUWE BEHANDELINGSMETHODE VOOR LAGERE URINEWEG DYSFUNCTIE

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

Proefschrift

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Promotores:
Prof. dr. B.L.H. Bemelmans (VU Medisch Centrum Amsterdam)
Prof. dr. F.M.J. Debruyne (Andros Mannenkliniek Arnhem)

Copromotor:
Dr. J.P.F.A. Heesakkers

Manuscriptcommissie:
Prof. dr. J.L.H.R. Bosch (UMC Utrecht)
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CONTENTS

CHAPTER 1

OUTLINE OF THE THESIS

Overactive bladder syndrome (OAB) is a very bothersome condition. Abrams estimates that worldwide about 200 million people suffer from urinary incontinence [Abrams, 1999]. A recent European study reported a prevalence of nearly 17% of subjects describing symptoms consistent with OAB complaints [Milson et al., 2001]. Detrusor overactivity is an urodynamic finding that can cause OAB complaints. It is commonly seen in neurological disease or after neurological injury. Also aging, inflammation, bladder outlet obstruction, or irritation can cause OAB symptoms. When no specific cause is found, detrusor overactivity is defined as idiopathic.
Failure to empty the bladder results from decreased bladder contractility, increased outlet resistance, or both. This condition can also be caused by a neurological disorder or after neurological injury. For men, bladder outlet obstruction is most often secondary to prostate hyperplasia. In women it is seen after anti-incontinence surgery, urethral stricture or dysfunctional voiding. When no obvious cause is found, the term idiopathic voiding dysfunction remains. For OAB as well as voiding dysfunction behavioral therapy, life style changes, or pelvic floor therapy can be applied with or without the support of anticholinergics, spasmolytics or botoxulinum toxine injections. Before recommending irreversible surgery, electrical stimulation has gained an important place in treatment flow charts. Electrical stimulation can be applied on different parts of the body. Percutaneous Tibial Nerve Stimulation (PTNS) is a very simple method of stimulating the tibial nerve through needling at the level of the ankle. It is thought that stimulation of this large nerve has an effect on the roots and their target organs. PTNS can be applied both for OAB symptoms as for voiding dysfunction. It has also been applied for pelvic pain syndrome. Since 1999 subjects with OAB complaints and voiding dysfunction have been enrolled in the PTNS protocol to investigate the effect of PTNS on their symptoms. The aim of this thesis is to investigate if PTNS is a useful alternative treatment option for patients with OAB or voiding dysfunction. Analysis of these data will be presented in this thesis.

Chapter 2 provides an introduction in urological anatomy of the lower urinary tract as well as the working mechanism of storage of urine.

Chapter 3 summarizes neurological and non-neurological causes of both OAB and voiding dysfunction. Some insights in pathophysiological changes of the bladder and innervation are discussed. During the research on PTNS, definitions and terms have changed. Definitions and terms have been replaced in all articles conform the latest International Continence Society (ICS) guidelines [Abrams et al., 2002]. New and relevant definitions for this thesis have been summarized and explained.

Urinary problems have been discussed more openly in recent years, but the real prevalence of these distressing and disabling conditions remains unclear. For the Netherlands, up to 46 % of the married

female population has experienced some degree of urinary incontinence according to the Dutch national postal questionnaire survey (**chapter 4**).

Using electrical eels, ancient Egyptians believed in the healing capacity of electric shocks. It was Galvani who observed a muscle twitch when he accidentally electrostimulated a frog leg in 1791. Further experiments with electricity followed. In the mid nineteenth century, Duchenne conducted extensive studies on the use of electricity in medicine. Most physicians had electrotherapeutic machines in their offices and prescribed electrotherapeutic baths and belts for home use [Devinsky, 1993]. Soon medical applications followed, so that following other organs, the bladder was targeted as an organ for stimulation. Electrostimulation therapy has recently been introduced as a promising treatment modality for overactive bladder and voiding dysfunction. Dr. Stoller stimulated afferent nerves of Macaca apes and found an effect on their micturition pattern. Soon stimulation of the posterior nerve in patients with OAB was investigated. PTNS is a simple procedure with an easily accessible stimulation site at the level of the ankle. **Chapter 5** provides an overview of all kinds of electrical stimulations that had been performed to treat voiding complaints. The PTNS protocol, technique, inclusion and exclusion criteria are also documented in this section.

In 1999 the first patients were enrolled in the PTNS protocol in the Netherlands. These very first results of PTNS are presented in **chapter 6**.

Stimulated by the promising results, patients all over the Netherlands and patients from the collaborating University of Rome, Italy, were enrolled. Protocols were completed and sent back to the investigating site the University Medical Centre St. Radboud, Nijmegen. **Chapter 7 and 8** present the analysis of data from patients with OAB respectively voiding dysfunction, who underwent PTNS in 12 weekly sessions.

Although the subjective improvement of the patient should be the main goal of a treatment, it is clear that in a research setting objectivity should be formost. Regarding bladder function, bladder diaries and urodynamics were chosen as objective tools to investigate the effect of PTNS. In **chapter 9** the urodynamic data of patients with OAB are described and in **chapter 10** the data of candidates with voiding dysfunctions are presented. For both groups, predictive factors for success were investigated.

Finally, conclusions are drawn and future prospectives are listed in **chapter 11**.

Chapter 12 contains a Dutch translation of this summary and conclusion.

CHAPTER 2

Anatomy and physiology of the lower urinary tract

2.1 ANATOMY

The main function of the lower urinary tract is to store and expel urine. The urinary bladder is a hollow organ with strong muscular walls, the detrusor muscle, which functions as a reservoir. When empty, the bladder is entirely located within the pelvis. As it fills, it can contain about 500 cc or more while it rises into the abdominal cavity. The bladder neck, urethra and pelvic floor form the bladder outlet and facilitate urine evacuation. From both sides the ureters penetrate the bladder in its posterolateral wall after tunnelling the bladder wall obliquely over a 1-2 cm long traject to end as the ureteral orifices. The posterolateral angles formed by the ureters orifices and the internal orifice of the urethra form a triangular area: trigonium vesicae. The bladder is composed of four layers: serous, muscular, submucosal and mucosal layers. The tunica mucosa is continuous with the lining membrane of the ureters and renal pelvis, and below with that of the proximal urethra. The areolar tissue of the tunica submucosa connects the mucosa only slightly; it makes the bladder look wrinkled when contracted. Over the trigonium vesicae the mucous membrane is firmly attached to the muscular coat, and thus looks smooth and flat. The tunica muscularis consists of three layers. The internal longitudinal layer is thin, fibres are organised for the most part in a longitudinal direction. In the middle layer, the fibres are irregularly scattered, but circularly arranged toward the lower part forming a thick circular sphincter vesicae around the urethral orifice. In male the sphincter fibres are continuous with the muscular fibres of the prostate. The external layer has been named the detrusor urinae muscle and is composed of fibres organised in a longitudinal arrangement. It arises from the posterior pubovesical muscle, passes over the vertex and attach to the prostate or anterior vagina. At the lateral sides fibres pass obliquely and intersect one another. The outer tunica serosa is derived from the peritoneum. The physiological internal sphincter maintains continence by closure of the bladder neck and proximal urethra. Continence is thought to be dependent on a combination of urethral wall tension, the calibre of the urethral lumen and the functional length. The striated muscles surrounding the urethra are not essential for urinary incontinence but are important in the voluntary termination of urine flow and prevention of stress incontinence [de Groat W et al., 1993; Gray H, 1995; Steers W, 1998].

2.2 INNERVATION

Storage and expulsion of urine is the result of complex neural network interactions. Different neural circuits located in brain, brain stem, spinal cord and peripheral nerves and ganglia regulate bladder filling and coordinated micturition. Interaction of somatic and autonomic efferent signals, voluntary on-off control mechanism and learned behaviour modulate the lower urinary tract's function.

The innervation of the lower urinary tract is derived from three sets of peripheral nerves:

- sacral parasympathetic (pelvic nerves)
- thoracolumbar (ortho)-sympathetic (hypogastric nerves and sympathetic chain)
- sacral somatic (predominantly pudendal nerves)

2.2.1 SACRAL PARASYMPATHETIC (PS) PATHWAY

Sacral parasympathetic efferent outflow originates from the S2-S3-S4 segments of the spinal cord and is conveyed by the pelvic nerve projecting to the bladder, urethra and prostate. The perikarya are organised in a viscerotopic manner in the intermediolateral columns of the spinal cord, this explains why discrete lesions can spare some of the pelvic visceral functions. The curvilinear plexus lies in the pelvic fascia on either side of the lower genitourinary tract and rectum. It coordinates visceral and somatic function of pelvic organs (micturition, defecation, erection, ejaculation and lower limb movements) [Steers W, 1998]. Parasympathetic input excites the bladder through preganglionic cholinergic neurons to ganglionic cells in the pelvic plexus and bladder wall. Through nicotinic cholinergic mechanism, transmission in bladder ganglia is mediated and in turn excites the bladder smooth muscle through muscarinic receptors. The human bladder is endowed with M2 and M3 receptors. M2 receptors are voltage linked as M3 receptors are G protein or Calcium mediated. Blocking one type of receptor may not completely abolish bladder contraction. Aside from different types of receptors, the binding properties of these receptors may be altered following smooth muscle hypertrophy or nerve injury. Changes can be rapid, e.g. in a few hours after bladder outlet obstruction. Therapy resistant overactivity of the bladder may also be caused by other non-cholinergic mechanisms. For example Adenosine trifosphate (ATP) causes bladder contractions in animal experiments. Zhong et al. suggest that ATP may play an important role in mediating urinary bladder filling and nociception [Zhong Y, et al., 2003]. Most probably, a cascade of mediators, released from the urothelium and the suburothelium plexus of nerves in response to bladder distension, can initiate or depress activation of the bladder. The firing of suburothelial afferent nerves and the threshold for bladder activation may be modified by both inhibitory (e.g., nitric oxide) and stimulatory (e.g., ATP, tachykinins, prostanoids) mediators. These mechanisms can be involved in the generation of bladder overactivity, causing urgency, frequency and incontinence, and thus seems to be interesting targets for pharmacologic intervention [Andersson K-E., 2002].

2.2.2 SOMATIC EFFERENT PATHWAYS

Somatic efferent pathways to the external urethral sphincter are carried in the pudendal nerve from the anterior horn cells in the second, third and fourth sacral segments. The motor neurons are topographical organised in the nucleus of Onuf. Cells within Onuf's nucleus are unique in that their properties and size more closely resemble autonomic neurons rather than other somatic motoneurons within the spinal cord. The pudendal nerve divides into two terminal branches; the perineal nerve (innervating the skin of the scrotum or labia) and the dorsal nerve of the penis or clitoris. Muscular branches are distributed to the superficial transverse perineal muscle, bulbocavernous muscle, ischiocavernosous muscle and urethral constrictor muscle. Visceral branches arise from the fourth and third and sometimes second sacral nerve and are supplying the bladder and rectum, and in women the vagina. They communicate with the pelvic plexuses of the sympathetic pathway. Before its division it gives off the inferior hemorrhoidal nerve [Gray H, 1995].

2.2.3 (ORTHO) SYMPATHETIC (OS) PATHWAY

Sympathetic preganglionic pathways arise from Th10-L2 spinal segments; pass to the sympathetic chain ganglia and then to the prevertebral ganglia in the superior hypogastric and pelvic plexuses. Efferent signals reach adrenergic neurons in the bladder and urethra. Adrenergic receptors are classified according to their responses to norepinephrine and its compounds. α-receptors are found in the smooth muscles of small arterioles and sphincter muscles of the bladder; activation produces smooth muscle contraction. Stimulation of β-receptors found in the bladder wall muscles causes bladder relaxation. Sympathetic postganglionic nerves release norepinephrine and provide an excitatory input to smooth muscle of the urethra and bladder base, an inhibitory input to smooth muscle in the body of the bladder, as well as inhibitory and facilitary input to vesical parasympathetic ganglia. The vesicosympathetic reflex is a negative feedback mechanism: an increase in bladder pressure results in an increase in inhibitory input, allowing the bladder to fill to larger volumes [de Groat WC, 1993].

2.2.4 AFFERENT PATHWAYS

Afferent activity arising in the bladder is conveyed to the central nervous system over both sets of autonomic nerves. Ascending routes transmitting both bladder sensation and trigger voiding,

travel in the lateral spinothalamic tract [Nathan and Smith 1958]. The most important afferents for initiating micturition are those running in the pelvic nerve to the sacral spinal cord. These afferents consist of small myelinated (Aδ) and unmyelinated (C) fibres, which convey impulses from tension receptors and nociceptors in the bladder wall [de Groat, 1997]. Electrophysiological studies in the cat have shown that Aδ afferents respond to passive distension and contraction of the bladder. These afferents are activated at 5-15 mmHg intravesical pressure; this pressure range corresponds to the first sensation of bladder filling.

High threshold C fibres (unmyelinated) afferents have also been detected in cat bladder. Under normal conditions, the large majority of these afferents do not respond to bladder distension, and therefore are termed silent C fibres. But many are activated by chemical irritation of the bladder mucosa or cold. After chemical irritation or cold water irrigation (Bors' ice water test), C fibres exhibit spontaneous firing with the bladder empty and increase firing during bladder distension. Activation of C fibres facilitates the micturition reflex and decreases bladder capacity. Administration of capsaicin, a neurotoxin that desensitises C fibres, blocks facilitation, but the neurotoxin does not block the micturition reflex in normal animals, indicating that C fibres pathways are not essential for normal voiding [de Groat, 1997; Fall et al., 1996].

2.3 ALL OR NOTHING

When sufficiently activated, mechanoreceptors of the bladder trigger a coordinated response via the pontine centre: a spinobulbospinal reflex. The reflex detrusor contraction generates an increased bladder wall tension and also a stronger activation of the bladder mechanoreceptors. In turn, this reinforces bladder output and leads to further increase in pressure which in its turn enhances receptor activation. This control mechanism is considered as a positive feed-back, self-generating to a large extent once initiated and explain the all-or-nothing behaviour of the parasympathetic motor pathway to the bladder. Once urine pass the urethra, contraction is further enhanced by reflex excitation from urethral receptors [Fall M et al., 1991].

2.4 SAFETY ROUTES

The system of interacting neural networks can easily become unstable. Any stimulus that increases intravesical pressure may trigger a full-blown micturition reflex. Fortunately the micturition cyclus is modified by several pathways. The best known spinal mechanism is the guarding reflex where reflex activation of the urethral sphincter is enhanced in response to bladder mechanoreceptor activation.

An analogous mechanism is the Edvardsen's reflex which, in response to increased intravesical pressure, will activate the sympathetic inhibitory efferents [Fall M et al., 1991]. Other spinal inhibitory systems are signals arising from the afferent anorectal branches of the pelvic nerves, the dorsal clitoral and penile branches of the pudendal nerves and various nerves from the lower limbs. They activate the inhibitory sympathetic neurons and inhibit the bladder motoneurons via direct sacral route [Lindstrom et al., 1989; Fall et al., 1991].

2.5 CENTRAL PROCESSING

Stimulation and lesioning studies in the cat have revealed localisation of specific areas controlling micturition. Sacral inputs from the bladder terminate in the ventrolateral periaquaductal gray area (PAG). Here signals are processed and projected to the micturition centre. A discrete dorsomedial region in the pons (M region) contacts dendrites of the parasympathetic bladder motor neurons producing bladder contraction and relaxation of anal and urethral sphincters. Bilateral lesioning of the M region in cats produces detrusor-sphincter dyssynergia. The M region or Pontine Micturition Centre (PMC) or Barrington's nucleus receives information from various regions of the brain. Cortical regions (medial frontal gyrus and anterior cingulated lobe) as well as subcortical regions (medial preoptic region of the hypothalamus, the septum and amygdale) all send projections to the M region. These pathways explain emotional and homeostatic influences on micturition and indicate that micturition may begin in ideal circumstances [Holstege et al., 1986; Blok and Holstege 1994]. Stimulation of a more lateral region (L region) projects directly to the nucleus of Onuf in the sacral cord and produces both contraction and relaxation of the external urethral sphincter in cats and rats; bilateral destruction induces bladder hyperactivity and urinary incontinence. As the PMC/ M region facilitates bladder activity, the L region regulates the bladder storage function through stimulation of the pelvic floor muscles. Stimulation of the L region results in strong excitation of the pelvic floor and increase in urethral pressure.

Emotions or psychological stressors can have profound influence on voiding. For example psychogenic retention or anxiety is associated with non-relaxation of the bladder neck or acontractility of the detrusor. The role of basal ganglia, parietal, frontal cortex and cerebellum has been documented by studies describing lower urinary tract dysfunction after CVA, epilepsy and intracranial tumours. Although both excitatory and inhibitory effects have been described, the net effect is often overactivity resulting in overactive detrusor and incontinence [Morrison J, 2002].

2.6 STORAGE AND FILLING

Under normal conditions, the urinary bladder and the outlet exhibit a reciprocal relation in effecting the storage and elimination of urine. During filling, the bladder neck and proximal urethra are closed and the intraurethral pressure range from 20 to 50 cm H20. During this time the detrusor muscle is quiescent, allowing the intravesical pressure to remain low (5-10 cm H20) over a wide range of bladder volumes. Information about the degree of filling is conveyed by the pelvic nerve through the lumbosacral cord to the periaquaductal grey (PAG). Bladder filling is a primarily passive phenomenon that is dependent on the intrinsic properties of the vesical smooth muscle and the inactivity of the parasympathetic efferent pathway [de Groat, 1997].

During filling the activity of the sphincter increases reflecting increased efferent firing from the pudendal nerve (Onuf). Pudendal motorneuron firing occurs when the bladder is filled or following sudden increase in intravesical pressure: the guarding of continence reflex. Hypogastric firing is initiated by a lumbosacral intersegmental spinal reflex: pelvic afferents enter the sacral cord and ascend to thoracolumbar sympathetic preganglionic fibres. The storage reflex represents a negative feedback mechanism whereby elevations in intravesical pressure trigger inhibitory input to the bladder and allow greater urine accommodation.

When the bladder is filled to such a degree that voiding can take place, PAG activates neurons in the PMC/M region. Descending axons projected to sacral preganglionic neurons are responsible for bladder contraction and urethral relaxation, as well as inhibition of pudendal motoneurons in Onuf's nucleus, which innervate the striated external urethral sphincter [Steers WD, 1998; Blok, 1998]. For micturition, the initial event is a reduction of intraurethral pressure, which reflects a relaxation of the pelvic floor and the paraurethral striated muscles. Then the urethra shortens and the bladder neck opens. Changes in the urethra are quickly followed by contractions of the detrusor and a rise in intravesical pressure that is maintained until the bladder empties.

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CHAPTER 3

Voiding dysfunction: causes, pathophysiology and definitions

Candidates for Percutaneous Posterior Tibial Nerve Stimulation were mainly patients with idiopathic voiding dysfunction. Meaning that patients with an obvious neurological disorder that caused their voiding dysfunction complaints were excluded. Also inflammation, bladder outlet obstruction or other treatable causes were exclusion criteria for PTNS treatment. Neurological and non-neurological causes for voiding dysfunction as well as the pathophysiology are summarized in this chapter.

3.1 BLADDER OVERACTIVITY

A European study of nearly 17, 000 subjects over the age of 40, reported that 16.6% of the participants (or an estimated prevalence of 22.2 million) have symptoms consistent with OAB. As this age group is increasing, the impact of OAB will increase in the future. Quality of life surveys document that urinary frequency, urgency and nocturia are some of the most bothersome aspects of voiding dysfunction [Milson et al., 2001]. Detrusor overactivity is commonly seen in neurological disease or after neurological injury. Diseases at or above the brain stem, involving the spinal cord or distal to the spinal cord often results in detrusor overactivity. Aging, inflammation, bladder outlet obstruction or irritation of the bladder wall can induce overactivity. Furthermore gender and depression can predispose to overactive bladder complaints. When there is no specific cause, the overactivity is defined as idiopathic. Storage failure can also occur in the absence of detrusor overactivity, secondary to pain or hypersensitivity. Interstitial Cystitis or painful bladder syndrome is a classic example [Wein, 1998].

3.1.1 NEUROLOGICAL CAUSES

DISEASES AT OR ABOVE THE BRAIN STEM

Disorders at or above the brain stem often results in detrusor overactivity. Examples are cerebrovascular disease, dementia, concussion, brain tumour, cerebellar ataxia, normal pressure hydrocephalus, cerebral palsy, Parkinson's disease and Shy-Drager syndrome. Cerebrovascular disease includes thrombosis, occlusion and hemorrhage and can lead to ischemia and infarction of variably sized areas in the brain. The effect on micturition depends on localization and size of the damage. After an initial acute episode urinary retention may occur. The most commonly long-term dysfunction is detrusor overactivity. Cerebral infarction causes plasticity in GABA (Gamma-amino butyric acid) mediated inhibitory neurons and glutaminergic excitatory transmission, resulting in OAB. In 44 to 83% of the patients overactivity is accompanied by incontinence shortly after the "cerebral shock", in 80 % continence will be regained. Estimations place the incidence of underactivity or acontractility as high as 20%. Dementia disease is poorly understood but involves atrophy and loss of gray and white matter of the brain, particularly in the frontal lobes. If voiding dysfunction occurs,

this results often in incontinence. This can be due to detrusor overactivity or weak striated sphincter or failure of mentation with micturition inappropriately timed. Parkinson's disease is a degenerative disease that affects the dopaminergic substantia nigra and corpus striatum pathway, resulting in a dopamine deficiency and cholinergic predominance in the corpus striatum and loss of pigmented neurons characterized by the intracytoplasmatic inclusion bodies called Lewy bodies. Projections of dopamine containing neurons from the substantia nigra have opposing effects on the bladder. In Parkinson's disease excitatory signals for micturition are increased whereas rostral fibres that elevate the micturition threshold are inhibited. This results in a net excitatory effect on micturition reflexes with a reduced volume threshold and unstable bladder contractions. Voiding dysfunction occurs in 35 to 70 % of the patients. 50 to 70% of the symptoms consist of urgency, frequency, nocturia and incontinence. The remainder has obstructive complaints. The most common urodynamic finding is detrusor overactivity with synergic micturition. Pseudodyssynergia may occur as a delay in striated sphincter relaxation at the onset of voiding. Also impaired detrusor contractility can occur. Detection of poor sphincter control is important as desobstructive prostatectomy can result in such cases to worsening of voiding complaints and /or incontinence.

DISEASES PRIMARILY INVOLVING THE SPINAL CORD

Such diseases are for instance multiple sclerosis, spinal cord injury and disease, neurospinal dysraphism, tabes dorsalis, pernicious anemia and poliomyelitis. Multiple Sclerosis is caused by an autoimmune-induced focal neural demyelination, generally characterized by axonal sparing, in the brain and spinal cord. Demyelination causes reduced conduction in axonal pathways, resulting in various neurological abnormalities. This process commonly affects the laterocorticospinal (pyramidal) and reticulospinal columns of the cervical spine that might lead to voiding dysfunction and sphincter dysfunction. 50 to 90% of the patients will have urinary complaints at some point. Lower urinary tract symptoms may represent the sole initial complaint in up to 10% of patients. Detrusor overactivity is the most commonly detected urodynamic abnormality. When present, coexistent sphincter dyssynergia is present in 30-65% of the patients. Hypo- or acontractile detrusor activity can also occur. Spinal cord injury can be divided in complete or incomplete lesions and in suprasacral and sacral cord lesions. Sacral spinal cord begins at spinal column level T12 to L1. The spinal cord terminates in the cauda equina at approximately the spinal column level of L2. After a spinal shock phase, with a flaccid bladder and competent bladder neck, complete suprasacral spinal cord lesions will result in detrusor overactivity with internal sphincter synergia and external sphincter dyssynergia. This is mediated by spinal micturition reflex that emerges in response to a reorganisation of synaptic connections in the spinal cord. Capsaicin-sensitive C fibres, normally silent, mediate spinal reflexes. These C fibres are also thought to play a role in upper motoneuron disease such as Parkinson's disease and multiple sclerosis. Plasticity in dorsal root ganglia cell of the bladder manifests in enlargements of these cells and increased excitability. Also NGF is involved in hypertrophy of these cells.

DISEASES DISTAL TO THE SPINAL CORD

Spinal stenosis, radical pelvic surgery, herpes zoster, diabetes mellitus and Guillain-Barré are examples of disorders distal to the spinal cord that can cause overactive bladders. Occasionally patients with disc prolaps may have overactive bladder complaints due to irritation of the nerve roots. Generally these patients will present with difficult voiding. In spinal stenosis symptoms may range from cervical spinal cord compression to cauda equina syndrome. Herpes Zoster may lead to detrusor hyperreflexia probably due to nerve root irritation. However urinary retention during the first days or weeks is the result of viral invasion of the sacral dorsal root and posterior nerve roots. Diabetes mellitus is the most common cause of peripheral neuropathy in Europe and North America. The classic example of voiding dysfunction due to diabetes is that of a neuropathy affecting complete emptying of the bladder. However detrusor overactivity may also be seen. The cause for neuropathic changes must then be sought outside the bladder.

3.1.2 NON-NEUROLOGICAL CAUSES

Aging, inflammation, bladder outlet obstruction or irritation of the bladder wall or idiopathic detrusor overactivity can induce overactive bladder complaints. Bladder outlet obstruction often produces detrusor hypertrophy and detrusor overactivity (DO). Obstruction induced DO has been attributed to a denervation supersensitivity. Bladder outlet obstruction stimulates an increased expression of certain genes (e.g. GAP-43) which has been associated with axonal sprouting. It suggests enhancement or de novo development of new spinal circuits following bladder obstruction. Bladder outlet obstruction appears to initiate the morphological and electrophysiological afferent plasticity via a mechanism involving Nerve Growth Factor NGF. NGF is responsible for the growth and maintenance of sympathetic and sensory neurons and has been shown responsible for neuronal regrowth after injury. NGF content is increased in obstructed bladders and can result in neuron enlargement and development of urinary frequency. Relief of obstruction might reverse the neuroplasticity to normal voiding. Also inflammation is accompanied by neuroplasticity in sensory nerves.

Reduced threshold for bladder afferents occurs. Increased expression of the early-mediated gene c-fos, has been detected in lumbosacral cord and increased expression of nitric oxide synthase occurs in bladder afferent neurons [Birder et al., 1998; Vizzard 1996]. The neuroplasticity and involvement of NGF in inflammation conditions resemble to that of bladder obstruction.

The lower urinary tract changes with age even in the absence of disease. Bladder contractility, capacity and ability to postpone voiding decline in both sexes. In women, urethral length and maximum closure pressure deteriorate, whereas in half of the men prostate enlargement causes urodynamic obstruction. Prevalence of detrusor overactivity increases and postvoid residuals increase. The

mnemonic "DIAPERS" or Delirium, Infection, Atrophic urethritis/ vaginitis, Pharmaceuticals, Excess urine output, Restricted mobility and Stool impaction commonly contributes to geriatric incontinence. Nearly 60% of the incontinent institutionalized persons revealed to have OAB. The distinction between detrusor overactivity and central nerve lesions such as past stroke or Alzheimer's disease is at high age often unclear. Elbadawi et al. found abundant protrusion junctions and abutments on detailed ultra structure smooth muscle studies. These changes are thought to be involved in the increased electrical coupling and generating overactivity [Elbadawi et al., 1993]. Some studies found an increased response to α-adrenergic excitatory response and decreased β-adrenergic inhibitory response resulting in a net contracting effect of noradrenaline in the aged bladder in contrast to the relaxing effect of noradrenaline in young bladders. This finally might reduce the functional capacity and result in urinary frequency and urgency in the elderly patients [Wein, 1998]. Wolfe et al. suggest that depression, anxiety, feeding disturbances, pain, irritable bowel syndrome, fibromyalgia and changes in voiding are associated with disturbances of serotonin or 5-hydroxytryptamine (5-HT) [Wolfe et al., 1997]. The strongest evidence for this theory is the remarkable effect of selective serotonin re-uptake inhibitors (SSRI-s) in this group of patients. Pharmacological data suggest that 5-HT inhibits micturition reflex pathways. Thus reduced 5-HT transmission may lead to enhanced bladder activity and lowered volume threshold for voiding [Zorn et al., 1999]. Reviews suggest that women are more prone to urge incontinence and depression than men, and that both conditions are more common at times of hormonal changes [Morrison J, 2002]. Levels of 5-HT are substantially lower (nearly 50%) in female brains. In rats, administration of estradiol increases the density of 5-HT receptors in the brain. Furthermore estradiol modifies cognition, emotions, pain and autonomic function by acting on 5-HT neural pathways. Data support the linkage of reduced activity of 5-HT and hormonal influences, and depression and overactive bladder.

Idiopathic detrusor overactivity can be diagnosed when all other possible causes are excluded. Idiopathic detrusor overactivity seems to respond better to anticholinergics than the neurological forms suggesting increased local release of acetylcholine (Koelbl H et al., 2002)

3.1.3 PATHOPHYSIOLOGY OF OAB

Disturbances of peripheral nerves and tissue can cause bladder overactivity. A new appreciation is that long-term events involves growth factors, such as NGF, neurotransmitters and prostaglandins, that provide communication between muscle and nerve. NGF can induce regrowth and sprouting of affected neurons and hereby affect micturition. Common features of human and animal overactive bladders showed increased spontaneous myogenic activity, fused tetanic contractions, altered responsiveness to stimuli, characteristic changes in smooth muscle ultrastructure (e.g. protrusion

junctions and ultra-close abutments between smooth muscle cells, which is rarely seen in normal tissue) [Elbadawi et al., 1993].

Detrusor smooth muscle bundles are not well coupled as in most visceral smooth muscles. This poor coupling prevents that under normal conditions, spontaneous activation of a bundle resulting in a synchronous activation of bladder wall smooth muscles. Denser innervation allows more synchronous activation and thus detrusor activity. This theory correlates with the ultrastructural findings of close abutments and protrusion junctions in muscle strips of overactive bladders. Increased excitability combined with greater connectivity could result in generation of a focus of electrical activity that can rapidly spread and produce an involuntary contraction [Mills et al., 1999].

Section of bladder wall from overactive human bladder frequently showed patchy denervation of muscle bundles [German et al., 1999]. The denervated areas become infiltrated with connective tissue elements such as collagen and elastin, also hypertrophy of smooth muscle is seen. Animal experiments showed that spinal section or urethral obstruction resulted in increase of size of both afferent roots of the dorsal root ganglia as the efferent neurons from the pelvic plexus [Steers et al., 1990]. After spinal injury electrophysiological measurements showed a shorter delay in micturition reflex. The hypothesis is that neuronal reorganisation remodulates the spinobulbospinal pathway into a purely spino-spinal pathway. In these overactive bladders, ice water test can trigger the activation of -normally silent- C fibres. Intravesical instillation of capsaicin or resiniferatoxin is then an effective treatment for many overactive bladders [Geirsson et al., 1993; Geirsson et al., 1997].

The patchy denervation suggests the death of some intrinsic neurons most likely due to ischemia. Experiments showed that a rise in intravesical pressure higher than 40 cm water can seriously compromise the bladder wall blood supply [Brading et al., 1999; Greenland et al., 1996]. Increased metabolic demand is seen in hypertrophic wall due to outflow obstruction or detrusor sphincter dyssynergia. Increased workload of the bladder increase the release of NGF. This may induce sprouting and new abnormal connection of axon terminals between interneurons or motoneurons with for instance the silent C fibres [Steers et al., 1996].

Coolsaet et al. suggest that urgency is triggered by local distortions in the bladder wall [Coolsaet et al., 1993]. This would activate a population of nerve fibres that might specifically mediate the sensation of urgency. In overactive bladders this activity might spread because of increased electrical connectivity and result in premature sensation of urgency and involuntary rise of pressure. This theory supports the working of anticholinergics suppressing the urgency feeling and overactivity caused by the overactive sensory nerves, but still allow normal micturition.

3.1.4 TREATMENT

First behavioral therapy educates the patient, informs him or she about lifestyle changes and retrains the bladder by time-voiding or pelvic floor physiotherapy. This requires motivated patients. Furthermore, treatment is directed toward inhibiting bladder contractility (by means of anticholinergics or injection of botulinum toxin), decreasing sensory input (for example by instillation with capsaicin), mechanically increasing bladder capacity (Helmstein procedure), or increasing outlet resistance (bulk injection or suspension of the urethra), either continuously or just during increasing intra-abdominal pressure. Electrical stimulation has been used to treat disorders of both bladder storage and emptying. If conservative methods fail surgical option include denervation procedure (e.g. sacral rhizotomy) to augmentation cystoplasty [Wein et al., 1998].

3.2 URINARY RETENTION

Absolute or relative failure to empty the bladder results from decreased bladder contractility with a decrease in magnitude or duration, increased outlet resistance or both. Decreased detrusor activity may result from temporary or permanent alteration in neuromuscular mechanism that initiates or maintains detrusor contraction.

3.2.1 NEUROLOGICAL CAUSES:

DISEASES AT OR ABOVE THE BRAIN STEM

Acute urinary retention can occur after CVA; but has also been described in brain tumours in the frontal cortex or posterior fossa. In Parkinson's disease also impaired detrusor contractility can occur.

DISEASES PRIMARILY INVOLVING THE SPINAL CORD

In the spinal shock phase after spinal cord injury, retention is the rule. A complete sacral spinal cord lesion or a lesion of the sacral roots, result in skeletal flaccidity below that level. This results in detrusor acontractility and attempted voiding that is insufficient to decrease residual urine to less than 10% of bladder capacity. For patients with MS obstructive symptoms with urinary retention occur in 2% to 52%. Also here the form of acute retention may be the sole initial complaint of MS.

DISEASES DISTAL TO THE SPINAL CORD

Disc prolaps can compress the spinal roots in L4-L5 and L5-S1 vertebral interspaces. If voiding dysfunction is present, the most urodynamic finding is that of a normal compliant acontractile bladder associated with normal innervations or incomplete denervation of the perineal floor musculature. Laminectomy may not always reverse the bladder function. Radical pelvic surgery like abdominoperineal resection and radical hysterectomy can cause pelvic plexus injury and lead to voiding dysfunction. It has been estimated that in 15 to 20% of affected individuals, the voiding dysfunction is permanent. The injury may be a consequence to denervation, tethering, or encasement of the nerves in the scar, direct bladder or urethral trauma, or bladder devascularisation. Adjuvant chemotherapy or radiation may play a role as well. Generally there will be a failure of adequate bladder contraction. Diabetes mellitus is the most common cause of peripheral neuropathy in Europe and North America. The classic example of voiding dysfunction due to diabetes is that of a neuropathy affecting the sensory afferent pathways causing an insidious onset of impaired bladder sensation. The danger of increased overdistension and decompensation eventually occur. Urodynamically impaired sensation, increased capacity, decreased contractility, impaired flowmetry and increased residual volumes characterize the diabetic cystopathy [Wein et al., 1998]. Herpes Zoster may produce urinary retention after viral invasion of dorsal sacral roots and posterior nerve roots. But also the painful mucosal eruptions can play a role in inhibition of the micturition.

3.2.2 NON-NEUROLOGICAL CAUSES

BLADDER OUTLET OBSTRUCTION AND RETENTION

Increased outlet resistance is generally seen in men and most often secondary to prostate hyperplasia, but it may be due to a failure of coordination of the striated or smooth sphincter, to a urethral stricture or bladder neck dysfunction. Striated sphincter dyssynergia is a common cause of functional obstruction in patients with neurological disease or injury [Wein et al., 1998]. Urinary retention is fairly common in adult men, but in women it occurs less. Potential causes are neurological, pharmacological, anatomic, myopathic, functional or psychogenic. Bladder outlet obstruction in women is seen because of urethral stricture, dysfunctional voiding, true sphincter dyssynergia, urethra diverticulum, primary bladder neck obstruction, or after anti-incontinence surgery. The Fowler syndrome refers to a particular syndrome of urinary retention in young women in the absence of any overt neurological disease (Fowler, 1999). On concentric needle electrodes examination of the striated muscles of the urethral sphincter, Fowler described a unique EMG abnormality with complex repetitive discharges and decelerating bursts. These patients often have polycystic ovaries, raising the possibility to a hormonal abnormality.

POSTOPERATIVE URINARY RETENTION

Postoperative urinary retention is a well recognized but poorly understood event. Its incidence quoted overall as 4 to 25 %. Contributing factors are traumatic catheterisation, bladder overdistension, diminished awareness of bladders sensation, decreased bladder contractility, increased outlet resistance, decreased micturition reflex activity, nociceptive inhibitory reflex and pre-existent outlet pathology. The incidence of voiding dysfunction after radical pelvic surgery is estimated to be 20% to 68% and in 15-20% of affected individuals the dysfunction is permanent.

INHIBITION OF VOIDING REFLEX AND NON-NEUROGENIC IMPAIRMENT

This can occur secondary to painful stimuli, especially if it arise from the pelvic or perineal areas (e.g. seen with herpes infection) or such an inhibition can be psychogenic. Non-neurogenic impairment of bladder function can be the result of overdistension, severe infection or fibrosis [Wein et al., 1998].

3.2.2 PATHOPHYSIOLOGY OF URINARY RETENTION

Bladder outlet obstruction has been postulated to be associated with partial denervation, owing to damage of the intrinsic innervation of the bladder smooth muscle from a combination of pressure and ischemia [Turner et al., 1997]. A breakdown of the structure and function of the proteins that enable the smooth muscle cells to take up, store, and release calcium, would affect the calcium activation of the contractile mechanism [Zderic et al., 1998]. Voiding dysfunction secondary to diabetes is a peripheral and autonomic neuropathy that first affects sensory afferent pathways, causing the insidious onset of impaired bladder sensation. This results in a gradual increase in time interval between voiding, without sensing any real urgency. If this continues, detrusor distension, overdistension, and decompensation finally occur. Hyperglycemia is proposed to lead to microvascular and neurologic complications, the neurologic sequelae ultimately resulting in a loss of myelinated and unmyelinated fibers, Wallerian degeneration, and blunted nerve fiber reproduction and function [Clarck et al., 1995]. The proposed mechanisms include increased accumulation of polyols (sorbitol) inhibiting synthesis of myoinositol. This in turn depresses phosphoinositide metabolism and decreases Na+-K+-ATPase activity. Hyperglycemia also leads to the formation of advanced glycosylation end products of glucose. One also suggests that diabetes diminishes sodium pump activity, thereby inhibiting agonist-induced contractions in bladder smooth muscle by an increase in intracellular sodium concentration, the latter acting to diminish calcium influx. In elderly detrusor underactivity is usually idiopathic. In the absence of obstruction or neuropathy, it is characterized at cellular level by widespread degenerative changes of both muscle cells and axons [Elbadawi et al., 1993]. When it causes incontinence, detrusor underactivity is associated with “overflow incontinence” (<10% of geriatric incontinence). A

mild degree of bladder weakness occurs quite commonly in older individuals. Reduced energy supply (ATP) results in a decrease in tonic response of the urethra and pressure, contributing to urine loss in women. In men fatigued aged bladder generates a less strong and less sustained contraction resulting in a decreased flow rate and increased residual volume even in the absence of any obstruction. Animal experiments support the theory that aging is associated with progressive reduction in the ability of generating energy by oxidative phosphorylation, and reduce the capacity to sustain bladder contraction. Gilpin et al. found that the amount of nerve per square mm detrusor muscle decreased with age in both women and men, just as it happens for skeletal muscles [Gilpin et al., 1986]. With aging a decrease in bladder sensation is found, which is strongest in the eight and ninth decade.

3.2.3 TREATMENT

Treatment of emptying failure generally consists of attempts to increase intravesical pressure or facilitate the micturition reflex (for example by neuromodulation), to decrease outlet resistance (transurethral desobstructive resection of hyperplasic prostate tissue or coordinated physiotherapy) or both. If all else fails or the attempt is impractical, catheterisation is an effective way of circumventing emptying failure [Wein et al., 1998].

3.3 DEFINITIONS

During the past years, terminology describing lower urinary tract dysfunction has been changed. An effort in this thesis was made to conform to the ICS recommendations. This paragraph summarizes relevant terminology frequently used in the thesis [Abrams et al., 2002].

- Increased daytime frequency: the patient considers that he or she voids too often.
- Nocturia: the patient has to wake at night one or more times to void.
- Urgency: the complaint of a sudden compelling desire to pass urine, which is difficult to defer.
- Urinary incontinence (UI): the complaint of any involuntary leakage of urine.
  - Stress UI: the complaint of involuntary leakage of urine on effort or exertion, or on sneezing or coughing.
  - Urge UI: the complaint of involuntary leakage accompanied by or immediately preceeded by urgency.

- Mixed UI: the complaint of involuntary leakage associated with urgency and also on exertion, effort, sneezing or coughing.

The report suggests that UI should be described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, the measure used to contain the leakage, and whether or not the patient seeks or desires help because of UI. This information illustrates the impact of LUTD on patients' life. In our studies urodynamic investigation, bladder diaries and quality of life questionnaires correspond well to the ICS recommendations.

- Overactive bladder syndrome – urge syndrome –urgency/frequency syndrome: this syndrome is defined as the complaints of urgency, with or without urge incontinence, usually with frequency and nocturia.
  These terms are usually suggestive for urodynamically demonstrable detrusor overactivity, but can be due to other forms of urethro-vesical dysfunction.

- Bladder diary: the diary lists voiding time, volumes, incontinence episodes, pad usage and other information such as fluid intake, degree of urgency and degree of incontinence.

- Detrusor overactivity: an urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked.
  In the latest report there is no longer a limit defined for the amplitude of an involuntary detrusor contraction. In the PTNS urodynamic data detrusor overactivity was defined as an increase of 15 cm water pressure (the definition conforms to the definition in 1998) or of lower amplitude if accompanied with a distinct sensation of urgency.

- Detrusor overactivity incontinence: this is UI due to involuntary detrusor overactivity.

- Detrusor underactivity is the contraction of reduced strength and/ or duration, resulting in prolonged emptying and/ or failure to achieve complete bladder emptying within normal time span.

- Acontractile detrusor is one that cannot contract.

- Post void residual (PVR) is the volume left in the bladder at the end of micturition. In the PTNS urodynamica data PVR was measured to recalculate the cystometric capacity. Our observation that natural filling had an impact on the cystometric capacity was presented on the ICS congress in 2001 and later published [Heesakkers et al., 2003].

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CHAPTER 4

The prevalence of urinary incontinence in community dwelling married women: a matter of definition

Based on
THE PREVALENCE OF URINARY INCONTINENCE IN COMMUNITY DWELLING MARRIED WOMEN: A MATTER OF DEFINITION

V. VANDONINCK, B.L.H. BEMELMANS, C. MAZZETTA, C. ROBERTSON, M. KEECH, P. BOYLE, L.A. KIEMENEY
on behalf of the UREPIK study group *

V. Vandoninck, M.D., research fellow, Dept. of Urology, University Medical Centre Nijmegen (The Netherlands)
B.L.H. Bemelmans, M.D., Ph.D., urologist, Dept. of Urology, University Medical Centre Nijmegen (The Netherlands)
Prof. P Boyle, Ph.D., epidemiologist, C. Robertson, Ph.D., biostatistician, and C. Mazzetta, biostatistician, Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan (Italy).
M. Keech, M.D., Ph.D, Global Health Outcomes, GlaxoSmithKline, Greenford, Middlesex. UB6 0HE United Kingdom.
L.A. Kiemeney, Ph.D., epidemiologist, Dept. of Epidemiology and Dept. of Urology, University Medical Centre, Nijmegen (The Netherlands)

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OBJECTIVE

To determine the prevalence of female urinary incontinence (UI) and its impact on quality of life.

SUBJECTS AND METHODS

In a Dutch national postal questionnaire survey, 1460 spouses of 1771 men in the town of Boxmeer, age-stratified and randomly selected, were asked to participate. The prevalence of UI in the women was assessed in two ways. First, a total score on a short UI-specific questionnaire differentiated them into three groups, i.e. no symptoms (score 0-2), minimally (3-6) or severely incontinent (7-14). Second, a self-reported UI prevalence was calculated by asking respondents if they ever had urine loss. To conform to the International Continence Society (ICS) standard definition, spouses were also asked to complete a general (Short Form -12) and a lower urinary tract disease-specific quality of life questionnaire, and were asked about their need to seek help.

RESULTS

The questionnaires were returned by 1071 women (mean age 57 years, range 29-79; response rate 73%); 34% were regarded as minimally and 12 % as severely incontinent. The self-reported UI rate was 41%. Disease-specific and general quality of life was significantly lower for women with UI than for those with minimal or no urine loss; 38% of incontinent respondents had consulted a physician for their UI, and among respondents with minimal complaints this was 28%.

CONCLUSIONS

Up to 46% of the married female population had some degree of UI, and severe UI significantly compromised their quality of life

4.1 INTRODUCTION

Despite urinary incontinence (UI) being more openly discussed during recent years, the real prevalence of this distressing and disabling condition remains unclear. It is estimated that worldwide about 200 million people have urinary incontinence [Abrams, 1999]. For the Netherlands, official governmental bodies estimate the overall prevalence of urinary incontinence to be approximately 800 000 men and women using a so-called "broad" definition [Piepenbrink JF, 2000]. For a population of 16 million, this prevalence percentage is 5% and in sharp contrast with recent Dutch population-based studies, reporting UI rates of 23-57 % [van Geelen JM et al., 2000; van der Vaart CH et al., 2000; Rekers H et al., 1992; Kok et al., 1992]. This may be explained by the use of different definitions for UI. Dutch governmental bodies used the following definition: "Two or more episodes of involuntary urine loss per month, regardless of the amount of leakage". In a recent Dutch population-based study, Van der Vaart et al. used a positive response to one of the following questions as definition of incontinence: "Have you ever experienced involuntary urine loss during coughing, sneezing or physical exertion?" and "Have you ever experienced involuntary urine loss on occasions of strong urge to micturate?" Possibly, many women affirmed these latter questions on remembering accidental episodes of urine loss from the past, resulting in a high prevalence percentage of 57%. Also in international publications extensive variation in prevalence of UI is well recognized and depends on which definition of severity is used or in which context the questions were asked [Hunskaar S et al.,1998; Hampel C et al., 1997; Temml C et al., 2000; Hannestad YS et al., 2000; Moller LA et al., 2002; Fultz NH et al., 2000]. Nevertheless the prevalence of severe or significant UI has a narrower range than any form of incontinence (10-40 % versus 3-17 %) [Hunskaar S et al., 2002]. The ICS defines UI as: "the complaint of any involuntary leakage of urine"[Abrams P et al., 2002]. The report states that UI should be further described by specifying relevant factors such as type (stress, urge and mixed UI, nocturnal enuresis, continuous enuresis and other types), frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life (QoL), the measures used to contain the leakage and whether or not the individual seeks or desires help because of UI. The new ICS report aims to facilitate comparison of results and enable effective communication between investigators, but no proposals or guidelines have been offered about how to classify UI by frequency or severity, how to calculate the impact on social life or how to measure the leakages and classify the results. The guideline does not indicate the period of assessment and therefore does not distinguish actual and historical UI. This incomplete guideline still hinders good comparison of epidemiological studies.

In 1998 the Urepik-study was instituted in four countries to evaluate Lower Urinary Tract Symptoms (LUTS) and the impact on QoL of men and their partners; the present report presents the outcome of this study in 1071 Dutch community-dwelling married women. Urinary loss is still underestimated

by Dutch governmental institutes and Dutch publications give widely varying estimates depending on which definition of severity was used. Therefore, different scoring (i.e. no UI, mild and severely UI versus self-reported UI) was used within the same dataset to show the effect on prevalence. Second, an additional questionnaire inventoried the spouses' disease-specific and general QoL and their need to seek help within a period of 1 month. An effort was made to describe UI in most of its facets to conform to the ICS standard definition and thus allow future comparison in epidemiological studies.

4.2 PATIENTS AND METHODS

A postal survey was carried out in the town of Boxmeer (The Netherlands) in 1999. Questions addressed the prevalence and the impact on QoL of LUTS related to benign prostatic enlargement, erectile dysfunction and UI among males aged 40 to 80 years. This survey was part of an international project (the Urepik-study: Urological Epidemiology in Europe and Korea) co-coordinated by the European Institute of Oncology in Milan (Italy). Study centres from The Netherlands (Nijmegen), The United Kingdom (Birmingham), France (Auxerre) and South-Korea (Seoul) participated in this project [Boyle P et al., 1998]. Boxmeer, a small town in the South of the Netherlands, of 20, 000 inhabitants of which 4 067 men aged 40-80 years (Centraal Bureau voor Statistiek, kerncijfers 1997 http://www.nbs.nl/nl/ cijfers/kerncijfers/ accessed 2001). Using data from the council administration an age-stratified sample was drawn of 1 771 males with an increasing chance of being selected with increasing age. Their spouses (1460) were also asked to participate and to complete generic and lower urinary tract disease-specific questionnaires. The prevalence of UI was evaluated in two ways. First, a short questionnaire elicited the frequency and quantity of urinary leakage, the use of pads and the occurrence of stress UI during the past month (*Table 1*). This questionnaire was used previously in a Dutch incontinence survey [Milani AL et al., 1995]; it was discussed and evaluated and thought to be a valuable and informative questionnaire as (at that time) there was no consensus on which questionnaires should be used. The score range was 0 to 14, and groups were defined as 0-2 (no symptoms), 3-6 (mild symptoms) and 7-14 (severe symptoms). Second, a subjective self-reported UI rate was obtained asking respondents directly if they ever experience urinary leakage as the following question "Urinary incontinence means no complete control over your bladder that can lead to involuntary urine loss. Do you ever have involuntary urine loss?" Only a positive or negative answer was possible. This latter definition equates well to the new ICS definition: " the complaint of any involuntary leakage of urine".

Two internationally accepted and validated questionnaires were used to measure respondents' QoL: the benign prostatic hyperplasia (BPH) Impact Index (BII) [Barry MJ et al., 1995] and the Short-Form (SF) 12 questionnaire. Although the BII was constructed for assessing LUTS in men, we considered

Table 4.1: Incontinence specific questions modified by Vierhout et al., and age weighted prevalence (%) (100% minus missing values).

		%
A. During the past month: How often have you leaked urine?		
0	Never	54.5
1	Not more than once a week	19.6
2	More than one but less than three times a week	10.0
3	More than 3 times a week	6.0
4	Nearly always	8.6
B. During the past month: If you experienced urine loss, how much did you leak?		
0	I never leak	50.2
1	Some drops	32.2
2	A small stream	11.4
3	Protection material or clothes soaking wet	4.9
4	Leaking through pads or clothes	0.3
C. During the past month: how often did you use protection material		
0	Never	68.1
1	Occasionally	21.4
2	Nearly always	3.9
3	Always	5.8
D. During the past month: Did you lose urine on coughing or sneezing?		
0	Never	31.1
1	Occasionally	45.0
2	Nearly always	13.5
3	Always	9.3

the separate questions also valid to measure disease-specific QoL for women with UI. General QoL was assessed with the SF-12 questionnaire, calculating a physical component score (PCS) and mental component score (MCS). High values represent a better QoL. The outcomes can be compared with standardized population-based scores with a mean of 50 and a SD of 10 [Gandek et al., 1998].

All data were calculated using sampling weights based upon the ratio of the number of women in each age group in the samples to the number of women in the age group in the population. This was necessary because a stratified random sample of male respondents was used and the number of their spouses selected in each age group was not proportional to the number of women in the population. For the analysis, percentages and mean values were used. Differences in means were tested using analysis of variance and t-tests. For all statistical analyses SAS vs. 6.12 computer software was used (SAS Institute Inc., Cary, NC, USA).

4.3 RESULTS

In all, 1 071 questionnaires were completed and further evaluated (response rate 73 %); roughly 1 % of respondents returned an incomplete questionnaire. The mean (range) age of respondents was 56.9 (29-79) years, the mean parity 2.6 and 145 (13.5%) women were childless. The answers to the four incontinence questions are listed in *Table 1*. Scoring of the four questions categorized 12% (95% CI 10-14%) of the respondents as severely UI (score 7-14) and 34% (95% CI 31-37%) as minimally UI (score 3-6). About 68% of the participants had symptomatic stress UI. To the direct question: "Have you ever lost urine?" nearly 40% (95% CI 37-43%) affirmed this; more than a quarter of these self-perceived incontinent women lost drops of urine only incidentally.

There was no relationship between the mean parity or age and the presence of UI; only in the oldest category (70-79 years) were there significantly more complaints of UI (*Figure 1*). Of respondents with UI, 38% had consulted a physician for their UI; among respondents with minimal complaints this was 28%.

There was a clear relationship between involuntary urine loss and disease-specific QoL (BII); more severe UI was significantly associated with a higher BII score on each question (chi-square, $p < 0.01$; *Table 2*). Respondents with UI had more physical discomfort, were more worried about their health, more troubled and more frequently hindered in their social activities because of their urinary complaints. However, respondents who provided the most negative responses were few. This survey showed that 5% were troubled by their UI and that 3% felt restricted in their daily activities because of their leakages. There was no correlation between disease-specific QoL and age. There was a significant relation between UI and overall QoL (*Table 3*). For women with UI and for those self-reporting UI, the PCS and MCS on the SF-12 were lower ($p< 0.01$).

Table 4.2: Prevalence of urinary incontinence (UI) by age in 1071 women (mean age 56.9, range: 29-79 years) according to different classifications (total score and self-reported prevalence conform to the standard ICS definition).

		Age							
UI definition	**All**	**≤ 44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75-79y**
N=1071	%	138	140	163	169	179	149	102	31
UI Score									
Score 0-2	54	59	45	50	55	58	62	56	31
Score 3-6	34	34	41	38	34	32	24	29	31
Score 7-14	12	7	14	12	11	10	14	15	38
Score >3	46	41	55	40	45	42	38	44	69
Self-reported									
"no"	60	60	49	55	63	70	67	69	45
"yes"	40	40	51	45	37	30	33	31	50

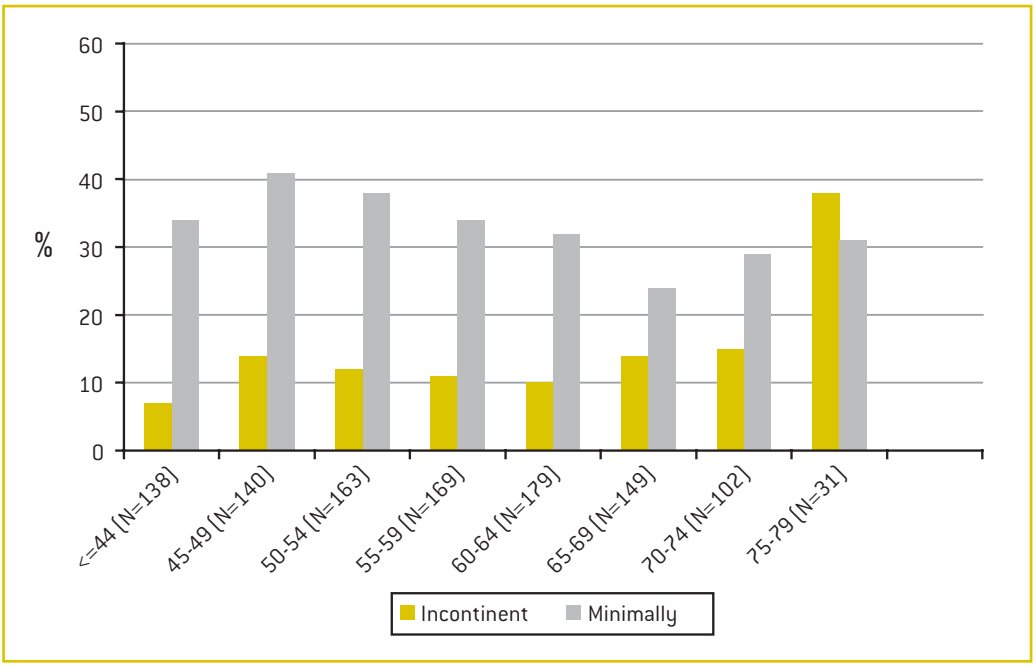

Figure 4.1: Age specific prevalence of incontinence according to UI score

4.4 DISCUSSION

Constructing a clear view of the prevalence of UI is not straightforward: the different approaches investigating the prevalence of incontinence in these 1071 women resulted in a wide variation in prevalence, from 12% (severe UI) and 40% self-reporting any leakage, to 46% (minimal and severe UI together). The criterion used by Dutch government bodies appears to underestimate the incontinent population. However, this study shows a much lower percentage than was found in the study by van der Vaart et al. [van der Vaart et al., 2000] (57% of women aged 45- 70 years). It therefore seems to be worthwhile to differentiate UI in different categories, a statement supported by the fact that a quarter of those who self-reported incontinence were only leaking some drops of urine less than once weekly, which may exclude them from the definition of minimal UI. Sandvik et al. [Sandvik H et al., 1993; Sandvik et al 2000] introduced such a UI severity index, using two questions and a simple scoring system. Recently, the index was compared to a 48h pad test and validated by a Scottish study [Hanley J et al., 2000] and used in the large Norwegian EPINCONT study [Hannestad YS et al., 2000]. Unfortunately, the UrEpiK study did not use the incontinence severity index but the questions used

Table 4.3: The BPH Impact Index (BII) consisting of 4 questions, measures disease specific quality of life on a scale of 0-13; high score represent a lower quality of life. Percentage of responses to BII items.

	Incontinence category		
Score	0-2	3-6	7-14
Number N=1064	N=578	N=355	N=131
1. Over the past month, how much physical discomfort did any urinary problem cause you?			
0. None	94	62	27
1. Only a little	5	32	37
2. Some	1	6	30
3. A lot			6
2. Over the past month, how much did you worry about your health because of any urinary problem?			
0. None	97	82	56
1. Only a little	2	15	27
2. Some	1	3	15
3. A lot			2
3. Overall, how bothersome has any trouble with urination been during the past month?			
0. Not at all bothersome	95	65	26
1. Bothers me a little	3	29	36
2. Bothers me some	1	5	29
3. Bothers me a lot	1	1	9
4. Over the past month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?			
0. Not at all bothersome	99	93	66
1. Bothers me a little	1	6	22
2. Bothers me some		1	8
3. Bothers me a lot			2
			2

were similar, dividing severity into five rather than four levels and quantity into fiverather than two levels. Moreover, it seemed useful to ask if protection was used, as an indicator of the severity of UI, and if there was a stress factor involved. Again, every effort that can result in an internationally accepted questionnaire should be encouraged.

In the present study there was a remarkable difference between the symptom- and perception- based UI rates (46% versus 40%). The most likely explanation for this was the context in which the survey questions were presented. Fewer women saw themselves as incontinent when they had to complete the confronting question "Do you ever have involuntary urine loss", probably viewing it as a natural phenomenon or even denying it. However the four questions (scoring for severity, quantity, protection and stress component) detected more spouses that had experienced urinary loss, representing "any form of urinary loss". Second, the difference could be explained by the different time restrictions used within the questions. Information was specifically asked about the situation in the past month for the four UI-specific questions. For the direct question there was no period indicated. Many women may have had transient UI in the past without considering themselves as incontinent at present. A spontaneous remission rate of 12 % was reported previously [Hunskaar S et al., 1998]. There was no apparent age-related prevalence of urine loss for women aged <70 years, although a small peak in prevalence at the perimenopausal age; this tendency was also reported previously [Hunskaar S et al., 1998].

Disease-specific QoL was lower among respondents having urinary leakage, but few respondents reported the most negative responses. This survey showed that 5% were troubled by their incontinence and that 3% were feeling restricted in their daily activities because of their leakages. Also van der Vaart et al. and Lagro-Janssen et al. [Lagro-Janssen AI et al., 1990] found that patients with UI were only a little bothered by their urine loss.

Women with UI scored significantly worse than those without on the mental and physical aspects of the QoL inventory. The negative impact of incontinence on vitality, social functioning, role-emotional and mental health (the MCS of the SF-12) is not surprising, but the important consequences for physical health are not so evident. Perhaps, this finding reflects the fact that women with UI restrict their everyday activities to avoid the occurrence and consequences of involuntary urine loss, and experience this as physical impairment. On the other hand, some co-morbidities (e.g. musculo-skeletal disorders or neurovascular diseases) can result in impaired mobility and consequently in functional UI.

That only 38% of respondents with UI sought medical advice for their UI suggests, on the one hand, that urine loss is still a condition that these women do not want to talk about, and on the other hand that some respondents may see urine loss as a part of the ageing process.

Last, UI has important socio-economic implications; in the USA the direct healthcare costs relating to UI were more than $10 billion in 1987 [Hu T, 1990]. For the Netherlands it was estimated that in

1999, 136 million Euros were spent on incontinence materials and aids. Other invisible expenses for absenteeism, extra protection materials, textile and laundry were not considered. If national expenses on UI products and aids were based on the present prevalence rates, estimated expenditures may increase substantially. For macro-economic planning it is therefore evident that exact prevalence figures become available. More clarity about the real prevalence is needed because UI has a large effect on the individuals' well-being, and may greatly influence strategic and macro-economic planning.

4.5 CONCLUSION

In conclusion, up to 46 % of the married women in Boxmeer had some degree of UI; the prevalence of UI assessed by a population-based, postal survey depends heavily on the definitions used (prevalence of 12-46%). Using a definition that considered relevant UI of the recent past, within a specified period, is warranted for epidemiological purposes. A consensus within the ICS on guidelines that classify severity of UI using a standard questionnaire and measures would make the results from epidemiological studies more consistent.

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Table 4.4: General quality of life was assessed using the SF-12 questionnaire calculating a physical component score (PCS) and mental component score (MCS). High values present better quality of life.

UI definition		SF-12		SF-12	
N=1071	**%**	**MCS**	**ANOVA**	**PCS**	**ANOVA**
UI Score					
Score 0-2	54	52.4		49.9	
Score 3-6	34	50.8		49.3	
Score 7-14	12	49.5	p=0.0004	43.6	p=0.0001
Self-reported					
"no"	60	52.1		49.5	
"yes"	40	50.5	p=0.004	48.1	p=0.02

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CHAPTER 5
From electrical fish to PTNS

Using electrical eels, ancient Egyptians believed in the heeling capacity of electrical shocks. This chapter briefly reviews the evolution from Galvani to Posterior Tibial Nerve Stimulation, from Macaca apes to urological patients. It describes the PTNS procedure and the inclusion and exclusion criteria.

5.1 HISTORICAL BACKGROUND

Bioelectrical phenomena have intrigued mankind for centuries. In 2750 BC detailed images of catfish possessing electrical organs were found on an Egyptian tomb. In the works of Socrates and Hippocrates the "numbing" ability of these fish was described, but the first medical application of electrical stimulation was described by Largus (46AD). Torpedo fish, electric eels and rays were used to treat headache and gout by placing a living black torpedo on the spot which was in pain [Kellaway, 1946; Schmidt and Tanagho, 1979; Sheon, 1984; Devinsky, 1993]. It took until the mid-eighteenth century to further explore bioelectrical processes. The development of the electrostatic generator and battery enabled physicians to further explore electrical therapy and its usage increased dramatically. In 1791 Galvani observed a muscle twitch when he accidentally electrostimulated a frog leg. Further experiments with electricity followed. In the mid-nineteenth century, Duchenne conducted extensive studies on the use of electricity in medicine during the century. Most physicians had electrotherapeutic machines in their offices and prescribed electrotherapeutic baths and belts for home use [Devinsky, 1993]. In 1848 the induction coil stimulator, producing a train of stimuli that could tetanise skeletal muscles, was introduced. The bladder was one of the first organs to be activated through stimulation of the cervical cord by Budge [Schmidt and Tanagho, 1979]. It took the development of the transistor (1950) for the first heart pacemaker to be implanted in 1960 which proved that medical implanted devices could function properly [Mullet, 1987]. Soon the first implantable electrodes in the urological field followed. For decennia electrostimulation has been applied to achieve voiding, to induce contraction of the external sphincter, to inhibit or abort detrusor activity or to relieve pelvic pain.

In 1963 Caldwell developed a sphincter stimulator to treat stress incontinence. The first implanted electrodes on the bladder wall elicited detrusor contraction but this method was limited by erosion and fibrosis and the painful supraphysiological current needed for adequate stimulation [Habib, 1965]. As the bladder can be stimulated directly but also indirectly via the nerves, other stimulation modalities were searched for. The S2-S4 roots are involved primarily in bladder control, with the S3 roots mainly innervating the detrusor and levator muscles [Hasan, 1996]. S3 nerve root contains sensory fibres from the pelvic floor, parasympathetic motor efferents to the detrusor and motor fibres to the pelvic sphincters and the pelvic floor muscles.

In 1969 Brindley developed an electrode for long-term stimulation of the spinal roots S2-S3, and in 1972 the first patient received a **Brindley Sacral Anterior Root Stimulator.** Later the implantation was combined with de-afferentation or dorsal rhizotomie to overcome neurogenic detrusor overactivity resulting in an enlarged bladder capacity. Also here stimulation is at a painful supraphysiologic level and thus only available for paraplegic patients [Brindley, 1977; Brindley, 1993; Saurwein 1990].

In 1878 Saxtorph used **intravesical stimulation** to treat urinary retention. In 1959 Katona et al. described a technique of intraluminal electrotherapy for various disorders of the gastrointestinal tract, and later for neurogenic bladder dysfunction [Katona, 1975]. Later in 1990 Madersbacher et al. reported good results for patients with neurogenic bladders treated by intravesical stimulation [Madersbacher, 1990]. It is thought that the electrostimulation depolarises the bladder mechanoreceptors and increases the bladder awareness. This treatment involved a time-consuming schedule as repeated sessions several times per week were needed and as it was combined with intensive bladder training. Special equipment and trained personnel were required.

Neurophysiology teaches us that afferent anorectal branches of the pelvic nerves and the dorsal clitoral and penile branches of the pudendal nerves can activate the inhibitory sympathetic neurons and inhibit via direct sacral route the bladder motoneurons. These reflexes will not be suppressed during micturition and are capable of interrupting detrusor contraction.

During the sixties, **intra-anal and intra-vaginal** probes were designed to exercise the pelvic floor and to inhibit detrusor overactivity. Fall treated patients with therapy resistant urgency and incontinence. Treated for an adequate period of at least three months, they improved substantially: bladder capacity increased, continence was obtained and in some patients detrusor overactivities were abolished. However small bleedings, vaginal pain, discharge and local necrosis was seen due to technical failure. After revision of the devices no serious side effects were seen [Fall M, 1978; Fall 1984]. Kock et al. showed that **rectal digital stimulation** could abort detrusor overactivities [Kock et al., 1963]. Janež et al. studied the urethra and bladder responses on anal electrical stimulation. In 55 patients with different urethra-bladder dysfunctions, only 50% of the patients showed normal reciprocal response [Janež et al., 1979]. In 1979 Merril treated patients with acute rectal stimulation: detrusor reflex threshold increased or bladder overactivities were abolished in 4 out of 20 patients. As they became dry, they received an implant. One of them only needed stimulation every 4 days, the interval required to control uninhibited detrusor contractions varied between 4 to 12 hours [Merril, 1979]. In 1996 Trsinar compared 73 children with anal MES to 21 controls. 32% became dry, 44% improved (>50% improved in urinary complaints), in the control group no changes were seen [Trsinar, 1996]. Esa applied anal plug stimulation for 30 minutes every 3 days to 1 week in 43 patients. 64% in the urgency/frequency group and 43% in the stress UI group was found to be successful. Urodynamic results did not correlate with the subjective improvement nor did the acute effect correlate with the chronic effect and subjective improvement. Especially the OAB group who had cerebral infarction, the anal plug stimulation was most effective [Esa, 1991].
In 1977 Teague transrectally stimulated the **pudendal nerve** in dogs which resulted in an increased urethral pressure and detrusor inhibition. Post stimulation effect occurred in all stimulations

concerning the urethral pressure and in 4 dogs the post stimulation inhibition on the detrusor was seen. Direct pudendal stimulation was less than after transsection at Th 8, suggesting that the mechanism of direct pudendal nerve stimulation in dogs is organised in the spinal cord and not in brain centra [Teague, 1977]. Nakamura investigated the pudendal branches. In ten out the twenty-two patients inhibition of detrusor overactivity was achieved by continuous **dorsal penile nerve stimulation**, the detrusor overactivity could be suppressed in seven out of ten patients but the **dorsal clitoral stimulation** seemed less effective [Nakamura, 1984].

Anorectal and pudendal stimulation seemed to be quite successful to restore normal voiding. It is thought that Aδ fibres are activated which give return to urge feeling and normal micturition pattern. Pudendal, vaginal electrodes stimulated the large somatic C fibres which will inhibit the small afferent Aδ fibres comparing to the pain gate control theory postulated by Melzack. Sensory output from the skin modulates pain perception and response on spinal segmental level [Melzack, 1965]. Unfortunately, due to the uncomfortable set-up, anorectal and pudendal stimulation is known as a low compliant therapy. Therefore other stimulation sites have been searched for.

Sacral Nerve Stimulation was introduced in the late eighties. An electrode was introduced through the sacral foramen to stimulate mainly S3 and connected to an implanted stimulator. The working mechanism is not yet clear but remarkable results were seen. Contraction of the bladder, hypertrophy and increased efficiency of the striated urethral sphincter was induced by prolonged electrostimulation of the sacral roots. Increased efficacy of the sphincter was thought to be due to hypertrophy and forming of intermediary fast but less fatigue-resistant fibres [Tanagho, 1993]. In addition contraction of the sphincter inhibits or aborts detrusor activity through a normal reflex. Sacral segmental nerve stimulation by a permanent foramen S3 electrode achieved detrusor inhibition by chronic stimulation of afferent somatic sacral nerve [Bosch et al., 1995]. The mechanism is believed to be comparable with the pain gate control theory postulated by Melzack. Sensory output from the skin modulates pain perception and response on spinal segmental level [Melzack, 1965]. Bosch et al. implanted a permanent foramen S3 electrode in 18 out of 31 patients. Fifteen of them (83%) were treated successfully. Though it has been shown to be an effective treatment, it was a costly and invasive procedure with a high revision rate (in 4 out of 18 patients) [Bosch, 1995]. After 7 years of experience Bosch et al. concluded that neuromodulation lead to symptomatic improvement and decrease or disappearance (in 46%) of detrusor overactivity. After 4 years some deterioration was seen [Bosch et al., 2000]. Weil et al. described a success rate of 52,8% (19 out of 36 patients, intention-to-treat based) after an average long-term follow-up of 37,8 months. All symptoms except urgency improved significantly [Weil et al., 1998]. Urodynamics showed significant increase of bladder capacity and volume at first sensation. The volume at first unstable bladder contraction increased but was

not statistically significant. Thirty seven re-operations have been performed, mostly to overcome technical problems. Nowadays the stimulator is implanted in the buttock resulting in less pain at the implantation site and a lower re-operation rate [Scheepens et al., 2001].

Parallel to the development of the SNS non-invasive ways to stimulate S3 were explored. **Transcutaneous Electrical Nerve Stimulation** (TENS) on the S3 segment is a useful alternative treatment modality in patients with detrusor overactivity. Webb et al. noticed 54% of the patients to become continent with S3 TENS [Webb, 1992]. Hasan et al. also reported these success figures in 1996. In his trial 20 patients received no TENS, S3 TENS or T12 TENS. The study revealed significant changes in urodynamic parameters in the group on S3 stimulation [Hasan , 1996]. Hasan investigated the urodynamic effect during TENS over the tibial nerve, however no significant changes were seen. Webb and Powell could abolish detrusor overactivity in 11 out of 24 patients (46%), a larger volume at first contraction was seen and 54% was considered continent [Webb and Powell, 1992]. TENS therapy unfortunately may induce skin irritation and allergy at the stimulation site due to chemical and mechanical irritation [Hasan et al., 1996; Oosterwijk et al., 1994]. Consequently, other stimulation approaches were searched for.

In 1997 **magnetic resonant stimulation** of the spinal cord was successfully used to suppress detrusor overactivity and the sensation of urge in all 12 patients. The effect remained for 70 seconds. Unfortunately 2 patients found the stimulation uncomfortable or painful. The stimulator is bulky, expensive and the stimulating coil could be overheated. Using a computer-triggered conditional magnetic suppression it was possible to suppress overactive contractions and to increase cystometric capacity. The mechanism is postulated to induce activation of the sensory parasympatic pathway producing inhibition of parasympatic efferents both directly and also possibly via sympathetic pathways [Mc Farlane, 1997].

Bladder inhibition is also provided by **limb afferents**. These reflexes serve to prevent urine leakage during physical activity. Research focussed on the effect of stimulation of afferent nerves in the lower limb. In cat experiments Lindström and Sudsuang showed detrusor inhibition through stimulation of the myelinated afferents of the hip adductor muscles [Lindstrom and Sudsuang, 1989]. Okada et al. tried to stimulate the **thigh muscles** for 20 minutes, every day for 2 weeks, and they observed increased bladder capacity in 11 out of 19 patients (>50%). In six of these 11 there was clinical improvement (carry-over effect) for several weeks to months [Okada, 1998].

Inspired by acupuncture points over the **tibial and peroneal nerve** to overcome bladder overactivity, Mc Guire et al. applied electrostimulation over these nerves. In a woman with herniated intervertebral

disc and at a volume of 200ml, continue stimulation of the posterior tibial nerve kept her dry. In a paraplegic man, detrusor overactivity could be suppressed for 4 hours. A female patient with detrusor overactivity and incontinence could control her bladder after common peroneal nerve stimulation. One female with Interstitial Cystitis was relieved from her symptoms for 3-4 hours [Mc Guire, 1983]. Kubista et al. found increased urethral pressures 30 minutes after acupuncture in 17 out of 20 patients. This phenomenon was nor seen in the control group nor in the placebo group [Kubista, 1976]. In 1999 Stoller proposed percutaneous Afferent Nerve Stimulation of the posterior tibial nerve for treatment of bladder and pelvic floor dysfunction [Stoller, 1999].

5.2 STOLLER AFFERENT NERVE STIMULATION (SANS) OR PERCUTANEOUS POSTERIOR TIBIAL NERVE STIMULATION (PTNS).

In an abstract published in 1987, Stoller presented his acupuncture observations in Macaca Nemestrina. A subset of these apes demonstrated detrusor overactivities for more than 7 years. The application of acupuncture on locus SP6 reduced or eliminated detrusor overactivity. Repetitive stimulation lengthened the interval between detrusor contractions. The physical properties of the SP6 locus revealed marked decrease in skin resistance and impedance. Needle stimulation abolished detrusor overactivity, disruption of vascular or lymphatic circulation did not interfere with the treatment, but an intact peripheral neurosensory system was required for the therapy to be effective. Anesthetized limbs elicited no response [Stoller ML, 1987]. Stoller proposed Stoller's Afferent Nerve Stimulation or SANS for treatment of bladder and pelvic floor dysfunction [Stoller, 1999]. In 1999 SANS was introduced in the Netherlands and later renamed **Percutaneous Posterior Tibial Nerve Stimulation** (PTNS). The afferent stimulation of the tibial nerve was introduced as a non-invasive method, simple to perform and of low cost. The first results included figures from 4 sites in the US and 5 sites in Europe. The preliminary study showed a success rate of 73%. No harmless effects were seen. In the Netherlands success rate was 60 % [van Balken et al., 2001] Success was obtained if micturition lists showed 25 % improvement of parameters or if subjectively the complaint no longer played a predominant role in their lives.

5.3 THE SANS USERS CLUB

In 1999 **the SANS Users Club** in the Netherlands was established. More than 25 Dutch urologists included patients with detrusor overactivity, pelvic pain or chronic voiding dysfunction. After careful selection, the candidates underwent PTNS in accordance with a written protocol. After 12 weeks,

the protocol booklets with treatment results, completed questionnaires and urodynamic findings were send back to the PTNS investigators (UMC St Radboud, Nijmegen). Also in Italy interest towards PTNS treatment rose. A close collaboration with Dr E. Finazzi Agrò from the department of Urology at the University Tor Vergata and IRCCS S Lucia in Rome resulted in reliable additional data. This thesis describes the analysis of data received from patients with overactive bladder syndrome and chronic voiding dysfunction.

5.4 CANDIDATE SELECTION

All candidates were examined by a urologist. A careful history was taken to exclude other treatable causes (urinary tract infections, urolithiasis, bladder cancer, etc) or neurological diseases. *Table 5.1* lists all general and disease specific inclusion and exclusion criteria. Patients included in the trial were patients with overactive bladder syndrome and chronic voiding dysfunction. Definitions used in the protocol are described in chapter 3.

Primary treatment modalities such as pelvic floor re-education or anticholinergics failed to relieve patients from their bladder complaints. Candidates underwent urodynamic investigation to identify baseline parameters and to exclude genuine stress incontinence. For urodynamic analysis a standard transurethral subtraction cystometry was conducted in the supine position. Sterile saline at room temperature was infused through a double lumen 8 F catheter at a filling rate of 50 ml/min. The volume at which detrusor overactivity occurred was noted. Detrusor overactivity was defined as an increase of 15 cm water pressure or of lower amplitude if accompanied with a distinct sensation of urgency. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted [Abrams et al., 2002]; [Abrams et al.; 1988].

Patients were asked to complete bladder diaries and quality of life questionnaires at baseline and throughout the study period on a regularly basis. For incontinence specific quality of life the I-QoL questionnaire was used [Patrick et al., 1999]. For the estimation of generic functional status and well-being, the MOS 36 items Short-Form health survey (SF-36) was completed [Ware et al., 1992]. Higher scores indicate better quality of life. Informed consent was achieved.

Table 5.1: In- and exclusioncriteria for PTNS procedure.

General Inclusion criteria:	General Exclusion criteria:
• the patient has signed informed consent • the patient is older than 18 • The patient has a documented normal urinary tract. • The patient has an intact peripheric neurosensoric nervous system • If the patient is under medicamental treatment a 60 day wash out period is necessary or the daily dosis should be kept unchanged during the study period • The patient understands the procedure, the advantages and possible adverse effects of Percutaneous Tibial Nerve Stimulation. • The patient shows an adequate muscular and sensoric response during the test stimulation • The patient agreed and is capable to complete bladder diaries • The patient agreed and is capable to complete the quality of life questionnaires • The patient agreed and is capable to undergo the treatment as described in the protocol guidelines	• The patient is mentally not capable to understand the protocol guidelines or not capable to sign informed consent • aged under 18 • Medical conditions that could influence th outcome of PTNS: pacemakers, defibrillator, serious cardiopulmonic disorders • Pregnancy or the wish to get pregnant during the study period. If the patient becomes pregnant the PTNS treatment will be ceased immediately • Active urinary tract infection or recurrent urinary tract infections (> 4 times a year). Urinary fistula, bladder stones, cystoscopic abnormalities suggesting malignancies • neurogenic detrusor overactivity (CVA, Parkinson, Multiple Sclerosis) • uncontrolled diabetes or periferic neuropathy • The usage of Elmiron® or other bladder instillation products (DMSO, BCG, Heparine, etc)
Inclusion criteria: Overactive Bladder Syndrome	**Inclusion criteria:Chronic voiding dysfunction**
• The patient has a documented detrusor overactivity: urinary frequency is more than 7 times per day and / or the patient experience minimal one episode of urinary incontinence during three consecutive days recorded in their bladder diaries • The urine loss is not due to stress incontinence (based on the urodynamic investigation that is a part of the normal work up investigation for overactive bladder complaints) • The patient has a minimal bladder capacity of 100 ml	• The patient has a documented detrusor underactivity or acontractile detrusor. The patient catheterises and fails to achieve complete bladder emptying on bladder diaries.

5.5 THE PTNS PROCEDURE

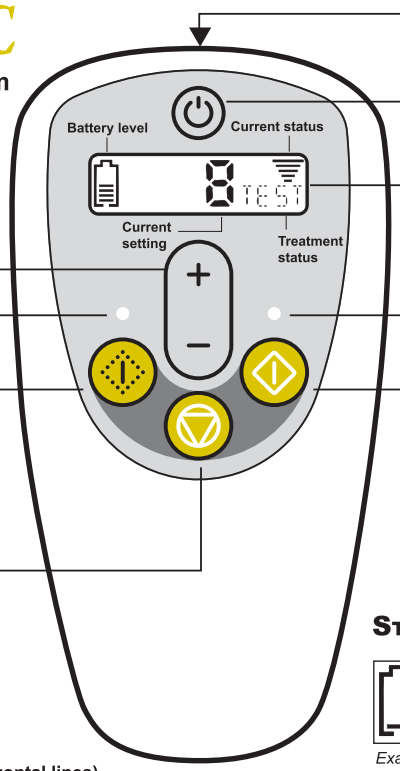
The patient was asked to sit in a frog position with the legs slightly benched and feet inverted. For PTNS a 34-gauge needle was inserted percutaneous, approximately 5 cm cephalic to the medial malleoleus of the right or left ankle (*fig 5.1*). A surface electrode was placed on the medial aspect of the ipsilateral calcaneus. The needle and electrode were connected to a low voltage (9 V) electrical stimulator (Urosurge, Coralville, Iowa, later: Urgent PC®, Uroplasty Minnetonka, USA). The technical information is summarized in *table 5.2*. Stimulation current (0-10mA) with a fixed frequency of 20 Hz and a pulse width of 200 μsec, was increased until curling of the big toe or fanning of all toes became noticeable. If no clear motor response was found, the needle was removed and the insertion procedure was repeated. In most patients the motor response was accompanied by a sensory response of a radiating sensation spreading in the sole of the foot. The current was set at a well-tolerable level. During a session elevation of the current was allowed whenever fading of this sensation was experienced due to adaptation. Stimulation sessions lasted for 30 minutes and were repeated on a weekly basis for a period of 12 weeks in an outpatient setting. After the first 12 weeks, an evaluation through bladder diaries, QoL questionnaires and urodynamics were obtained. These findings in combination with the patient's self-perception of reduced symptoms resulted in the decision if treatment was successful. Successful treated candidates underwent maintenance therapy. The intervals between stimulation sessions were chosen individually in order to maintain the acquired reduction of their complaints.

Figure 5.1

URGENT® PC

Neuromodulation System

STIMULATOR



Current Adjustment button
- Current is adjustable in Test and Therapy modes
- 19 adjustment increments, reflect range of 0 - 9 mA

Test mode LED
- Test mode is active when lit

Test button
- Depress ~2 seconds to activate Test mode
- Test mode is a prerequisite for Therapy mode

Stop button
- Immediately stops flow of current in Test and Therapy modes
- Treatment will need to be restarted

Power button
- Depress ~2 seconds to activate

LCD status screen
(additional detail below)

Therapy mode LED
- Therapy mode is active when lit

Therapy button
- Depress ~2 seconds to activate Therapy mode
- Test mode is a prerequisite for Therapy mode
- Therapy time is preset to 30 minutes

STATUS SCREEN ICONS

Battery Level icon (1-7 horizontal lines)
- 7 lines = full battery
- 1 line = battery nearly empty
- 1 line + flashing = battery needs to be replaced

Inactive Current icon
- Current NOT flowing through Lead Set
- If indicator appears during Treatment or Therapy modes, check connections

Active Current icon
- Current is actively flowing through Lead Set

Lead Status icon
- New Lead Set is needed

Service Required icon
- Fault detected, restart Stimulator
- If icon remains after restart, contact Uroplasty

STATUS SCREEN EXAMPLES

Example 1: Start-up
New Lead Set needed, change battery

Example 2: Start-up
Lead Set is in place, ready to begin Test mode

Example 3: Test mode
Current is active, Test mode operational

Example 4: Therapy mode
Therapy mode active, 28:59 minutes remaining

Example 5: Therapy completion
Therapy is complete, current is inactive

Uroplasty

Uroplasty, Inc. Tel: 866 258 2182, e-mail: info.usa@uroplasty.com
Uroplasty BV Tel: + 31 (0)46 423 79 20, e-mail: info.holland@uroplasty.com

Table 5.2

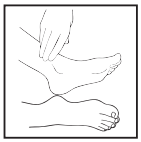
Treatment Protocol for each treatment session

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician. For complete instructions for use, storage, warnings, indications, contraindications, precautions, adverse reactions and disclaimer of warranties, please refer to the insert accompanying each Urgent PC product.

1. Check Battery Level

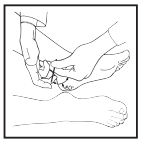
- Before beginning any treatment session, it is advisable to check the battery level. To check the battery level, turn on the Stimulator by pressing and holding the Power Button for approximately 2 seconds. An audible tone will sound and icons will appear on the screen. Battery replacement is recommended when there is only one line remaining in the Battery Level icon. To conserve battery power, the Stimulator may be turned off during patient preparation.

2. Insert the Needle Electrode



? Locate the insertion site for the Needle Electrode by identifying the location on the lower inner aspect of either leg that is approximately three fingerbreadths (5 cm or 2") cephalad to the medial malleolus and approximately one fingerbreadth (2 cm or ¾") posterior to the tibia.

- To prepare the Needle Electrode insertion site, open the Lead Set packaging. Remove and open the Alcohol Pad. Use the Alcohol Pad to clean the skin area surrounding the identified insertion site.
- Place the patient in a comfortable position, supine or sitting, for easy access to the insertion site; for example, the patient may sit with the soles of the feet together and knees abducted and flexed. Open the sterile Needle Electrode package and remove the Needle Electrode/guide tube assembly.
- Place the Needle Electrode/guide tube assembly over the identified and cleaned insertion site in a position that creates a 60-degree angle between the Needle Electrode and the ankle. Remove the stop plug in the guide tube to release the Needle Electrode.



- Gently tap the Needle Electrode head to pierce the skin. Once the Needle Electrode has penetrated the skin, remove the guide tube and advance the Needle Electrode using a rotating motion to facilitate entry.
  Note: it is important to maintain a 60-degree angle with the Needle Electrode while advancing it in a path that is parallel to the tibia. When appropriately inserted, about half of the tip of the Needle Electrode will be inserted in the leg, with about 2 cm (¾") left exposed.

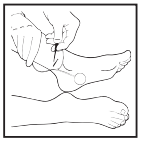
3. Connect Lead Wire to the Stimulator

- Plug the one-way fit connector of the Lead Wire into the Stimulator's connection site. Verify that the one-way fit connector is inserted correctly.

4. Attach the Surface Electrode

- Remove the adhesive backing from the Surface Electrode.
- Place the Surface Electrode near the medial aspect of the calcaneus on the same leg as the Needle Electrode insertion.

5. Attach Needle Electrode Clip



- Depress the plunger on the Needle Electrode Clip to expose the connection hook at the tip. Loop the connection hook around the Needle Electrode and release.

6. Determine Current Setting for Therapy

- Turn on the Stimulator by pressing and holding the Power button for approximately 2 seconds. An audible tone will sound and symbols will appear on the screen.
- Enter Test mode by pressing and holding the Test button for approximately 2 seconds. The default setting for Test mode is level 0 (0mA current).
- Using the Current Adjustment button, slowly increase the current while observing the patient's foot for a response. Patient response is generally a toe flex or fan, or an extension of the entire foot.

- Once a patient response is observed, reduce current setting by one level and begin Therapy mode.
- If the incremental adjustment of amplitude fails to elicit toe flex or fan, press the Stop button and reposition the Needle Electrode slightly. Re-enter Test mode using the preceding instructions.
- If repositioning the Needle Electrode and repeating the current step-up procedure fails to elicit patient response, discard the Needle Electrode. Open the second Needle Electrode included in the Lead Set and repeat the procedure on the other leg.

7. Conduct Therapy

- After completing Test mode, Therapy mode can be entered by either:

  1) Pressing the Stop button to end Test mode and then pressing the Therapy button to start Therapy mode.

or 2) Pressing the Therapy button while the Test mode is still active.

- To ensure optimal treatment, the default current setting for Therapy mode will be the final current setting in Test mode. However, the Current Adjustment button can be used to increase or decrease the current level at any time during Therapy mode.
- Therapy mode time is automatically set for 30 minutes.
- When the therapy time has elapsed, Therapy mode will automatically end, the current will be inactive, and the Stimulator will emit a series of three beeps.

8. Complete Treatment Session

- Turn off the Stimulator by holding down the Power button for approximately 2 seconds.
- Remove the Needle Electrode Clip from the Needle Electrode.
- Using a smooth, fluid motion, quickly remove the Needle Electrode from the leg. If bleeding occurs, apply slight pressure and bandage.
- Disconnect the Lead Wire from the Stimulator and properly dispose of Lead Set components.
- The treatment session is now complete.

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CHAPTER 6

The first results of PTNS as neuromodulative treatment of lower urinary tract dysfunction

Based on
POSTERIOR TIBIAL NERVE STIMULATION AS NEUROMODULATIVE TREATMENT OF LOWER URINARY TRACT DYSFUNCTION

MR VAN BALKEN[1], V VANDONINCK[2], KWH GISOLF[3], H VERGUNST[1], LALM KIEMENEY[2,4], FMJ DEBRUYNE[2], BLH BEMELMANS[2]

1 Departments of Urology Canisius-Wilhelmina Hospital, Nijmegen,
2 University Medical Centre Nijmegen and
3 University Hospital Utrecht,
4 Department of Epidemiology University Medical Centre Nijmegen, The Netherlands.

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OBJECTIVE

Recently, intermittent PTNS was introduced as a treatment modality filling the gap between conservative and surgical therapies in patients with certain types of lower urinary tract dysfunction.

SUBJECTS AND METHODS

In a prospective multicentre trial PTNS was evaluated in 37 patients with symptoms of overactive bladder complaints and 12 patients with non-obstructive urinary retention. Results were recorded in bladder diaries and quality of life questionnaires (SF-36 and I-QOL) before and after treatment. Patients were classified as responders, including those in whom therapy was successful and chose to continue treatment after the initial 12 weeks, and non-responders, those who chose to stop treatment.

RESULTS

Overall, a positive response was seen in 60% of all patients. In patients with bladder overactivity a statistically significant decrease was observed in leakage episodes, number of pads used, voiding frequency and nocturia, and an equal increase in mean and smallest volume voided. Improvements were also seen in non-obstructive urinary retention, including number of catheterisations, total and mean volume catheterised and total and mean volume voided. Disease specific quality of life and some domains of general quality of life improved, especially of bladder overactivity. Only mild side effects were observed.

CONCLUSIONS

PTNS is a minimally invasive and successful treatment option for patients with certain types of lower urinary tract dysfunction.

6.1 INTRODUCTION

Non-neurogenic lower urinary tract dysfunction is a common urological problem that strongly affects patient's quality of life. Patients can complain of overactive bladder (OAB) with or without incontinence or present themselves with urinary retention. In most patients the etiology of these complaints remains unclear [Hasan et al., 1996]. Conservative treatment options for OAB complaints consist of behavioral techniques with and without biofeedback, bladder reeducation, pelvic muscle exercises or pharmacotherapy involving anticholinergics, antispasmodics and tricyclic antidepressants. Patients with non-obstructive urinary retention can be treated with clean intermittent or permanent catheterisation. For refractory cases more aggressive surgical procedures, like bladder distension, ileocystoplasty or urinary diversion have been advocated. However, a high recurrence and complication rate limits the widespread application of these treatments.

Recently, continuous sacral root stimulation (Medtronic, Inc. Minneapolis, Minnesota) has been proposed as an alternative, less invasive therapeutic option for patients with non-neurogenic lower urinary tract dysfunction, not responding to conservative treatment [Bemelmans et al., 1999]. Although highly effective in select patients, this technique is expensive and requires explicit surgical skill.

PTNS is a technically less demanding and probably more cost-effective for management of lower urinary tract dysfunction. In this report we present our initial experience with this new neuromodulation technique in a prospective clinical trial.

6.2 PATIENTS AND METHODS

Between November 1999 and March 2000, 15 male and 34 female patients were enrolled in a prospective clinical multicentre trial that received approval by the institutional review board. All patients were evaluated for OAB complaints and non-obstructive retention by history, bladder diaries and physical as well as urological examination, including urodynamics.

For the OAB group, the following inclusion criteria were used: increased urinary frequency: more than 8 voids per 24 hours; urge urinary incontinence (urge UI) occurring at least 3 times weekly and/or phasic involuntary bladder contractions with concomitant incontinence on cystometry. Non-obstructive retention was distinguished by urinary retention, necessitating intermittent catheterisation at least 4 times a day, without urodynamic signs of outflow obstruction, as defined on the Abrams-Griffiths nomogram [Abrams et al., 1979].

The use of parasympatholytic medication or other pharmaceuticals influencing bladder function (like anti-depressive agents) should have been stopped two weeks or longer prior to PTNS or had to be

continued without dose changes during the entire study. Specific exclusion criteria for our study are given in the appendix.

Patients:

A total of 10 men and 27 women with a mean age of 52.5 years (range 23 to 74) were treated for OAB. These patients lived with symptoms for a median period of 4 years (range 1-30). The symptoms were said to be induced by childbirth in 3, pelvic surgery in 9 (including 7 hysterectomies, 1 anterior prolapse correction and 1 Burch colposuspension) and other events in 3 patients, including fracture of the coccygeal bone, urinary tract infection, bowel infection.

The remaining patients had no history of any pelvic event prior to the onset of symptoms. Of the 37 patients 32 (91.4%) received unsuccessful prior medical therapy, including anticholinergics with a mean number of 1.9 (range 1 to 5) drugs used. Almost half of all patients (48.6%) underwent up to 3 surgical procedures, most frequently colposuspension, for symptoms. Other unsuccessful therapies included physiotherapy and/or biofeedback in 22 (59.4%), including transcutaneous electrical nerve stimulation or peripheral nerve evaluation in 5 (13.5%) and alternative therapies, such as Chinese herbs in 5 patients (13.5%). Physical examination did not show overt or neuro-urological abnormalities in any patients.

There were 5 men and 7 women with a mean age of 50.8 years (range 36 to 64) treated for non-obstructive retention. These patients had symptoms for a median of 3.5 years (range 1 to 36 years). Initiation of symptoms was related to childbirth in 1, pelvic surgery, including Wertheim's-Meighs operation in 1 and Burch colposuspension in 1, other surgery, including hip replacement in 1 and inguinal hernia repair in 1 and benign prostatic hyperplasia without any effect of transurethral resection of the prostate in 1 patient. The remaining 6 patients had no history of any pelvic event prior to the onset of their complaints. Of the 12 patients 11 (92%) received unsuccessful medical therapy previously, including a-blockers or sympathomimetics. Almost half the patients (5 of 12) had undergone lower urinary tract surgery, mostly urethral dilatation or urethrotomy, for symptoms previously. Other unsuccessful therapies included physiotherapy and/or biofeedback in 3 (25%) and electrical stimulation in 1 patient. All patients were on clean intermittent catheterisation. In addition, physical examination did not show overt or neuro-urological abnormalities in these patients. Urodynamic investigations revealed hypocontractile detrusor in all patients.

Treatment method:

PTNS was applied according to Stoller [Stoller, 1999]. Patients are in supine position with the soles of the feet together and their knees abducted and flexed ('frog-position'). A 34-gauge stainless steel needle is inserted for approximately 3 to 4 cm about three fingerbreadths cephalad to the medial malleolus, between the posterior margin of the tibia and the soleus muscle. A stick on electrode is

placed on the same leg near the arch of the foot. The needle and electrode are connected to a low voltage (9 volts) Urosurge stimulator (Urosurge Coralville, Iowa USA) with adjustable pulse intensity of 0 to 10 mA., a fixed pulse width of 200 microseconds and a frequency of 20 Hz. The amplitude is slowly increased until the large toe starts to curl, or toes start to fan. If the large toe does not curl or pain occurs near the insertion site the stimulation device is switched off and the procedure is repeated. If patient's large toe curls or toes start to fan stimulation is applied at an intensity well tolerated by the patient. If necessary the amplitude can be increased during the session. Patients underwent 12 weekly outpatient treatment sessions, each lasting for 30 minutes. If a good response occurred the patient was offered chronic treatment.

Evaluation of results:

After providing informed consent all patients completed bladder diaries as well as general and disease-specific quality of life questionnaires at study entry and completion of the 12-week treatment. In the 24hour bladder diary frequency and voided volumes, number and volume of catheterisations, number of leakage periods, leakage severity as well as the number of pads or diapers used were recorded. The leakage severity was scored on a scale of 0 to 3 and included 0—no leakage, 1—leakage of some drops, 2—loss of a small amount and 3—loss of a massive amount of urine that required a change of clothes. General and disease specific quality of life was evaluated using the 36-item short-form health survey (SF-36) and the adjusted quality of life questionnaire, respectively [Ware et al., 1992; Wagner et al., 1996] respectively. The SF-36 consists of 36 items regarding 8 distinct health status concepts and 1 item measuring self-reported health transition, including physical function, role-physical, pain, general health, emotional well-being, role-emotional, social functioning, energy and fatigue and change in general health. The maximum score for each domain is 100 and a high score relates to better quality of life. The quality of life questionnaire consists of 22 items, each with a 5 point response scale. As with the SF-36, a high score means good quality of life.

Success was defined as the patient request for continued chronic treatment for maintenance. Analysis was done on an intention-to-treat basis. Within the group comparisons of parametric results at baseline and 12-week treatment were conducted with the paired sample t-test. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, USA).

6.3 RESULTS

6.3.1 Bladder overactivity

Of the 444 treatment sessions stimulation was performed on the right posterior tibial nerve with a

mean pulse intensity of 3.7 mA (range 1.4 to 6.8) per session in 265 (60%). Complications, including minor bleeding or a temporary painful feeling at the insertion site, were seen only rarely. Of the 37 patients PTNS in 7 men and 15 women (59,4%) was considered successful because they requested continuation of therapy after completion of the 12-week treatment (group 1, responders). In 3 male and 12 female patients treatment was unsuccessful since they did not choose maintenance therapy (group 2, non-responders).

At completion of the 12-week treatment all 33 patients with increased urinary frequency had a significant improvement of voiding frequency during day and night (*table 6.1* and *figure 6.1 A*). When discriminating group 1 (21 responders) from group 2 (12 non-responders), these improvements appeared to be significant only in group 1. The smallest mean volumes and mean volumes voided also improved, whereas the largest volumes voided did not change in this group.

Table 6.1: Voiding parameters in 33 patients with OAB

	All patients (N=33)		**Group 1 (N=21)**		**Group 2 (N=12)**	
	Mean ± SD (0 weeks)	**Mean change (95% CI)**	**Mean ± SD (0 weeks)**	**Mean change (95% CI)**	**Mean ± SD (0 weeks)**	**Mean change (95% CI)**
Frequency	16.5 ± 6.8	-2.8 (-0.8;-4.9)*	16.1 ± 6.1	-4.8 (-2.7;-6.8)***	17.1 ± 8.3	+0.8 (+5;-3.3)
Nocturia	2.6 ± 2.3	-1 (-0.2;-1.8)*	2.5 ± 2.7	-1.4 (-0.4;-2.3)*	2.7 ± 1.6	-0.2 (+1.3;-1.6)
Smallest volume voided	65 ± 49.3	+14.2 (+32.8;-4.5)	62.6 ± 52.1	+29.8 (+49.2; +10.3)**	71 ± 44.8	-18.5 (+19.4;-56.4)
Largest volume voided	289.8 ± 161	+13.9 (+48.7;-20.9)	268.8 ± 146.4	+9.5 (+50.6;-31.6)	334 ± 188.5	+23 (+100.6;-54.6)
Mean volume voided	140 ± 82.2	+19.3 (+40.3;-1.7)	133 ± 82.8	+35.1 (+62.6;+7.7)*	153.6 ± 83.7	-14 (+8.5;-36.5)

* $p < 0.05$ ** $p < 0.005$ *** $p < 0.0005$

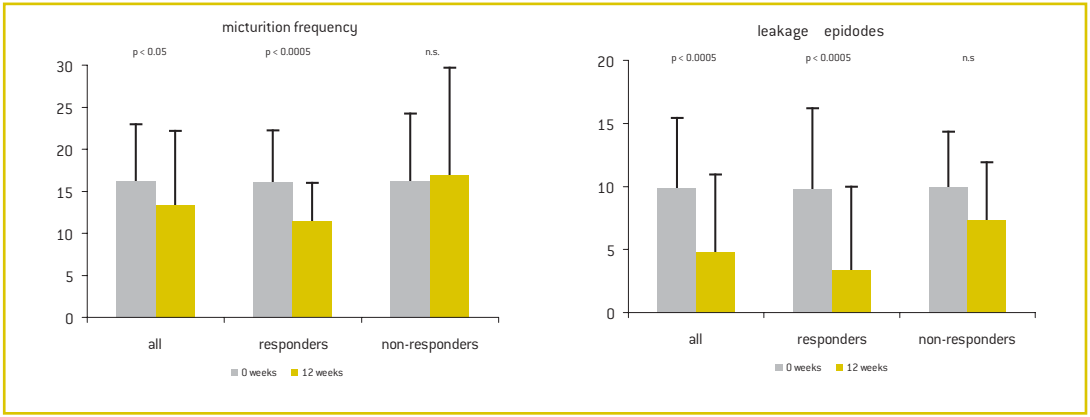

Figure 6.1: Before and after PTNS for responders, non-responders and both combined. A, voiding frequency. B, number of leakage episodes. Error-bar represents SD. ns, not significant.

A statistically significant overall decrease in incontinence was seen in the 30 patients who were urge urinary incontinent (*table 6.2* and *fig. 6.1, B*). When comparing group 1 (18 responders) with group 2 (12 non-responders), improvements found in leakage episodes and number of pads used appeared to be greater in group 1. Leakage severity scores showed improvement in all patients, who were incontinent. In groups 1 and 2, general quality of life improved in regard to physical and social functioning in all patients with OAB. Mean physical functioning plus or minus SD was 53.7 ± 27.9 (mean change +9.1 (95% confidence interval [CI]: +14.1; +4, p<0.005 and social functioning 64.7 ± 31.2 (mean change +10.3, 95% CI: +16.5; +4.1, p<0.005) at 0 weeks. In group 1 both scores also increased. Mean physical functioning plus or minus SD was 61.6 ± 26.3 (mean change +11.2 ,95% CI: +18.8; +3.5, p<0.05) and social functioning 70.6 ± 26.7 (mean change +11.6, 95% CI: +20.9;

Table 6.2: Voiding parameters in 30 patients with OAB

	All patients (N=30)		**Group 1 (N=18)**		**Group 2 (N=12)**	
	Mean ± SD (0 weeks)	**Mean change (95% CI)**	**Mean ± SD (0 weeks)**	**Mean change (95% CI)**	**Mean ± SD (0 weeks)**	**Mean change (95% CI)**
Leakage episodes	9.8 ± 5.6	-4.8 (-2.2;-7.5)**	9.8 ± 6.4	-6.2 (-2.9;-9.5)**	9.8 ± 4.4	-2.4 (+2.4;-7.3)
Pads used	6.3 ± 3.2	-2.5 (-1.2;-3.9)**	5.8 ± 2.6	-3.3 (-1.5;-5.1)**	7.1 ± 3.9	-1.3 (+0.9;-3.4)
Leakage severity	1.7 ± 0.5	-0.7 (-0.4;-1.0)**	1.6 ± 0.5	-0.8 (-0.3;-1.3)**	1.9 ± 0.5	-0.5 (-0.2;-0.8)*

* p < 0.05 ** p < 0.005

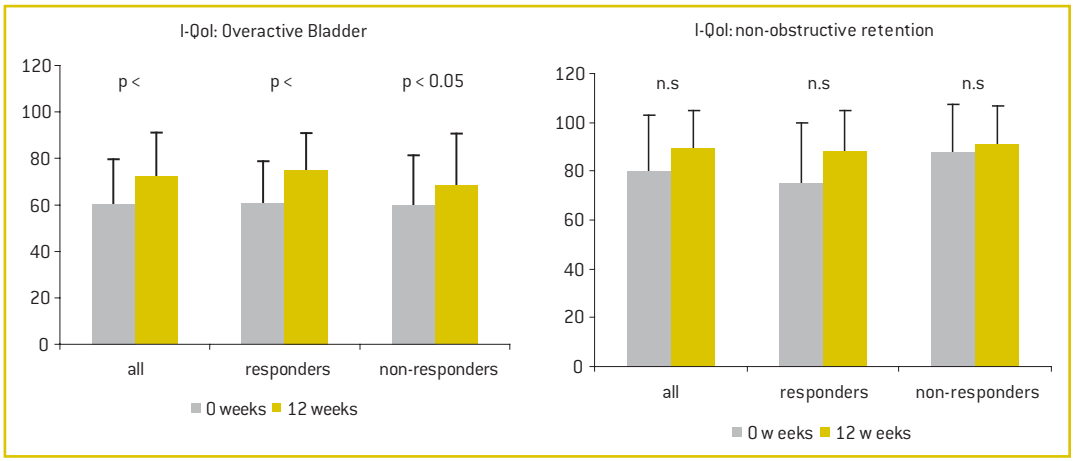

Figure 6.2: Before and after PTNS for responders, non-responders and both combined. A, disease specific quality of life scores in patients with OAB. B, non-obstructive retention. Maximum disease specific quality of life score was 110. Error-bar represents SD. ns, not significant.

+2.3, p<0.05) at 0 weeks. Only social functioning improved (55.9 ± 35.9 (mean change +8.4, 95% CI: +16.6; +0.2, p<0.05) at 0 weeks in group 2. Disease specific quality of life showed improvement in all patients (60.3 ± 19.3 (mean change +12.3, 95% CI: +17.3; +6.8, p=0.00004), as well as in patients in group 1 (60.6 ± 18.2 (mean change +14.4, 95% CI: +22.3; +6.6, p<0.005) and group 2 (59.9 ± 21.5 (mean change +8.5, 95% CI: +15.1; +2, p<0.05), respectively at 0 weeks (*fig. 6.2A*).

6.3.2 Non-obstructive retention group

Of the 144 treatment sessions stimulation was performed on the right posterior tibial nerve with a mean pulse intensity of 4 mA (range 2,5 to 7) per session in 87 (60%). As seen in patients treated for OAB, complications were rarely noted. Of the 12 patients PTNS was considered successful in 1 man and 6 women (58,3 %) because they requested continuation of therapy after completion of the 12-week treatment (group 3, responders). Treatment was unsuccessful in 4 men and 1 woman since they did not choose maintenance therapy (group 4, non-responders).

At completion of 12-week treatment all patients clearly had a decrease in number of catheterisations and mean and total volumes catheterised and an increase in mean and total volumes voided. However, statistical significance could not be obtained (*table 6.3*). When discriminating group 3 (7 responders) from group 4 (5 non-responders) these changes could also be observed in group 3, but not in group 4.

In regard to quality of life hardly any significant improvement could be found in the adjusted disease specific (*fig. 2, B*) or general quality of life questionnaire. The only exceptions appeared to be the SF-

Table 6.3: Voiding parameters in 12 patients with non-obstructive retention

	All patients (N=12)		Group 3 (N=7)		Group 4 (N=5)	
	Mean ± SD (0 wks.)	Mean chang (95% CI)	Mean ± SD (0 wks.)	Mean change (95% CI)	Mean ± SD (0 wks.)	Mean change (95% CI)
Number of catheterisations	5.3 ± 2,4	-0.8 (+0.6;-2.3)	5.9 ± 2.6	-1.4 (+1.2;-4.1)	4.4 ± 2	0 (+0.9;-0.9)
Mean volume catheterised	336 ± 171	-83.3 (+27.4;-194)	325 ± 181	-131.9 (+63.2;-326.9)	351 ± 176	-15.4 (+87.5;-118.4)
Total volume catheterised	1552 ± 776	-537 (+175;-1249)	1707 ± 915	-921.4 (+284.5;-2127.4)	1335 ± 547	+1 (+659.7;-657.7)
Mean volume voided	206 ± 192	+5.9 (+113.2;-101.4)	141 ± 107	+94.3 (+233.3;-44.7)	297 ± 258	-117.8 (+16.5; 252.1)
Total volume voided	919 ± 658	+173.8 (+639.2;-291.7)	758 ± 567	+482.1 (+1164.7;-200.4)	1145 ± 774	-258 (+374.6;-890.6)

36 score for emotional well-being, which increased (58,3 ± 12,2, mean change +14.3, 95% CI: +20.6; +7.9, p<0.005) in patients who thought treatment was successful (group 3), and the score for change of health, which significantly increased in all patients (45.8 ± 27.9, mean change +22.9 , 95% CI: +44.9; +1, p<0.05), but not in group 3 or in group 4 at 0 weeks, respectively.

6.4 DISCUSSION

For treatment of refractory urinary tract dysfunction various methods of intermittent neuromodulation have been advocated, including intravesical, anal, vaginal, penile and perineal stimulation, and transcutaneous electrical stimulation of the suprapubic or sacral region and the posterior tibial nerve [Madersbacher, 1990; Merril, 1979; Janež et al., 1979; Lindström et al., 1983; Nakamura et al., 1984; Vodušek et al., 1982; Fall et al., 1994; Walsh et al., 1999; McGuire et al., 1983]. Because of poor results or uncomfortable stimulation sites, most of the aforementioned treatment modalities did not gain widespread acceptance. In the 1980s implantable neurostimulation electrodes became available for modulation of the sacral spinal nerves, especially S3 [Schmidt, 1988]. Stimulation could be performed continuously, leading to better results, but drawbacks included invasiveness of the procedure, the high costs involved and the limited service life of the stimulation device, which was 7 to 10 years. In addition, symptoms appear to recur almost immediately after discontinuation

of the stimulation [Bemelmans et al., 1999]. Therefore, the development of an easy applicable, non-invasive or minimally invasive, cost-effective neuromodulation device, with good treatment outcome was anticipated. The recent advent of PTNS may offer urologists a treatment modality that meets the aforementioned criteria [Stoller, 1999; Klinger et al., 2000].

Stimulation of the tibial nerve was first described by McGuire et al in 1983 [McGuire, 1983] In studies of nonhuman primates with spinal cord injury, bipolar anal sphincter stimulation resulted in inhibition of detrusor activity. Similar results could be obtained by applying current through a transcutaneous electrode over the common peroneal or posterior tibial nerve, with a ground electrode being placed contralaterally over the same nerves. The idea of stimulating these nerves was based on the traditional Chinese practice of using acupuncture points over the common peroneal or posterior tibial nerves to affect bladder activity [McGuire, 1983]. Electrical stimulation of the tibial nerve was subsequently performed in 22 patients with detrusor overactivity, interstitial or radiation cystitis or neurological diseases with promising results, including continence in 12 and urodynamic improvements in 7. However, in a prospective study by Geirsson et al in patients with painful bladder syndrome, transcutaneous tibial nerve stimulation or traditional Chinese acupuncture treatment revealed no difference in voiding frequency, mean and maximal voided volumes and visual analogue symptom scores before or after either one of the treatment modalities [Geirsson et al., 1993].

In our study percutaneous stimulation resulted in a success rate of about 60% of 49 patients with OAB or non-obstructive urinary retention. Although our definition of success was a subjective one, responders differed significantly from non-responders in almost every semi-objective parameter. The same result was observed in disease specific and several domains of general quality of life scores. Because our study was not placebo-controlled, the observed improvements might theoretically be the result of regression to the mean, synchronous other treatment or placebo-effect, rather then a positive response to PTNS. Regression to the mean is not likely as all patients included had to present with symptoms for at least 6 months (median 4 years). To prevent interference by other treatment modalities, concomitant physiotherapy during PTNS was not permitted, as was the case with starting parasympatholytic medication or other pharmaceuticals influencing bladder function, including antidepressant agents, within 2 weeks before treatment. In patients who were already using any of the aforementioned drugs, medication had to be stopped 2 weeks before beginning PTNS or continued without dose changes during the entire 12 weeks. In placebo-controlled studies, success rates in the placebo group are usually much lower than the response rate of about 60% in our study. Because most patients had symptoms for a long period and had undergone various treatments before trying neuromodulation, it is not likely that they were highly susceptible to the placebo-effect of this treatment modality. Nevertheless, to validate these data a properly designed placebo-controlled study is warranted. However, it can be anticipated that the feasibility of such studies will be difficult.

Not withstanding the promising results and only mild complications of this neuromodulation

technique found in our study, this therapy also has some disadvantages, including percutaneous insertion of the stimulation electrode, necessity of regular visits to the outpatient clinic and, the thus far, unknown results of chronic treatment in initially successful patients. In the near future most of the aforementioned problems may be solved by an implantable subcutaneous electrode, which can be radiographically stimulated by the patients at home and on a regular basis. Studies regarding long-term results are ongoing, but results are not yet available. In conclusion, although thorough research is anticipated to improve patients' selection criteria, optimize the technique and help learn more about the precise mode of action, PTNS is a promising, cost-effective and easily applicable treatment option for patients with lower urinary tract dysfunction.

Appendix: Exclusion criteria

Exclusion criteria:	
Age under 18	Uncontrolled diabetes
Symptoms existing for less than 6 months	Diabetes with peripheral nerve involvement
Pregnancy or the intention to become pregnant during the course of the study	Neurological disease like MS, M. Parkinson, CVA, spina bifida or spinal cord lesion
Active urinary tract infection or recurrent urinary tractinfections (recurrent infections: ≥ 5 during the last 12 months), carcinoma in situ, bladder malignancy, interstitial cystitis	Change in parasympaticolytic medication or other pharmaceuticalsinfluencing bladder function (like anti-depressive agents) within 2 weeks prior to or during the study
Bladder or kidney stone	Physiotherapy at the same time as the study
Severe cardiopulmonary disease	Bladder outlet obstruction (Abrams-Griffiths nomogram)
Use of Elmiron or bladder installations like DMSO,BCG, Chloropectin or Heparin	Transurethral instrumentation £ 4 weeks prior to or during the study

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CHAPTER 7

PTNS in the treatment of overactive bladder syndrome complaints

Based on
PTNS IN THE TREATMENT OF URGE INCONTINENCE.

V VANDONINCK1, MR VAN BALKEN1, EF AGRÒ3, F PETTA3, C CALTAGIRONA3, JPFA HEESAKKERS1, FMJ M.J. DEBRUYNE1, LALM KIEMENEY2, BLH. BEMELMANS1

1 Dept. of Urology and Epidemiology2, University Medical Centre Nijmegen, The Netherlands
3 Dept. of Urology, University "Tor Vergata" AND IRCCS S. Lucia, Rome

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OBJECTIVE

The objective of this study was to evaluate the effect of PTNS for treatment of symptomatic overactive bladder syndrome (OAB) complaints.

SUBJECTS AND METHODS

In a prospective multicentre study, 35 patients with complaints of OAB underwent 12 weekly sessions of PTNS at one of 5 sites in the Netherlands and one site in Italy. Bladder diaries, I-QOL and SF-36 questionnaires were completed at 0 and 12 weeks. Success was analysed using subjective and objective criteria. Overall subjective success was defined as the willingness to continue treatment, whereas objective success was defined as a significant decrease (to <50%) in total number of leakage episodes.

RESULTS

Twenty-two patients (63 percent) reported a subjective success. Twenty-four patients (70 percent) showed a 50 % or greater reduction in total number of leakage episodes. Sixteen (46 percent) of these patients were completely cured (i.e., no leakage episode) after 12 sessions. Quality of life parameters improved significantly.

CONCLUSIONS

We conclude that PTNS is an effective, minimal invasive option for treatment of patients with complaints of OAB. Improvement was seen in subjective as well as objective parameters.

7.1 INTRODUCTION

Treatment of chronic lower urinary tract dysfunction can be challenging and difficult. Behavioural and medical therapies in patients with urge incontinence often result in unsatisfactory outcomes, leaving the refractory patient no other option but surgery (e.g. bladder transsection, phenolization, clam-ileocystoplasty) [Stephenson and Mundy, 2001]. To side-step surgery, electrostimulation offers an alternative for therapy-resistant urge incontinence. During the past decades electrical stimulation of the bladder, sacral roots and pudendal nerves has been explored with varying success. However, these treatments involve technical problems, high costs or low patient compliance because of the discomfort of treatment procedures [Esa et al., 1991; Kock and Pompeius, 1963; Habib, 1967; Janez et al., 1979; Merrill, 1979; Schmidt, 1988; Dijkema et al., 1993; Bosch and Groen, 1995; Primus et al., 1996; McFarlane et al., 1997; Weil et al., 1998; Bemelmans et al., 1999]. Transcutaneous electrical nerve stimulation (TENS) of the S3 segment is a useful alternative in patients with detrusor overactivity [Webb, 1992]. Hasan et al. reported significant changes in urodynamic parameters in patients applying TENS for treatment of the overactive bladder. [Hasan et al.,1996a]. Okada et al. stimulated thigh muscles and observed clinical improvement for several weeks to months [Okada et al., 1998]. However, TENS therapy can induce skin irritation and allergy at the stimulation site due to chemical and mechanical irritation [Hasan et al., 1996b; Oosterwijk et al., 1994; Hasan et al., 1996a]. Consequently, other stimulation approaches were explored. Research focussed on the effect of stimulation of afferent nerves in the lower limb. In cat experiments, Lindström and Sudsuang showed detrusor inhibition through stimulation of the myelinated afferents of the hip adductor muscles [Lindström and Sudsuang, 1989]. Inspired by acupuncture points over the tibial and peroneal nerves, McGuire et al applied electrostimulation of these nerves to treat bladder overactivity. They reported restoration of bladder control in a small group of patients [McGuire et al., 1983]. Stoller proposed PTNS for treatment of bladder and pelvic floor dysfunction [Stoller, 1999]. This study presents the results of a multicentre study using PTNS for the treatment of symptoms related to bladder overactivity.

7.2 PATIENTS AND METHODS

Between November 1999 and July 2000, 35 patients with therapy resistant OAB complaints were enrolled in an international prospective clinical trial in five sites in the Netherlands and one site in Italy. In all patients, an extensive medical history was taken, focusing on urinary symptoms, previous and present treatments, neurological disease, and medication. Physical examination was performed to rule out any relevant pathology such as urogynaecological or neurological abnormalities.

Symptoms existed for a minimum of 6 months. Inclusion criteria were at least one episode of symptomatic incontinence per 24 hours and the capability and willingness to fill out questionnaires and to keep an accurate bladder diary. For this study urge urinary incontinence (urge UI) was defined as the involuntary loss of urine associated with a strong desire to void. In all cases, urodynamic investigations were performed to confirm the diagnosis of incontinence accompanied with detrusor overactivity, and to exclude stress urinary incontinence. Exclusion criteria were all other treatable causes for the complaints (e.g. urinary tract infection, bladder stones, transitional cell carcinoma), pregnancy, age under 18, central or peripheral neurological disorders and severe cardiopulmonary disease. All patients gave their informed consent. Methods, units and definitions used in this study conform to the standard recommended by the International Continence Society [Abrams et al., 1988; Abrams et al., 1999].

For PTNS a 34-gauge needle was inserted percutaneously approximately 5 cm cephalad to the medial malleolus of the right or left ankle. A surface electrode was placed on the medial aspect of the ipsilateral calcaneus. The needle and electrode were connected to a low-voltage (9 V) electrical stimulator. Stimulation current (0-10mA) with a fixed frequency of 20 Hz and a pulse width of 200 msec, was increased until curling of the big toe or fanning of all toes became noticeable. If no clear motor response was found, the needle was removed and the insertion procedure repeated. In most of the patients the motor response was accompanied by a sensory response of a radiating sensation spreading in the sole of the foot. The current was set at a well-tolerable level. During a session, elevation of the current was allowed whenever fading of this sensation was experienced due to adaptation. Stimulation sessions lasted for 30 minutes and were repeated weekly for a period of 12 weeks in an outpatient setting.

Study outcome was based on subjective and objective criteria. Subjective success was defined as the patients' positive response resulting in the request for continuing treatment : these patients were called "responders". Objective outcome was based on bladder diary variables. Patients were asked to complete a single-day chart at baseline and at 12 weeks of treatment. The bladder diary included 24h recording of voiding frequency, voided volumes, number of leakage episodes, incontinence severity on a scale from 1 to 3 (1= some drops, 2= small amount, 3= severe urine loss necessitating change of clothing) and number of pads used. A single-day chart was preferred as 24h recordings prove to be sufficient to assess patients voiding and incontinence pattern [Gisolf et al., 2000; Mazurick and Landis,2000; van Melick at al., 2001]. Objective success was defined as a 50% reduction in leakage episodes (primary outcome measure). Secondary outcome measures were change in voiding frequency, incontinence severity, and the numbers of pads used. To assess change in voiding pattern, we used criteria proposed by Klingler et al., i.e., a posttreatment voiding frequency of 9-10 times per day (partial response to treatment) or 8 or less times a day (complete response) [Klingler et al.,

2000]. Additionally, quality of life was assessed at week 0 and at week 12. For incontinence specific quality of life assessment, the I-QoL was used containing 22 items, each with a five-point Likert-type response scale. The 22 items were summed and then transformed to a scale of 0-100 for easier interpretation, with the higher scores representing better quality of life [Patrick et al., 1999]. For the assessment of generic functional status and well-being, the MOS 36 items short-form health survey (SF-36) was used containing eight subscales (physical function, role-physical, pain, general health, emotional well being, role-emotional, social functioning, energy/fatigue and change in general health) [Ware and Sherbourne, 1992]. Higher scores indicate better quality of life.

Efficacy of PTNS was analysed for all patients on an intention-to-treat basis. Descriptive data were reported as median values and range, and as mean change with 95% confidence interval (CI) [Gardner and Altman, 1986]. Within-group comparisons of results were conducted by the Wilcoxon signed rank test. Tests were performed on a two-tailed basis and level of statistical significance was set at 5%. To evaluate whether it is possible to predict subjective success with baseline characteristics we performed univariate and multivariate logistic regression analyses. In these analyses, subjective success was defined as dependent variable. Odds ratios with their 95% confidence intervals were calculated as a measure for the predictive power of each characteristic. On the basis of the outcome of the multivariable analyses, we constructed a Receiver Operating Characteristic (ROC) curve to visualize the predictive power of the combination of the variables. The area under the ROC curve quantified this predictive power. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, USA).

7.3 RESULTS

Patients' characteristics

This study included a total of 35 patients with symptoms of OAB with incontinence (10 men, 25 females; median age, 57 years; range, 29-82 years). *Table 7.1* shows an overview of baseline characteristics and treatments undergone for complaints prior to PTNS. Urodynamic evaluation showed detrusor overactivity in 23 patients, and no detrusor overactivity in 12. Stress incontinence was excluded in all cases.

Baseline bladder diary and QoL data (*table 7.2*):

All patients presented with at least one episodes of urine leakage per 24 hours (range, 1 – 22, *Table 7.2*). Nine patients (6 male, 3 female) did not use pads at baseline or at week 12. Italian patients presented with a significantly smaller number of leakages and less severe urine loss and they also scored lower on the incontinence specific QoL score. SF-36 score was comparable between the two nationalities, indicating a similar generic functional status and well-being at baseline.

Table 7.1: Baseline characteristics , previous treatments undergone for complaints and survey data of 35 patients with OAB:

Patients (n)	**All (35)**		**NL (22)**		**Italy (13)**	
Patients' characteristics:	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Age in years (y)	57	29-82	57	30-82	50	29-77
Duration of symptoms (y):	4	1-56	5.5	1-56	3	1-11
Stimulation (mA):	3.9	1.4-6.8	4	1.4-6.8	4.1	2.5-6.1
Interventions for complaints	**Number of patients**	**(%)**	**Number of patients**	**(%)**	**Number of patients**	**(%)**
Medication	34	97	21	95	13	100
-One	13	37	6	27	7	54
-Two	15	43	9	41	6	46
-More than two	6	17	6	27	0	0
Pelvic floor/bladder retraining:	18	51	12	55	6	46
Electrotherapy	10	29	4	18	6	46
Surgical intervention	11	31	11	50	0	0
-One	8	23	8	36	0	0
-Two	2	6	2	9	0	0
-More than two	1	3	1	5	0	0
Bladder diary and QoL data:	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
24h voids	12.5	6-32	14	7-32	12	6-16
Nocturia	2	0-5	2	0-5	2	1-5
Mean capacity	119	41-250	135	41-244	100	70-250
24h leakages	5	1-22	6.5	1-22	4	1-5
Severity of incontinence	2	1-3	2	1-2.8	2	1-3
24h pads	3.5	0-11	5	0-11	3	0-6
I-QoL	41	20-84	56	20-84	25	20-39
SF-36 total score	57	24-84	64	28-82	56	24-81

*Medication: anticholinergics (oxybutynin, tolterodine, flavoxate hydrocloride), antibiotics, alpha-blocker; Electrotherapy: TENS, PNE; Surgery: colposuspension.

Table 7.2: Bladder diary, Incontinence specific quality of life (I-QoL) and generic functional status and well-being (SF-36) data of 35 patients with OAB treated with 12 weekly PTNS sessions.

Bladder diary data and QoI variable		Baseline		Week 12		Mean change	Within-group comparison
	N	Median	Range	Median	Range	MC (95% CI)	p value[a]
All (nr responders)	**35 (22)**						
24h voids	34	12.5	6-32	10	4-20	-4.1 (-5.6;-2.5)	<0.01
Nocturia	33	2	0-5	1	0-7	-1.1 (-1.7;-0.6)	<0.01
Mean capacity	34	119	41-250	191	76-363	+61 (+37;+86)	<0.01
24h leakages	34	5	1-22	1	0-16	-4.2 (-2.3;-6)	<0.01
Severity of leakage[b]	34	2	1-3	1	0-3	-0.9 (-1.4;-0.5)	<0.01
24h pads	34	3.5	0-11	0	0-10	-2.3 (-1.3;-3.3)	<0.01
I-QoL	35	41	20-84	75	0-100	+26 (+16; +35)	<0.01
SF-36 total score	34	57	24-84	62	24-81	+1.5 (-4.4;+7.4)	0.3

[a] Within-group comparison: baseline versus 12 week values. Wilcoxon signed rank test: significance level set at 5%.
[b] Incontinence severity on a scale from 1 to 3 (1, some drops; 2, small amount; 3, clothes needed to be changed due to urine loss).

Subjective success:

One patient dropped out because of personal reasons before follow-up surveys could be completed. Thirty-four patients completed their bladder diaries and QoL questionnaires. Twenty-two of 35 patients (63%) considered their situation much better or improved and hence were called a therapeutic success (subjective success rate).

Bladder diary and QoL data statistics:

All voiding parameters improved significantly (*see table 7.2*). I-QoL score improved significantly for all

patients. Non-responders did not achieve a higher I-QoL score after treatment (*see table 7.3*). For all patients, SF-36 questionnaire total score or scores on one of the eight health concepts did not change significantly. However, responders improved in emotional well-being (mean change in score +6 for responders compared to -9 for non-responders) and role-emotional domains (mean change +18 versus -11), whereas non-responders scored significantly lower on the energy-fatigue item (mean change -15 for non-responders versus +1 for responders) (*see table 7.3*).

Table 7.3: Mean change (95% CI) in Incontinence specific quality of life (I-QoL) and generic functional status and well-being SF-36 (total score and 8 domains) 22 responders and 12 non-responders after 12 weekly PTNS sessions for OAB complaints.

QoL change after PTNS	Responders (n=22) MC (95%CI)	Non-responders (n=12) MC (95%CI)
I-QoL-score	+32 (+22; +44)	+6 (-3; +16)
Total SF-score	+6 (-0.7; +13)	-7 (-18; +5)
8 domains:		
Physical functioning	+5 (-2; +12)	+2 (-7; +10)
Role-physical	+10 (-11; -31)	-21 (-55; +13)
Pain	+4 (-6; +14)	-11 (-32; +11)
General health	+2 (-4; +7)	-3 (-14; +8)
Emotional well-being	+6 (+0.6; +11)	-9 (-27; +9)
Role-emotional	+18 (+3; +34)	-11 (-39; +17)
Social functioning	+7 (-2; +15)	+5 (-13; +23)
Energy/fatigue	+1(-9; +11)	-15 (-27; -2)
Chance in general health	+6 (-4; +15)	-3 (-16; +12)

QoL, quality of life; CI, confidence interval; mc,mean change

Objective success; descriptive figures:

A total of 24 patients (69 %) showed a reduction in incontinence episodes (primary outcome measure) of more than 50 percent; of these 24 patients 16 had no leakage episodes. When one of the secondary outcome measures was used to define objective success, the following figures were found.

Urinary frequency: 11 patients (31%) regained a normal voiding pattern (less than 8 voids per day); another 10 patients (29%) could decrease their voiding frequency to 10 times a day. In total, 21 patients (60%) regained a voiding frequency of no more than 10 times per day.

Nocturia: 20 patients (57%) showed more than 50% decrease in nocturnal toilet visits. Incontinence: Severity of incontinence and number of pads used, decreased more than 50 % in 19 (54%) and 20 patients (57%), respectively. The percentage of patients using protection material decreased from 74 % to 47 % after 12 weekly sessions. If protection material was still being used, fewer pads were needed (*table 7.4*).

Table 7.4: Usage of pads by 35 patients with OAB complaints and incontinence, before and after 12 weekly PTNS sessions.

Sort of pads	% Patients (at baseline)	% Patients (after 12 weeks)
None	25.7	54.3
Small hygienic pad	5.7	5.7
Incontinence towel	54.3	37.1
Diaper	14.3	2.9

Influencing factors on outcome:

The results from the univariate and multivarite logistic regression analyses are presented in *table 7.5.* None of the baseline characteristics proved to be a significant predictor for subjective success. However, this may also be due to the limited number of study participants. There was some suggestion that certain characteristics can predict outcome to a certain extent. For example, for each milliamp increase in stimulation intensity, the chance of subjective success is increased with a factor 1.6. In contrast, nationality and duration of symptoms seemed to be of minimal predictive value. When all variables are combined the area under the ROC curve (*Figure 7.1*) appears to be 0.83 (95% CI: 0.70-0.97). The ROC curve constructed without the variables nationality and duration of symptoms did not alter its predictive power (0.80).

Table 7.5: Univariate and multivariate logistic regression analyses of baseline characteristics to calculate predictive value for subjective success in 35 patients with OAB complaints treated with 12 weekly PTNS sessions.

Baseline characteristics	Univariate analysisOR (95%CI)	Multivariate analysisOR (95% CI)
Sex (male versus female)	0.47 (0.11; 2.10)	0.24 (0.03;1.78)
Nationality (Italians versus Dutch)	0.54 (0.13; 2.23)	0.71 (0.08; 6.22)
Age (each increment of 1 year)	0.97 (0.92; 1.02)	0.95 (0.89; 1.03)
Duration of complaints (each increment of 1 year)	0.98 (0.92; 1.05)	0.98 (0.87; 1.10)
Number operation (per operation)	3.37 (0.74; 15.32)	5.7 (0.57; 57.7)
Stimulation intensity (each mA increment)	1.63 (0.83; 3.18)	2.4 (0.92; 6.26)

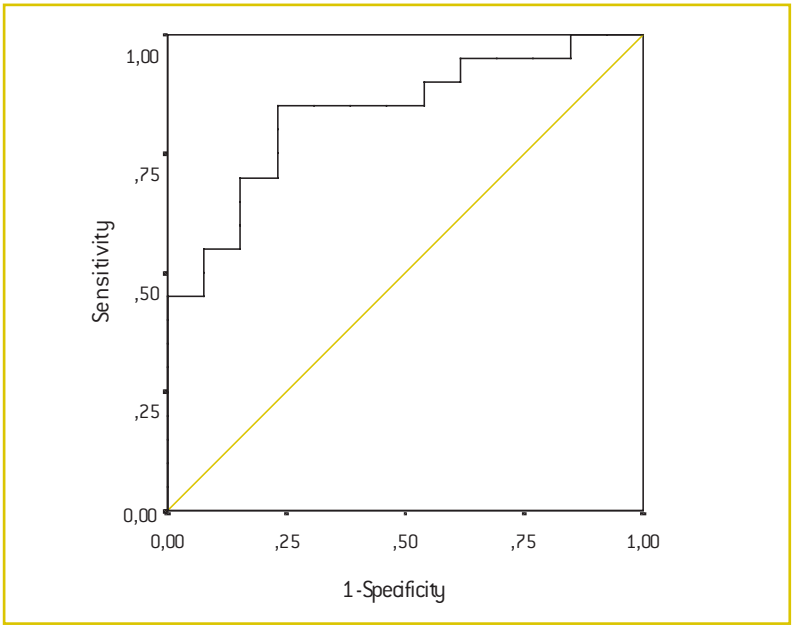

Figure 7.1: Receiver Operating Characteristic (ROC) curve constructed in order to visualize the predictive power of the combination of the variables (baseline characteristics, see table 7.5) of 35 patients with OAB treated with 12 weekly PTNS sessions.

Side effects:

No serious side effects were reported, although transient pain at the stimulation site was noticed. Diarrhoea, cramps, headaches and lower back pain were reported but not considered to be related to PTNS nor by the doctors nor by the patients.

7.4 DISCUSSION

This paper describes a new method of neuromodulation through electrical PTNS in the treatment of OAB. The aetiology of non-neurogenic bladder overactivity is unknown, but the hypothesis is that there is an imbalance between inhibitory and excitatory impulses that govern bladder function. The mode of action of neuromodulation is also obscure, but it is believed to restore the balance within the central nervous system [Bemelmans et al., 1999]. The posterior tibial nerve is a mixed nerve, containing motor and sensory nerve fibres. Correct placement of the needle electrode induces a

motor and sensory response. Centrally, the posterior tibial nerve projects to the sacral spinal cord in the same area where bladder projections are found (i.e., the sacral micturition centre and the nucleus of Onuf). These are most probably the areas where the therapeutical effect of neuromodulation of the bladder through PTNS takes place. PTNS has a clear carry-over effect: 30 minutes of stimulation induces a lasting beneficial effect. Cat experiments in which a 5-minute stimulation of afferent nerves resulted in more than 1 hour bladder inhibition, confirm the existence of this carry-over effect [Jiang and Lindström, 1999]. Perhaps some kind of learned behaviour is activated by intermittent stimulation as in PTNS. This supposition suggests that also higher regions within the cortical central nervous system are involved. Furthermore, in rats, PTNS exerted its influence on c-fos expression, suggesting neuromodulation action [Chang et al., 1998]. Also activation of endorphin pathways at sites within the spinal cord could affect detrusor behaviour [Oosterwijk et al., 1994, Murray et al., 1982; Clement-Jones et al., 1980]. Parallel to the gate control theory for pain, it can be suggested that stimulation of large somatic fibres could modulate/inhibit the thinner afferent A-delta or C fibres, thus decreasing the perception of urgency [Melzack and Wall, 1965]. By using 12 weekly sessions of PTNS, remarkable clinical results were obtained. Sixty-three percent of the patients with complaints of OAB reported a subjective success. These patients chose to continue treatment and were entered into a tapering protocol that individualizes the treatment frequency to the patients' personal requirements. In practice, this tapering meant that they had to be treated every 2-3 weeks. Objective success criteria showed equally good results: 69% of the patients had a decrease in the number of incontinence episodes of more than 50%. Apart from a clear decrease of incontinence, significant improvements in voiding frequency, nocturia, mean bladder capacity, severity of leakages and numbers of pads were found. 31% of patients regain a normal micturition pattern; 29% achieved "only" a partial response. However, in this study, patients who had a high baseline urinary frequency feel comforted even having a " pathological" number of voids per day. Surprisingly, before PTNS, nine patients never used pads (6 males, 3 females) although they were all incontinent (three lost some drops, two experienced drops and small amounts of urine, four always leaked small amounts of urine). This finding, underlines the stigmatic impact pads have on patients and how high the resistance to their use can be. Moreover, it seems debatable if the number of pads correlates well with severity or existence of urine loss. Some patients chose to change clothes several times a day rather than to wear protective means that are easily associated with mental regression. On the other hand some patients kept on using pads to be on the safe side.

Although nationality was not of predictive value, Dutch participants were more prone to be successful. Furthermore, the intensity of stimulation of the tibial nerve seems to be of importance, requiring more basic research to investigate optimal stimulation parameters. At baseline, Italian patients scored lower on the I-QoL instrument. This might be linked to cultural differences: perhaps Italian patients are more bothered by their incontinence then their Dutch counterparts. However, this finding might

also be attributable to the age difference between the two groups, the Italian patients being younger. It can be postulated that younger patients are less willing to accept their incontinence than the elderly, a feature previously reported in a study evaluating the I-QoL questionnaire [Patrick et al., 1999]. If improvement in quality of life scores occurred, it surely reflected the positive effect obtained by the therapeutical intervention, because there was a noticeable difference between the post-treatment I-QoL score of responders and non-responders. Improvement in emotional functioning emphasizes how patients' bladder dysfunction impaired daily activities before PTNS.

One possible explanation for the benefits found in our patients is the placebo-effect. Because every therapy has a propensity to induce placebo-effects, percutaneous stimulation of the tibial nerve is no exception to this rule. The design of a good placebo-controlled PTNS-study seems tedious and its execution impossible. Reports of placebo-controlled pharmacotherapeutic trials for urge-incontinence show placebo-effects in 28-43% of the patients [Burgio et al., 1998; Madersbacher et al., 1999, Thuroff et al., 1991]. This suggests that a high success rate as was found in our study is not likely to be due to placebo-effect alone.

Neuromodulation of the posterior tibial nerve is a simple way to treat this category of patient, i.e. those who have already undergone every possible type of conservative therapy and who might be on the verge of deciding to undergo irreversible surgical therapy. That PTNS is efficacious and at the same time cost-effective makes this therapeutic modality an attractive option for physicians and patients. At present, the introduction of a device for home-based treatment is under way. This device will enable patients to treat themselves at home as often as they consider it necessary and it will make this revolutionary technique for the treatment of urge-incontinence available for long-term use.

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CHAPTER 8

Posterior tibial nerve stimulation in the treatment of idiopathic non-obstructive voiding dysfunction

Based on
POSTERIOR TIBIAL NERVE STIMULATION IN THE TREATMENT OF IDIOPATHIC NON-OBSTRUCTIVE VOIDING DYSFUNCTION

V VANDONINCK[1], MR VAN BALKEN[1], EF AGRÒ[3], F PETTA[3], F MICALI[3], JPFA HEESAKKERS[1], FMJ M.J. DEBRUYNE[1], LALM KIEMENEY[2], BLH. BEMELMANS[1]

1 Dept. of Urology and Epidemiology
2, University Medical Centre Nijmegen, The Netherlands
3 Dept. of Urology, University "Tor Vergata" AND IRCCS S. Lucia, Rome

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OBJECTIVE

To evaluate the effect of stimulation of PTNS for treatment of voiding dysfunction.

SUBJECTS AND METHODS

Thirthy-nine patients with chronic voiding dysfunction necessitating clean intermittent catheterisation were enrolled in a prospective multicentre trial in the Netherlands (n=19) and in Italy (n=20). They underwent 12 weekly sessions of posterior tibial nerve stimulation (PTNS). Bladder diaries, an incontinence quality of life questionnaire (I-QoL) and the MOS 36 items Short-Form Health Survey were completed at 0 and 12 weeks. Subjective success was defined by the patient's positive response resulting in a request to continue treatment. Efficacy was based on analysis of the bladder diary data, comparing the baseline values with the data at 12 weeks. A reduction of 50 % or more in total catheterised volume was considered as an objective success (primary outcome measurement).

RESULTS

Of the 39 patients, 23 (59 %) chose to continue treatment. Bladder diary data showed a 50% decrease in total catheterised volume in 16 (41%) of the 39 patients. Additionally, 10 patients (26%) noticed a reduction of 25% to 50% in their total catheterised volume. For all patients, the total catheterised volume decreased by a mean of –228 ml (range: -528; -49). I-QoL and SF-36 parameters improved significantly.

CONCLUSIONS

PTNS seems to be an effective, minimally invasive option worth trying in patients with idiopathic voiding dysfunction. Improvement was seen in objective micturition parameters as well as in subjective quality of life data.

8.1 INTRODUCTION

The presence of a significant amount of residual urine is indicative of voiding dysfunction and, in particular of a weak or acontractile detrusor or of functional or mechanical outlet obstruction. For men outlet obstruction due to benign prostatic hyperplasia is the main cause, but sometimes it can be due to impaired or absent detrusor contractions. In females, old textbooks used to ascribe retention to hysteria. Today the whole concept of voiding dysfunction in women is still not as well defined as in men. In the absence of overt neuropathy and pathological disorders causing distortion or compression of the urethra, retention most commonly occurs following unrelated surgical procedures or childbirth [Farrar at el, 1994]. Furthermore, recent neurophysiologic research has revealed a new type of voiding dysfunction in young women. Sphincter electromyography has demonstrated an abnormal but characteristic activity: sound recordings from the urethral sphincter likened to whales sounds. This phenomenon, described as the Fowler syndrome, seemed to be associated with hormonal imbalance and polycystic ovaries. The striated urethral muscle fibres, hormonally sensitive, lose their membrane instability, resulting in abnormal activity [Fowler et al., 1994].

The inability to empty the bladder completely may result in urinary tract infections or overflow incontinence. Non-surgical treatment options are more or less discouraging. The use of cholinergic agents to stimulate detrusor contractions is debatable. Studies demonstrated patients benefiting clinically from treatment with distigmine but without statistically significant changes [Shah et al., 1983; Tanaka et al., 2001]. Urethral dilation can be performed on empiric grounds, but often the patient is left no other option than lifelong clean intermittent catheterisation. Unfortunately, catheterisation is at the expense of quality of life. Electrostimulation was brought up as an alternative for therapy-resistant voiding dysfunction and is preferred to urinary diversion, which may still be required as a last resort in some cases. Intravesical electrostimulation, conus implantation according to Nashold, and sacral root stimulation (SRS) introduced in the mid 1980s, were revolutionary concepts to regain bladder control [Katona et al., 1975; Nashold et al., 1974; Madersbacher et al., 1982; Schmidt et al., 1979]. Restoring of voiding capability, decreased urinary tract infection rate, and an improved quality of life owing to alleviation of the need for clean intermittent catheterisation were found [Shaker et al., 1998; Jonas et al., 2001]. Unfortunately implantation is a costly invasive procedure sometimes complicated by battery failure, implant infection and electrode migration resulting in a high reoperation rate. The performance of intravesical stimulation is time consuming, requiring an intensive bladder training programme and external biofeedback to achieve the goal and the presence of experienced nurse and adequate facilities [Madersbacher et al., 1990]. Inspired by acupuncture points over the tibial and peroneal nerve to overcome bladder overactivity, Mc Guire et al. applied transcutaneous electrostimulation over these nerves [Mc Guire et al., 1983]. Stoller proposed PTNS for treatment of pelvic floor dysfunction [Stoller, 1999]. The aim of this study was to determine the effect of PTNS among patients with idiopathic non-obstructive voiding dysfunction.

8.2 MATERIALS AND METHODS

Between November 1999 and July 2000, 39 consecutive patients with idiopathic non-obstructive voiding dysfunction were enrolled in a prospective multicentre clinical trial in the Netherlands (Nijmegen and Utrecht, n=19) and in Italy (Rome, n=20). Patients underwent 12 weekly PTNS.

Definitions and criteria

All patients enrolled, failed in achieving complete bladder emptying, and 2 patients had complete urinary retention. The symptoms had existed for a minimum of 6 months. The inclusion criteria were one or both of the following: complete retention or failure to achieve complete bladder emptying and the need for clean intermittent catheterisation. The exclusion criteria were bladder outlet obstruction for men (defined by the Abrams-Griffiths nomogram), any urogynaecological, central or peripheral neurological disorders, pregnancy, age younger than 18 years and severe cardiopulmonary disease [Abrams and Griffiths, 1979]. Urodynamic investigations consisting of medium-fill water cystometry and pressure-flow studies, were performed at baseline in all patients. The methods, definitions and units conformed to the standards recommended by the International Continence Society, except where specifically noted [Abrams et al., 1988]. All patients gave informed consent.

PTNS procedure has been extensively described in previous reports [van Balken, 2001; Klingler et al., 2000]. In brief, a percutaneous needle was inserted a few inches above the medial malleolus and connected to a low-voltage battery. Stimulation of the posterior tibial nerve gave a typical motor (plantair flexion of digit I or fanning of the toes) and sensory response (a tingling feeling spreading from the heel to the sole of the foot). Treatment consisted of 12 weekly sessions of 30 minutes each.

Primary outcome measure, positive response rate and quality of life

Study outcome was based on subjective and objective criteria. Subjective success was defined as the patients' positive response resulting in the request for continuing treatment. Objective outcome was based on bladder diary data. Patients were asked to complete a single-day chart at baseline and at 12 weeks of treatment. Parallel to Blaivas' proposals concerning how to assess efficacy of neuromodulation, a 50% reduction in total catheterised volume per 24h was taken as the primary outcome measure to assess objectively PTNS efficacy [Blaivas, 2001]. Disease-specific quality of life and generic functional status and well-being (MOS Short-Form 36-items [SF-36]) were assessed at week 0 and at week 12 [Patrick et al., 1999; Ware et al., 1992]. Higher scores indicated a better quality of life.

Statistical analysis and predictive factors

The efficacy of PTNS was analysed for all patients on an intention-to-treat basis. Descriptive data were reported as the median values and range, and as mean change with 95% confidence interval (CI)

[Gardner et al., 1986]. Within-group comparisons of results were conducted by the non-parametric Wilcoxon signed rank test. Tests were performed on a two-tailed basis and level of significance was set at 5%. In order to evaluate whether it is possible to predict subjective success with baseline characteristics, we performed univariate and multivariate logistics regression analyses. We believe the most relevant outcome measurement is patients' perception of the PTNS effect on their voiding disorder, because despite good improvement in bladder diary data, patients can experience the net effect as unsatisfactory and vice versa. Therefore, in these analyses, subjective, not objective, success was defined as the dependent variable. Odds ratios with their 95% CIs were calculated as a measure of the predictive power of each characteristic. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, USA).

8.3 RESULTS

Patient characteristics (*table 8.1*)

A total of 39 patients (12 men and 27 women; median age 53 years, range 28 to 77) were enrolled in this study. The baseline values are summarized in *table 8.1*. One patient catheterised 400 ml once daily, another catheterised aliquots of 74 ml four times daily. Bladder diary data illustrated a geographic difference in the baseline parameters and I-QoI scores: Italian patients presented with less severe voiding problems, but scored lower on the quality of life questionnaires.

Subjective success

Of the 39 patients,23 (59 %) chose to continue treatment. One patient dropped out of the study after six sessions because of aggravation of pre-existing arrhythmia, assumed not to be related to PTNS.

Bladder diary data and QoL data analysis (*See Table 2*)

The bladder diary data were completed after 12 weeks by 38 patients (*Table 8.2*). All patients improved significantly in all bladder diary data except for the total voided volume. In contrast to Italian patients, the Dutch patients did not achieve significant changes in voiding (eg, mean change in total catheterised volume was -350 ml (95% CI: -862; +161) for the Dutch participants and -230 ml (95%CI: -328; -131) for Italian patients. The total catheterised volume per 24 hours stagnated in non-responders (median volume: 800ml at 0 weeks; 865ml after 12 PTNS sessions); responders improved after the 12 sessions (from 515ml to 190ml/24hours). For the patient group as a whole, quality of life parameters improved significantly: I-QoL, total SF-36 score and its subdomains of emotional well-being, energy-fatigue and change in health ($p<0.01$-0.05).

Table 8.1: Medical background and therapies used for urinary symptoms in 39 patients with idiopathic non-obstructive voiding dysfunction.

(% Of patients)	All (39)		NL (19)		Italy (20)	
Patient characteristics:	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Male/female (n)	12/27		8/11		4/16	
Age in years (y)	53	28-77	54	36-77	52	28-75
Duration of symptoms (y)	3	1-36	3	1-36	3	1-17
Current intensity (mA)	4	1.4-7.6	4	1.4-7.6	4.1	2.5-5.7
Treatments prior to PTNS (%):	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**
Medic. for complaints: - One - Two	31 19 12	80 49 31	16 12 4	84 63 21	15 7 8	75 35 40
Pelvic floor/bladder retraining:	8	21	4	21	4	20
Electrotherapy:	5	13	1	5	4	20
Surgical intervention: - One - Two	11 8 3	29 21 8	9 6 3	48 32 16	2 2	10 10
Baseline voiding parameters:	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Total catheterised volume	800	210-3000	1350	895-3000	375	210-1080
Mean catheterised volume	241	74-675	300	74-675	188	105-540
Number of catheterisations	2.5	1-10	5	2-10	2	1-4
Total voided volume	1000	95-2700	1050	95-2520	1000	420-2700
Baseline QoL score:	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
I-QoL	62	26-99	78	34-99	59	26-90
SF-36	65	19-92	57	19-92	65	20-92

NL: The Netherlands; PTNS : percutaneous posterior tibial nerve stimulation; QOL: quality of life; SF-36: 36-item short form health survey.

Table 8.2: Bladder diary data after 12 weekly sessions with PTNS.

	Week 0		Week 12		Mean change (95% CI)	Within-group comp:
Bladder diary data:	**Median**	**Range**	**Median**	**Range**	**MC (95%CI)**	**P value**
Total catheterised volume	800	210-3000	450	0-2450	-228 (-528; -49)	<0.01
Mean catheterised volume	241	74-675	163	0-163	-76 (-39; -113)	<0.01
Number of catheterisations	2.5	1-10	2	1-7	-0.5 (-0.9; -0.04)	0.024
Total voided volume	1000	95-2700	1260	50-310	+116 (+8; +323)	0.053
Quality of life scores:	56	8-91	67	56-86	+6 (+3; +10)	<0.01
I-QoL	62	26-99	86	0-100	+14 (+5; +22)	<0.01
SF-36	65	19-92	70	17-91	+7 (+3; +11)	<0.01

Objective success; descriptive figures

In 16 (41%) of the 39 patients the 24hour total catheterised volume was reduced by 50% or more (primary outcome measure). Another 10 participants (26%) noticed a 25-50% decrement in their residual urine volume. At 12 weeks 7 patients catheterised only once daily. Four of them had residual urine below 100ml and another two had no residual urine on bladder diaries. Nobody became catheter free.

Factors influencing outcome

Univariate logistic regression analysis showed that none of the baseline characteristics proved to be a significant predictor for subjective success. This may also be due to the small number of study participants. There was some suggestion that certain characteristics can predict outcome to a certain extent. For example, for each milliampere increment in stimulation intensity, the chance of subjective success decreased by a factor of 0.55 (Odds Ratio OR: 0.55; 95%CI: 0.33-1.0). The analysis further suggested that Italian nationality increase change of success (OR: 4.13; CI: 1.06-16.1). In contrast, age

(OR: 0.97;CI: 0.92-1.02), duration of symptoms (OR: 1.09; CI: 0.94-1.25), or the amount of baseline total catheterised volume (OR: 1.0; CI: 0.99-1.001) seemed to be of minimal or even no predictive value. The analysis was limited to univariate logistic regression because multivariate analysis appeared to be not feasible owing to the small number of participants and thus responders.

Side effects

No serious side effects were reported. Transient pain at the stimulation site was noticed. Diarrhea, headaches, calf cramps and low back pain were reported. One patient did not complete the treatment because of aggravating pre-existent heart rhythm problems. However these adverse effects were not considered to be related to PTNS.

8.4 DISCUSSION

Nearly 60 % of the patients considered PTNS successful, and this figures was supported by the objective criteria derived from the bladder diary data. Nevertheless, the high success rate of 74% reported in a recent Sacral Nerve Stimulation (SNS) report was not achieved [Jonas et al., 2001]. A possible explanation for this might be that for PTNS, we treated consecutive cases whereas in SNS studies, patients were already preselected by strict inclusion criteria such as the pelvic nerve evaluation test. The pioneers of intravesical electrostimulation reported promising high success rates. Katona treated 420 patients with paralyzed bladders, 314 of them regained micturition control. In a rehabilitation program of Madersbacher et al., 28 of 30 patients with spinal cord lesions restored bladder function and ended up with residual volumes of less than 50 ml [Katona, 1975; Madersbacher et al., 1982]. Primus et al. reported 19 (54%) of 35 patients with neurogenic acontractile or hypocontractile bladders became catheter free after transurethral bladder stimulation [Primus et al., 1996].

PTNS resulted in 15 (39%) of 39 patients with a mean catheterised volume smaller than 100 ml (13 patients) or 0 (2 patients). As discussed recently by Blaivas, this parameter should not be used as outcome measurement: the mean residual volume can only be interpreted properly when catheterisation frequency is given [Blaivas, 2001]. For example, from these 15 subjects with a mean residual of 100 ml or less, only 6 reduced their catheterisation rate to once daily. In this study nobody became catheterisation free; even the 2 patients that had 0 residual after catheterisation, still continued catheterisation, probably to be on the safe side. The primary outcome measurement (greater than 50% reduction in 24hour residual volume) was found in 41%.

PTNS is believed to relieve symptoms due to an overactive and underactive bladder, a phenomenon also seen in SNS [Jonas, 2001]. The underlying neurophysiologic mechanisms have not yet been elucidated. Remarkably, the results of univariate analysis in this study seem to indicate

that application of low current applied over the tibial nerve increases the change of successful outcome. This is in contrast to our previous results of PTNS treatment for an overactive bladder in which higher stimulation intensity seemed to be more successful. Schultz-Lampel et al. found that unilateral S2 low-intensity stimulation in cats induced excitatory effects on the bladder and higher intensities produced complete bladder inhibition [Schultz-Lampel et al., 1998]. In their experiment they also found frequency-dependent effects; because in our study a fixed frequency of 20Hz was used, such effects could not be evaluated. Low-current intensity selectively activates the largest diameter fibres first and, as stimulus intensity increases, successively smaller diameter fibres are recruited. Stimulus intensity-dependent activation of diverse fibres together with our statistical interpretation could suggest activation of different pathways and their particular action on bladder function. Nevertheless because of vagaries in current flow owing to inhomogeneous character of each nerve, the recruitment of fibres by size may not always be perfectly related to stimulus intensity. Furthermore, actual current values depend on the type of stimulator, pulse characteristics, physical environment and type of stimulated nerve [Swett et al., 1981]. The use of thresholds or biological effectiveness -such as muscle contraction- to describe the current intensity used to stimulate nerves should be recommended, allowing comparisons between research groups. This creates an interesting topic for future investigation.

Interestingly, patients reported a more accentuated awareness of a desire to void, supporting the hypothesis of an excitatory effect on bladder function by PTNS, a feature also reported in various transurethral bladder stimulation studies. The recent work of Athwal et al., suggest that urge to void sensations and appreciation of bladder fullness are localised in distinct areas in the brain of healthy volunteers [Athwal et al., 2001]. The effect achieved by SNS returns to baseline values after switching off the device, as opposed to long-term effect of a few weeks after stimulation by PTNS. The long-term effect through PTNS could be explained by the carry-over effect found in cat experiments where a 5-minute stimulation of afferent nerves resulted in a lasting effect of more than 1 hour [Jiang et al., 1999].

The Italian patients improved more than the Dutch ones, and at first sight it seemed that the less severe baseline condition of these participants was of importance. However statistical analysis could not reveal one single important baseline characteristic - even the lower total catheterised volume at baseline- except for the fact that being Italian increases the change of success. Aside from both nationalities belonging to the same European white race: cultural differences may be important for subjective bother impact andquality of life scores, but not for objective urinary parameters.

Before exploring the mechanism of PTNS on voiding disorders, the contribution of placebo-effect in this particularly patient group should be quantified. Every therapy has a susceptibility to induce placebo-effects and certain aspects of PTNS could play an important role: meeting fellow-sufferers, intensive guidance and attention by medical care providers, and frequent completion of questionnaires and

charts. Therefore, in the future a placebo-controlled PTNS-study is mandatory. Unfortunately certain features of PTNS (e.g. electrical stimulation, motor and sensory response and use of needles) make the realization difficult.
In conclusion, PTNS is an attractive first-line option. It is cheap, minimally invasive and easy to perform. However, to date, PTNS is still a young therapy modality requiring additional research to establish optimal stimulation parameters and valuable predictive factors.

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CHAPTER 9

Posterior tibial nerve stimulation in the treatment of overactive bladder: urodynamic data

Based on
POSTERIOR TIBIAL NERVE STIMULATION IN THE TREATMENT OF OVERACTIVE BLADDER: URODYNAMIC DATA.

V VANDONINCK[1], MR VAN BALKEN[1], E FINNAZZI AGRÒ[3], F PETTA[3], F MICALI[3], JPFA HEESAKKERS[1], FMJ DEBRUYNE[1], LALM KIEMENEY[2], BLH BEMELMANS[1]

1 Dept. of Urology and Epidemiology
2, University Medical Centre Nijmegen, The Netherlands
3 Dept. of Urology, University "Tor Vergata" AND IRCCS S. Lucia, Rome

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OBJECTIVE

The aim of this study was to evaluate urodynamic changes after PTNS for the treatment of complaints related to overactive bladder syndrome and to search for urodynamic-based predictive factors.

SUBJECTS AND METHODS

Ninety consecutive patients with symptoms related to overactive bladder syndrome were enrolled in this study. Patients underwent 12 PTNS sessions. For evaluating objective success, the primary outcome measure was a reduction in number of urinary leakage episodes of 50% or more per 24 hours. Patients' request for continuation of therapy was considered subjective success. This study focussed on urodynamic features at baseline and on changes found after 12 PTNS treatments.

RESULTS

The objective success rate was 56% (leakages/24hours). Subjective success rate was 64%. Bladder diary data and quality of life scores improved significantly ($p<0.01$). Urodynamic data before and after PTNS stimulation, was available from 46 participants. Detrusor overactivity (DO) could be abolished in a few cases only. Increments in cystometric bladder capacity and in volume at DO were significant ($p=0.043$ and 0.012 respectively). Subjects without detrusor overactivity at baseline were 1.7 times more prone to respond to PTNS (OR: 1.75; 95% CI: 0.67- 4.6). The more the bladder overactivity was pronounced, the less these patients were found to respond to PTNS, the area under the ROC curve was 0.644 (95% CI: 0.48-0.804).

CONCLUSIONS

PTNS could not abolish DO. PTNS increased cystometric capacity and delayed the onset of DO. Cystometry seemed useful to select good candidates: patients without DO or with late DO onset showed to be the best candidates for PTNS.

9.1 INTRODUCTION

Electrostimulation has been exploited both for overactive bladder and for hypocontractile bladder alike. Recently, PTNS has been introduced for the treatment of lower urinary tract dysfunction. The tibial nerve is a mixed nerve containing L4-S3 fibres, and originates from the same spinal segments as the innervation to the bladder and pelvic floor. Therefore, it is not surprising that efforts were made to stimulate these fibres to treat bladder disturbances [Mc Guire et al., 1983; Stoller, 1999; Klingler et al., 2000; van Balken et al., 2001]. In previous studies, we have discussed extensively subjective success, quality of life scores and bladder diary data [van Balken et al., 2001; Vandoninck et al., 2003] Therefore, this article presents the urodynamic features found in patients who underwent PTNS for symptoms of overactive bladder syndrome. Three issues will be addressed: First, the primary outcome measures based on charts and questionnaires will be described briefly. Second, the urodynamic changes after PTNS treatment will be discussed and lastly, the predictive value of baseline urodynamic parameters on treatment outcome will be reported.

9.2 MATERIALS AND METHODS

Between November of 1999 and August of 2001, a total of 90 consecutive patients with a diagnosis of overactive bladder syndrome were enrolled in an international multicentre prospective clinical trial in five sites in the Netherlands and one site in Italy. Patients underwent 12 sessions of PTNS. Overactive bladder syndrome was defined as urgency, frequency and/or urge urinary incontinence. For urgency and urge incontinence, International Continence Society (ICS) definitions were used [Abrams et al., 2002]. For this study, an increased urinary frequency was defined as eight voids or more per 24 hours. Stress urinary incontinence was excluded through urodynamic investigation.

Inclusion and exclusion criteria as well as the PTNS technique have been extensively described in a previous study [van Balken et al., 2001]. In short, the procedure was as follows: the posterior tibial nerve was located through percutaneous insertion of a needle a few inches above the medial malleolus. After connection to a low voltage stimulator (Cystomedix, Anoka, Minnesota, USA) and placement of a ground surface electrode on the ipsilateral calcaneus, the tibial nerve was stimulated. This resulted in a tickling sensation in the sole of the foot and flexion of the toes.

Following the consideration of Blaivas on how to assess new treatment modalities, the subsequent parameters were evaluated: the number of leakage episodes, the amount of urine loss, urinary frequency, and subjective patient assessment [Blaivas, 2001]. A reduction in the number of leakage episodes of at least 50% on 24hour bladder diaries was taken as primary outcome measure.

Furthermore, a reduction in leakage severity of at least 50% was a secondary outcome measure (scale score 1: some drops; 2: small amount; 3: severe urine loss necessitating change of clothing). A reduction in urinary frequency was regarded clinically significant when a normal voiding pattern of less than 8 voids per 24h could be obtained. Patients' request for continuation of treatment was regarded a subjective success and these patients were called "positive responders". In addition, quality of life was determined at week 0 and at week 12. For incontinence specific Quality of life the I-QoL was used [Patrick et al., 1999]. For the estimation of generic functional status and well-being, the MOS 36-items Short-Form health survey (SF-36) was completed [Ware et al., 1992]. Higher scores indicate better quality of life. All patients gave their informed consent.

Both at baseline and after 12 sessions, urodynamic investigations were performed in all patients. For urodynamic analysis a standard transurethral subtraction cystometry was performed in the supine position. Sterile saline at room temperature was infused through a double-lumen 8-French catheter at a filling rate of 50 ml/min. The volume at which detrusor overactivity (DO) occurred was noted. DO was defined as an increase of 15 cm water pressure or of lower amplitude if accompanied with a distinct sensation of urgency. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted [Abrams et al., 2002].
Descriptive data were reported as median values and range and with a median change and range. Within-group comparisons of results were conducted by the non-parametric Wilcoxon signed ranks test. Tests were performed on a two-tailed basis and level of significance was set at 5%. To evaluate whether it is possible to predict subjective success with urodynamic characteristics, we performed univariate and multivariate logistics regression analyses. The dependent variable was "subjective success" because this feature is the clinically most relevant outcome measure: despite good improvement in bladder diary data, a patient can experience the net effect as unsatisfactory and vice versa. Odds ratios (OR) with their 95% confidence intervals (95% CI) were calculated as a measure for the predictive power of each characteristic. Based on the outcome of the multivariate analyses, a Receiver Operating Characteristic (ROC) curve was constructed to visualize the predictive power of the combination of the variables. The area under the ROC curve quantified this predictive power. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, USA).

9.3 RESULTS

Baseline characteristics

90 patients (67 females and 23 males) with a median age of 51 years (range, 19-82 years) were enrolled in this study (*See Table 9.1*). Duration of symptoms ranged between 1 and 56 years with a

Table 9.1: 24hour bladder diary data, urodynamic data and quality of life scores in 90 patients receiving 12 PTNS sessions for overactive bladder complaints.

Parameter	M	N	Baseline	N	End	Change	p value
24h bladder diary:							
Leakages	30	60	5 (1;19)	59	2 (0;16)	-3 (-19;+7)	<0.01
Incontinence severity	30	60	2 (1;3)	58	1 (0;3)	-1 (-3;+1)	<0.01
Urinary frequency	10	80	13 (4;41)	75	10 (4;53)	-3 (-18;+12)	<0.001
Mean Voided Volume	11	79	135 (20;327)	74	191 (47;410)	+27 (-96;+200)	<0.001
Quality of life scores:							
I-QoL	9	81	49 (20;100)	80	67 (20;100)	+10 (-31;+88)	<0.001
SF-36	11	79	57(10;93)	82	67 (13;93)	+4 (-42;+56)	<0.001
Cystometric data:							
Cystometric capacity	7	82	263 (30;745)				
Subjects with DO	42	48	59%				
Volume DO	42	48	150 (30;350)				
Pdet DO	42	48	41 (4;123)				

M: missing values at baseline because not complete or not relevant; N: number of valid values; Pdet DO: Detrusor pressure at DO. Data represent mean values with ranges in parantheses. Wilcoxon signed ranks test, significance level set at 5%.

median of 4.5 years. A total of 80 of 90 bladder diaries were completed correctly and used for further analysis (10 of 90: 11% missing values). 60 of 80 (75%) of these patients were incontinent and leaked at least once a day. From those patient who filled in correctly the bladder diaries, 73 of 80 (91%) patients had an increased urinary frequency at baseline and 7 of 80 (9%) had a normal voiding frequency of less than eight voids per 24 hours. 81 I-QoL and 82 SF-36 surveys were found suitable for further examination. At baseline, 82 urodynamic reports were suitable for evaluation. DO occurred in 48 of 82 (59%) patients.

Evaluation after 12 PTNS sessions

Reduction in leakage episodes, severity of urine loss and urinary frequency

After 12 PTNS treatments 78 complete bladder diaries were available for evaluation (12 of 90:13% missing values). All parameters improved significantly (*see Table 10.1*). At baseline 75% of the subjects with daily incontinence was reduced to 44% (35 of 80) of subjects after 12 PTNS (35 of 78 incontinent; 43 of 78 not incontinent, 12 of 90 missing values). End evaluation considered 23 of 60 (38%) patients dry, that is cured. However, four of these wished to discontinue treatment. An additional 11 of 60 (18%) incontinent subjects achieved at least 50% reduction in the number of leakage episodes. This evidence resulted in a success rate of 56% (primary outcome measure). In positive responders a median reduction of 100% (+50; -100) was found whereas non-responders obtained a median reduction of 33% (+77; -100%). An at least 50% reduction in incontinence severity was found in 31 of 60 (52%) subjects. Positive responders and non-responders achieved a median reduction of 100% and 23%, respectively. At baseline 7 of 80 (9%) had a normal voiding frequency of less than 8 voids per day, 12 subjects voided 8 to 10 times a day (15%). After 12 PTNS sessions 20 of 80 (25 %) subjects achieved a voiding frequency of less than 8 times (primary outcome measure) and another 25 voided 8 to 10 times (31%)

Patients' assessment: subjective response and quality of life scores

58 out of 90 (64%) patients requested continuation of the therapy. I-QoL and SF-36 scores improved significantly as shown in *Table 9.1.*

Urodynamic profiles

In only 46 patients, urodynamic investigations were performed at baseline and after 12 PTNS sessions. Therefore, post-PTNS treatment urodynamic findings are based on data of 46 participants only (36 females, 10 males; median age, 51). Comparable subjective success rates in this subgroup were found: 32 of 46 (70%) vs. 58 of 90 (64%), this finding reduces the possible bias of having only successful patients undergoing a second urodynamic investigation. Baseline and end evaluation data are summarized in *Table 10.2*: a significant increment was seen in cystometric bladder capacity and in volume at which first detrusor overactivity occurred. At baseline DOs were noted in 34 of 46 participants (74%), 31 subjects continued to have DO, however these overactivities occurred at larger bladder volumes. In three patients, DO was eliminated, in three others de novo DO was noticed. Detrusor pressures recorded during the detrusor contractions decreased only slightly.

Table 9.2: 24hour bladder diary data, urodynamic data and quality of life scores in 46 patients receiving 12 PTNS sessions for overactive bladder complaints.

Parameter	Baseline	End	Change	p value	Change in responders n=32/46 (70%)	p value
24h bladder diary:						
Leakages	4 (1;19)	3 (1;16)	-2 (-19;+7)	0.001	-2(-19;+2)	<0.01
Severity of leakages	2 (1;3)	1.85 (1;3)	-1(-3;+1)	<0.001	-1 (-3;+1)	<0.01
Urinary frequency	13 (4;32)	9 (5;19)	-3(-18;+8)	<0.001	-3 (-18;+8)	<0.01
Mean Voided Volume	135 (28;275)	205 (76;300)	+50(-50;+200)	<0.001	+62 (-50;+200)	0.001
Quality of life scores:						
I-QoL	39 (22;94)	66(20;100)	+9(-19;+88)	<0.001	+19(-14;+88)	<0.01
SF-36	54 (17;93)	64 (19;89)	+5 (-42;+55)	0.003	+6 (-18;+56)	<0.01
Cystometric data:						
Cystometric Capacity	243 (30;745)	340 (70;500)	+30 (-324;+450)	0.043	+36 (-324;+450)	0.14
Subjects with DO	34/46 (70%)	34/46 (70%)			23/32 (72%)	
Volume DO	133 (30;350)	210 (50;375)	+60 (-183;+333)	0.012	+115(-183;+333)	0.031
Pdet DO	35 (4-120)	41 (10-93)	-5 (-63; 74)	0.67	-6.5(-46;+64)	0.69

Pdet DO: Detrusor pressure at DO; data represent mean values with ranges in parantheses. Wilcoxon signed ranks test, significance level set at 5%.

Influencing factors on outcome

Taking the small number of participants into account (n=82, though in only 48 patients the features of DO could be analysed) analysis of potential predictive factors among baseline characteristics revealed one strong prognostic factor: subjects having DO at baseline (n=48) were less likely to respond to PTNS. A stable bladder enhanced the chance for a successful outcome of the PTNS therapy by 1.75 times (OR: 1.75; 95%CI: 0.669-4.57).

Univariate logistic regression analysis showed that none of the baseline characteristics (cystometric capacity, volume at DO, detrusor pressure at DO) proved to be a significant predictor for subjective success. This finding may also be due to the small number of participants with overactive detrusor (n=48) There was some suggestion that the volume at DO, can predict outcome to a certain extent. For example, for each 100ml "delay in DO onset", chance for success increased 1.5 times (OR: 1.0043;

95% CI 0.997, 1.012). However the three baseline characteristics showed no statistical significance, a multivariate analysis combining these three factors revealed a predictive power of 0.64 (OR: 0.644; 95% CI 0.484, 0.804) (*Figure 10.1*) Also a slight tendency was seen that could support the idea that stronger stimulation inhibit detrusor overactivity: a participant having a 5 mA higher mean stimulation intensity had 1.8 times more change for success (OR: 1.13; 95% CI: 0.81; 1.6).

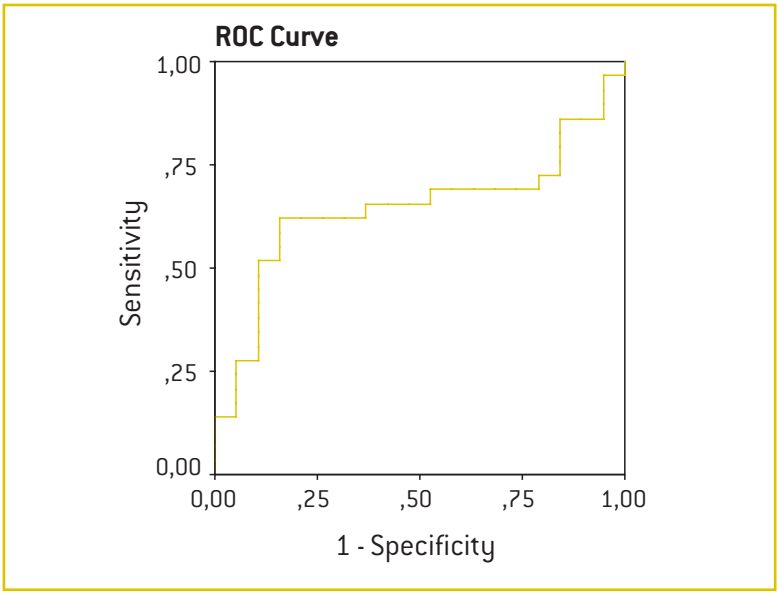

Figure 9.1: Receiver Operating Characteristic (ROC) curve constructed in order to visualize the predictive power of the combination of three variables (cystometric capacity, volume at DO, detrusor pressure at DO) of 46 patients with overactive bladder treated with 12 PTNS sessions.

9.4 DISCUSSION

The primary outcome measures that were taken to assess PTNS, were obtained in 56% of the patients with urinary leakage at baseline; 38% of them showed bladder diaries without any leakages, 52% of the patients noticed significant reduction in urine loss. Only 25% of all participants achieved a normal micturition pattern (less than 8 voids/24 hours). Patients treated by PTNS seem to regain their control on involuntary urine loss, but achievement of a normal micturition pattern is hardly feasible in most of them. Additionally, patients' assessment was determined through QoL questionnaires ($p<0.001$) and the number of requests to continue the treatment (64%). All together, it seems that PTNS can

be considered as a new treatment modality that can be offered to patients with intractable OAB symptoms; nearly 60% of such patients will benefit from PTNS.

This study was mentioned to detect the impact of PTNS by looking to these patients in a more objective way, namely by determining urodynamic changes. Examination of 46 patients with overactive bladder syndrome who underwent 12 PTNS sessions, revealed significant urodynamic changes, namely increment of total bladder capacity and volume at DO. For positive responders, the increment in cystometric capacity was not significant, this could be due to the rather large baseline capacity positive responders already had, which only increased slightly. Non-responders started with a median baseline capacity of 155ml (range: 77-550) and ended up with a capacity of 250ml (range: 70-500). For positive responders this change was 300ml (range 30-745) at week 0 and 340 ml (range: 103-500) after 12 PTNS sessions. These figures strongly suggest that patients with small cystometric capacity were more prone to fail. Even though the cystometric capacity of non-responders increased, the resultant capacity seemed of small clinical value for this group as they chose not to continue with PTNS. Remarkably, logistic regression analysis could not point out baseline capacity as a prognostic factor for success (OR: 1.0008; 95%CI: 0.998-1.004). The patient group that underwent pre- and posturodynamic evaluation contained more patients with an overactive detrusor than the baseline group did. The reason for this finding can be sought in the fact that mainly academic centres that participated received more second opinion patients often with intractable OAB with DO. Investigating the DO features revealed a significant delay in onset of DO. The clinical relevance of 60 ml increment in volume at which the first DO occurs seems perhaps questionable, but assuming a physiological filling rate of 1 mL/min, such an increment would delay the onset of urge or urge incontinence provoked by the DO, with nearly one hour or in case of responders (+115ml) with nearly two hours [Klevmark, 1999]! The reductions found in detrusor pressures during involuntary contractions were of minor size and presumable of minor clinical relevance. Furthermore, repetitive PTNS could not substantially decrease the number of subjects in whom detrusor overactivities were detected. Disappearance of DO was only seen in 3 of 90 patients. This rate is in contrast with Klingler et al., reporting an elimination of DO in 77% of the cases after 12 sessions of PTNS [Klingler et al., 2000]. It is questionable how relevant the finding of persistent DO is in evaluating therapeutic effects of neuromodulation. In fact, many neuromodulation studies reported failures to suppress DO [Philp et al., 1988; Geirsson et al., 1993; Hasan et al., 1996; Groen, et al., 2001]. Nevertheless, the presence of DO at baseline was found to be a strong predictive factor for therapeutic failure, especially when it occured early in the filling phase. So, OAB complaints without DO were more prone to respond well to PTNS. In conclusion, it seems advisable to include only those patients without DO, or those with late onset DO.

A common remark questions how intermittent stimulation in PTNS possibly can succeed, compared with the continuous stimulation patients receive when a sacral root neuromodulator is implanted. The inhibitory and long-lasting effect through PTNS can be explained by experiments performed in

Macaca monkeys. It was shown that repetitive tibial nerve stimulation powerfully inhibits nociceptive spinothalimic tract cells through Aδ fibres, provided a high enough intensity was applied [Chung et al., 1984]. This inhibition was thought to act on a spinal level. Although these experiments were not focused on the complex micturition system, extrapolation of these findings to voiding dysfunction can be made. Hypothetically, repetitive PTNS inhibits pathologic afferent information from the bladder to supraspinal levels, resulting in a decreased awareness of pathological sensations (less urge) and delayed onset of DO. Similar studies on these spinothalmic cells, demonstrated long-lasting inhibition for 30 minutes. Inhibition occurred more powerfully as stimulation intensity increased [Chung et al., 1984]. This can explain a carry-over effect found upon intermittent stimulation. To our knowledge, no research have been performed investigating how long this inhibition occurs in human, or how strongly this nerve has to be stimulated. Determination of the exact intensity applied through PTNS stimulation is difficult because of the inhomogeneous character of each nerve, recruitment of fibres by size, physical environment and type of stimulated nerve [Swett et al., 1981]. A stronger stimulation will surely be more effective as has been already proved in human experiments using supramaximal stimulation in spinal cord patients [Sheriff et al., 1996]. Also, this study provided some evidence for better therapy outcome in those patients in whom stronger stimulation currents were used. Even though the real stimulation intensity that reached the tibial nerve remains unknown, a slight tendency was seen that could support the former ideas: a participant receiving a 5 mA higher mean stimulation intensity, had 1.8 times more change for success. Unfortunately, application of higher current intensity through percutaneous needling is hardly feasible in individuals with intact sensation. Finding a more adequate way to stimulate the posterior tibial nerve, with better placement of the electrode and controlled applied intensity should be aimed and searched for.

Many factors seem to influence the outcome of PTNS. Presumably, complex interaction of several factors, such as bladder retraining by frequently completed bladder diaries, release of enkephalines or other neurotransmitters through needling, decreased c-fos expression by tibial nerve stimulation and attribution of some placebo-effect, will play an important role and finally add up resulting in a successful outcome. The urodynamic results refute, however, the possibility of a placebo-effect being the only explanation for the positive results found in this study.

9.5 CONCLUSIONS

PTNS sessions could not eliminate DO but resulted in increased bladder capacity and delayed onset of DO to such an extent that the patients experienced a clinical relevant decrease in leakage episodes, severity of incontinence and voiding frequency. The latter parameters can all be calculated from bladder diary data. Therefore, the value of urodynamic investigations to evaluate therapeutic effect of

neuromodulation is debatable. On the other hand, predictive factors related to cystometric parameters were found: patients with OAB but without DO are good candidates for PTNS treatment. When DO is present, it seems advisable to exclude those patients with severe forms of detrusor overactivity (i.e. early onset of DO) from PTNS treatment. In view of the facts that PTNS is an inexpensive treatment modality that is minimally invasive and simple to perform, it is an attractive first-line option for patients with overactive bladder syndrome before proceeding towards surgical interventions such as bladder augmentation or replacement. PTNS is a young therapy requiring further research, analysing predictive factors and optimal stimulation parameters.

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CHAPTER 10

Posterior tibial nerve stimulation in the treatment of voiding dysfunction: urodynamic data

Based on

POSTERIOR TIBIAL NERVE STIMULATION IN THE TREATMENT OF VOIDING DYSFUNCTION: URODYNAMIC DATA

V VANDONINCK[1], MR VAN BALKEN[1], E FINNAZZI AGRÒ[3], F PETTA[3], F MICALI[3], JPFA HEESAKKERS[1], FMJ DEBRUYNE[1], LALM KIEMENEY[2], BLH BEMELMANS[1]

1 Dept. of Urology and Epidemiology
2, University Medical Centre Nijmegen, The Netherlands
3 Dept. of Urology, University "Tor Vergata" AND IRCCS S. Lucia, Rome

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OBJECTIVE

To determine urodynamic changes and predictive factors in patients with voiding dysfunction who underwent 12 percutaneous tibial nerve stimulations (PTNS).

SUBJECTS AND METHODS

39 patients with chronic voiding dysfunction were enrolled in a prospective multicentre trial in the Netherlands (n=19) and in Italy (n=20). A 50% reduction in total catheterised volume per 24 h was taken as a primary objective outcome measure. Patients' request for continuation of treatment was regarded as subjective success. Objective urodynamic parameters and bladder indices were determined. Odds ratios and their 95% confidence interval were computed as a measure for predictive power in order to reveal predictive factors (Pdet at Qmax, Qmax, BE, and BCI).

RESULTS

Primary outcome measure was obtained in 41%, an additional 26% reduced their 24h residual volume with more than 25%. 59% of patients chose to continue treatment. Detrusor pressure at maximal flow, cystometric residual volumes and bladder indices improved significantly for all patients ($p<0.05$). Patients with minor voiding dysfunction were more prone to notice success (Odds ratio: 0.73; 95% CI: 0.51-0.94).

CONCLUSIONS

PTNS is a young treatment modality, minimal invasive and easy accessible. It might be an attractive first line option for patients with (minor) voiding dysfunction.

10.1 INTRODUCTION

Voiding dysfunction can be caused by neurological disorders, post-surgical conditions, infravesical obstruction, bladder overdistension, inflammation, drugs, psychogenic factors, learned voiding dysfunction, detrusor myopathy and urethral sphincter dysfunction [Dorflinger et al., 2001]. Therapeutic lower urinary tract rehabilitation includes pelvic floor training, biofeedback, behavioural modification, catheterisation, electrical stimulation or bladder expression and bladder reflex triggering in case of neurogenic disorders [Abrams et al., 2002]. Patients might benefit clinically from cholinergic agents [Shah et al., 1983; Tanaka et al., 2001]. Other treatment modalities are urethral dilatation, insertion of intraurethral device or desobstructive surgery. Often clean intermittent self-catheterisation is the most effective therapy for chronic bladder emptying problems. Unfortunately catheterisation is at the expense of patients' quality of life. During the last decades neuromodulation has gained interest as an alternative treatment for difficult to treat voiding dysfunction before proceeding towards more invasive surgical procedures. One of the newest modalities is percutaneous tibial nerve stimulation (PTNS). The posterior tibial nerve is a mixed nerve containing L4-S3 fibres, originating from the same spinal segments as the parasympatic innervation to the bladder. The first results of PTNS for patients with voiding dysfunction were already extensively reported in previous papers [van Balken et al., 2001; Vandoninck et al., 2003]. This paper focuses on urodynamic changes found in these patients and on determination of urodynamic predictive factors.

10.2 MATERIALS AND METHODS

Between November of 1999 and July of 2000, 39 consecutive patients with idiopathic non-obstructive voiding dysfunction were enrolled in an international prospective multicentre clinical trial in the Netherlands (n=19) and Italy (n=20). Patients underwent 12 weekly percutaneous stimulations of the posterior tibial nerve.

Definition and criteria

Idiopathic non-obstructive voiding dysfunction: all patients with abnormal detrusor function (detrusor underactivity or acontractile detrusor and postvoidal residual PVR) conform the definitions from the standardisation report 2002 [Abrams et al.; 2002]. Prior to the study, all patients failed in achieving complete bladder emptying, two of them had complete urinary retention and thus all patients catheterised.

In all patients extensive medical history was taken focussing on urinary symptoms, previous and

present treatments, neurological disease and medications. Physical examination was done to rule out any relevant pathology such as urogynaecological or neurological abnormalities. Symptoms existed for a minimum of 6 months. Exclusion criteria were bladder outlet obstruction related to benign prostatic hyperplasia (using the Abrams-Griffiths nomogram), any urogynaecological, central or peripheral neurological disorders, including dysfunctional voiding due to pelvic floor overactivity, pregnancy, age under 18 and severe cardiopulmonary disease. PTNS procedure was extensively described in a previous paper [van Balken et al., 2001]. In short, through percutaneous needling the posterior tibial nerve was stimulated above the medial malleolus. After connection to a low voltage stimulator (CystoMedix, Anoka, Minnesota, USA) and a ground electrode, this nerve was electrically stimulated which resulted in a sensory response (tickling sensation in the sole of the foot) and a typical motor response (plantair flexion of digit I or fanning of all toes). Treatment consisted of 12 weekly sessions of 30 minutes each. All patients gave their informed consent.

Primary Outcome Measure, Positive Response Rate, and quality of life

In line with Blaivas' proposals concerning how to assess efficacy of neuromodulation, 50% reduction in total catheterised volume per 24h was taken as primary objective outcome measure. Additionally the positive response rate and quality of life scores displayed patients' assessment [Blaivas, 2001]. Request for continuation of treatment was regarded a subjective success and these patients were called "positive responders". Quality of life scores were determined at week 0 and at week 12. For incontinence specific quality of life the I-QoL was used [Patrick et al., 1999]. For the estimation of generic functional status and well-being, the MOS 36 items Short-Form health survey (SF-36) was completed [Ware et al., 1992]. Higher scores indicate better quality of life.

Urodynamic data

Objective assessment of the efficacy of PTNS was done through urodynamic investigation and through calculating bladder indices. At baseline and after 12 PTNS sessions, a standard transurethral subtraction cystometry was performed in the supine position whereas the pressure flow study was carried out in the sitting position. Sterile saline at room temperature was infused through a double lumen 8 F catheter at a filling rate of 50 ml/min. The volume at which detrusor overactivities (DO) occurred was noted. DO was defined as an increase of 15 cm water pressure or of lower amplitude if accompanied with a distinct sensation of urgency. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted [Abrams et al., 2002].

Bladder indices based on bladder diaries and urodynamics

An effort to measure bladder contractility and voiding efficacy was made. Bladder Contractility Index

(BCI) was derived from the formula: BCI = Pdet x Qmax + 5 x Qmax; such that a strong bladder contractility is a BCI of >150, normal contractility a BCI of 100-150 and a weak contractility a BCI of < 100 [Abrams et al., 1999]. BCI was thus calculated from the urodynamic measurements. Bladder voiding efficiency (BVE) reflects bladder contractility against urethral resistance and is measured according to the degree of bladder emptying: BVE = 100 x (voided volume /total bladder capacity). Total bladder capacity is defined as the summation of voided volume and postvoidal residual volume [Abrams et al., 1999]. BVE was computed both from urodynamic and bladder diary data. Both bladder indices were determined at baseline and at week 12.

Statistical analysis and predictive factors

Efficacy of PTNS was analysed for all patients on an intention-to-treat basis. Descriptive data were reported as median values and range, and as mean change with 95% confidence interval (CI) [Gardner and Altman, 1986]. Within-group comparisons of results were conducted by the non-parametric Wilcoxon signed rank test. Tests were performed on a two-tailed basis and level of significance was set at 5%. In order to evaluate whether it is possible to predict subjective success with baseline characteristics we performed univariate and multivariate logistics regression analyses. In our opinion, the clinically most relevant outcome measurement is patients' perception of the PTNS effect on their voiding disorder: despite good improvement in bladder diary data, patients can experience the net effect as unsatisfactory and vice versa. Odds ratios with their 95% confidence intervals (CI) were calculated as a measure for the predictive power of each characteristic. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, USA).

10.3 RESULTS

Patient characteristics

39 patients (12 men, 27 women) with a median age 53 years (range: 28-77) were enrolled in this study. Patients' baseline characteristics and their medical history are summarized in *Table 10.1*. At baseline, one patient had a mean of 74 ml residual, catheterising four times a day on bladder diary data. All others had a mean residuals larger than 100 ml.

Primary outcome measure: more than 50% decrement in 24h total catheterised volume

Bladder diary data were completed after 12 weeks by 38 patients. All patients improved significantly in all bladder diary data (*See table 10.2*). In 16 of 39 (41%) patients' 24h total catheterised volume reduced with 50% or more (= primary outcome measure). Another 10 of 39 (26%) participants noticed a 25-50% decrement of their residuals. Thus, 26 (67%) patients noticed a reduction of 25% or more

Table 10.1: Medical background and therapies used for urinary symptoms in 39 patients with idiopathic non-obstructive voiding dysfunction.

(% of patients)	All (39)	
Patients characteristics:	**Median**	**Range**
Male/female	12/27	
Age in years (y)	53	28-77
duration of symptoms (y)	3	1-36
Current intensity (mA)	4	1.4-7.6
Treatments prior to PTNS (%):	**Number**	**Percent**
Medication for complaints: -One -Two	311912	804931
Pelvic floor/bladder retraining:	8	21
Electrotherapy:	5	13
Surgical intervention: -One -Two	1183	29218
Baseline voiding parameters:	**Median**	**Range**
Total catheterised volume	800	210-3000
Mean catheterised volume	241	74-675
Number of catheterisations	2.5	1-10
Total voided volume	1000	95-2700
Bladder Contractility Index	63	37-160
Bladder Voiding Efficiency (uds)	64	40-96
Bladder Voiding Efficiency (Bladder diary)	56	8-91
Baseline QoL score:	**Median**	**Range**
I-QoL	62	26-99
SF-36	65	19-92

in 24h total catheterised volume. A tendency to increment of the total voided volume was found (p=0.053). PTNS resulted in 15 of 39 patients with a mean catheterised volume smaller than 100 ml (13 patients) or zero (2 patients). Nobody became catheterisation free, even the two patients that had zero residual after catheterisation, still continued catheterising themselves once a day.

Subjective success: positive responders

23 out of 30 patients (59 %) chose to continue treatment. In 13 out of these 23 patients the primary

Table 10.2: Bladder diary data and quality of life results after 12 weekly sessions with PTNS, median (range) and median change

	Week 0			Week 12			Median change			Statistics
diary data:	N	Median	Range	N	Median	Range	N	Median	Range	p value
Tot CV(ml)	37	800	210-3000	38	450	0-2450	37	-200	-2700; +700	<0.01
Mean CV(ml)	38	241	74-675	38	163	0-163	38	-80	-375; 247	<0.01
No of cath.	38	2.5	1-10	38	2	1-7	38	0	-7; 2	0.024
Tot VV (ml)	37	1000	95-2700	36	1260	50-310	36	275	-500; 1720	0.053
BVE	37	64	40-96	38	77	0-100	37	9.5	-38; 78	<0.01
Quality of life:										
I-QoL	39	62	26; 99	39	86	29; 100	39	11	-2; 60	<0.01
SF-36	39	65	19; -92	38	70	17; 91	38	3	-18; 50	<0.01

Tot CV: total catheterised volume; Mean CV: mean catheterised volume, Tot VV: total voided volume
BCI: Bladder Contractility Index. BCI< 100: weak detrusor, 100-150: normal, >150: strong contractility.
BVE: Bladder voiding efficacy index based on the bladder diary data.

outcome measure (more than 50% reduction) was obtained, another eight subjects noticed a reduction of their 24h residual volume with more than 25%. For non-responders (n=16) the primary outcome measure was obtained in only two patients: two patients had more than 50% reduction in 24h catheterised volume and another two revealed more than 25% reduced residual volume. From these four patients, one patient stopped because of personal reasons, though she had nearly zero residuals. The other three persons noticed a good decrease in total amount of catheterised volume but they still had the same catheterisation rate and were thus not satisfied (e.g., from 5 x 340 to 4 x 220ml). One patient dropped out of the study after six sessions because of aggravation of pre-existing cardiac arrhythmia, assumed not to be related to PTNS.

Urodynamic data (*See Table 10.3***)**

At baseline 37 urodynamic investigations were performed (60% of these patients wanted to continue treatment: positive responders), after 12 PTNS sessions 27 patients (63 % positive responders) underwent a cystometry and pressure flow study. Patients' cystometric capacity remained the same, detrusor pressure at maximal flow increased significantly and a decrement in patient's residual volume after the pressure flow study was seen. Urodynamic examination revealed five patients (5 out of 39, 14%) with detrusor overactivity at baseline. After 12 treatment sessions involuntary detrusor contractions were seen in 3 participants, DO disappeared in two subjects and seven patients developed de novo DO. Added up, 10 participants had DO after 12 PTNS sessions (10 out of 27= 37%). Eight out of these 10 patients requested continuation of PTNS, mostly with a 2–3 weekly interval.

Table 10.3: Urodynamic results after 12 weekly sessions with PTNS, median (range) and median change (range) in 39 patients with idiopathic non-obstructive voiding dysfunction.

	Week 0			Week 12			Median change			Statistics
	N	Median	Range	N	Median	Range	N	Median change	range	p value
CC	37	500	165; 835	27	500	149; 800	27	0	-225; 300	0.930
P DI	5	37	16; 60	10	26.5	10; 48	3	1	-2; 3	0.59
VDI	5	150	50; 450	10	245	175; 480	3	70	-30; 130	0.29
P detr at Qmax	27	25	10; 70	24	33	10; 83	21	8	-5; 68	<0.01
Qmax	25	7	2; 27	25	10	4; 29	20	1	-12; 13	0.13
Residual V	31	270	35; 755	19	220	50; 450	19	-80	-280; 100	0.01
BCI	26	63	37; 160	25	83	5; 178	20	20	-52; 70	<0.01
BVE	31	56	8; 91	19	67	56; 86	19	6	-8.8; 18.1	<0.01
For subjective responders:										
CC	22	500	165; 835	17	500	149; 650	17	0	-225;300	0.9
Pdet at Q max	16	25	10; 70	16	34	15; 59	13	8	-5; 31	<0.01
Qmax	16	8.5	2; 16	16	10	4; 29	13	1	-4; 13	0.1
Residual Volume	18	285	80; 755	9	130	50; 400	9	-100	-200; 10	0.01
BCI	16	65	37; 120	16	85	55; 178	9	11	-1.5; 18.1	<0.01
BVE	18	62.5	40; 83	9	73	60; 86	13	20	-15; 70	0.011

CC: Cystometric Capacity in ml
P DI: Pressure of Detrusor Instability in cm H20
V DI: Volume at first Detrusor Instability in ml
Pdetr at Q max: Detrusor pressure at maximal Flow in cm H20
Q max: Maximal Flow in ml/sec
Residual V: Residual Volume in ml

Their total catheterised volume decreased with a mean of 51% (range: -26%, -87%).

Bladder indices based on bladder diaries

Bladder voiding efficacy (BVE) increased significantly with a median change of +9.5% (range: -38; +78%). For responders this was +18.2% (range: -16; +78%).

Bladder indices based on urodynamic data

The urodynamically based BVE improved in a similar way (median change: +6%, range: –9; +18%).

Responders noticed a median percentage increase of +11% (range: -8; +18%). Baseline BVE was not different among responders (median BVE: 62; range: 40-83) and non-responders (median BVE: 64; range: 50-96) (p=0.6). The BCI rose with 20 points (range: -52, + 70) for all patients. Responders revealed an addition of 20 points (range: -15; +70) whereas non-responders noticed a median improvement of 15 points (range: -52; +25). At baseline 23 patients had a weak (BCI >100), two a normal (BCI 100-150) and one participant had a strong detrusor contractility (BCI >150). After 12 PTNS sessions this was respectively seen in 20, 3 and 2 patients. The median baseline BCI score was not significantly different between responders (median BCI: 65; range: 37-120) and non-responders (median BCI: 59; range: 40-160) (p=0.8).

Predictive factors

Univariate logistic regressions analysis showed that none of the baseline urodynamic characteristics or bladder indices proved to be a significant predictor for subjective success. This may be due to the small number of study participants. There was some suggestion that certain characteristics can predict outcome to a certain extent. For example, for each 10 cm water increment in baseline detrusor pressure at maximal flow rate, the chance of subjective success increased with a factor 1.3 (Odds Ratio OR: 1.028; 95%CI: 0.977-1.083). Per 10 ml/sec increments in maximal flow rate, the change for success increased with 1.7 (OR: 0.947 95%CI: 0.804; 1.112). A 30% higher baseline BVE score was found to result in 1.7 times more change for patients to notice success. A multivariate analysis combining four urodynamic factors (maximal detrusor pressure, maximal flow rate, BVE and BCI) revealed a predictive power of 0.73 (OR: 0.73; 95% CI 0.51, 0.94) (*See Figure 10.1*).

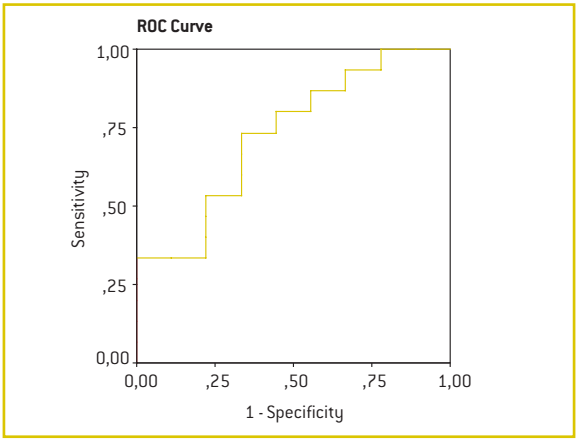

Table 10.4: Univariable logistic regression analyses of baseline characteristics to calculate predictive value for subjective success in 39 patients with non-obstructive voiding dysfunction treated with 12 weekly PTNS sessions.

Side effects

No serious side effects were reported. Transient pain at the stimulation site was noticed. Diarrhoea, headaches, calf cramps and low back pain were reported. One patient did not complete the treatment because of aggravating pre-existent heart rhythm problems. However these adverse effects were not considered to be related to PTNS.

10.4 DISCUSSION

The primary outcome measure was obtained in 41% of all patients (percentage based on intention-to-treat). An additional 26% of patients noticed a reduction in 24h total catheterised urine by 25-50%. The total of these 2 figures (67%) is comparable with the subjective response rate (59%). Nearly all responders also diminished their 24h residual volume with more than 25%. PTNS resulted in 15 out of 39 patients with a mean catheterised volume smaller than 100 ml and even the two patients that had zero residual after catheterisation, still continue catheterisation. Presumably these patients wanted to be on the safe side by checking their residual volumes once daily. Since PTNS is a young treatment modality, optimal stimulation parameters still have to be searched for. More adequate stimulation specified for voiding dysfunctional patients and directly placed on the tibial nerve, could hopefully lead to catheterisation free results. The intention of this study was to determine more objective indicators of a successful outcome, namely derived from urodynamic investigations. The total cystometric capacity in patients did not change at all, most patients had a normal bladder capacity before entering the study and this remained unchanged.

Surprisingly more detrusor instabilities (DI) were detected in patients with voiding dysfunction after the 12 weekly sessions (from 14 % to 37% of patients urodynamically investigated). Perhaps DI is an essential feature for a good outcome in PTNS for bladder emptying problems; the perception of DI may result in an accentuated awareness of bladder filling and this is believed to "train" the complex neural regulation system of voiding. Although 8 out of the 10 patients with DI considered their treatments as successful, the number of participants is too small to draw conclusions from these DI-related data. Moreover, the value of the presence or absence of DI should be further investigated as some even questions the whole concept of DI since this phenomenon can be seen in asymptomatic persons [Zinner, 2000]. This study found improvement in detrusor pressure at maximal flow, maximal flow rate, cystometric residual volume and bladder indices. The Bladder Contractility Index increased for most participants but left the main part of patients in the "weak detrusor" classification, suggesting that PTNS is not acting strongly on the detrusor muscle itself. Unfortunately EMG records of the pelvic floor and urethral striated sphincter were not available, it might be possible that PTNS also improves the detrusor-sphincter coordination. Uni- and multivariant analysis revealed no spectacular results:

participants with only minor voiding dysfunction were more prone to be successful. It seems therefore that patients with minimal voiding dysfunction are good candidates for PTNS. PTNS results in improved voiding parameters, higher quality of life and a high subjective response rate.

PTNS is believed to relieve symptoms related to bladder overactivity and underactivity, a phenomenon also seen in Sacral Nerve Stimulation SNS [van Balken et al., 2000; Jonas et al., 2001; Shaker et al., Hassouna at al.,2000]. The underlying neurophysiological mechanisms of such a bi-polar effect has not yet been elucidated. The result achieved by SNS returns to baseline values after switching off the device, as opposed to long-term effect of a few weeks after stimulation by PTNS [Jonas et al., 2001; van Balken et al., 2000; Klingler et al.,2000]. Schultz-Lampel et al. confirmed by cat experiments the hypothesis of a rebound phenomenon as mechanism of action for induction of spontaneous voiding in patients with chronic retention [Schultz-Lampe et al., 1998].

The long-term effect through PTNS could be explained by the carry-over effect found in cat experiments where a 5-minute stimulation of afferent nerves resulted in more than one hour lasting effect [Jiang et al., 1999]. In rats PTNS exerted its influence on c-fos expression suggesting neuromodulating action [Chang et al., 1998]. Presumably the combination of needling (resulting in a higher concentration of certain neurotransmitters), bladder retraining by completing voiding charts and induction of DI in some patients, and to some extent the attribution of a placebo-effect (meeting fellow sufferers, having a very intensive guidance and attention given by medical care-givers) finally results in a higher voiding efficacy.
PTNS is a cheap treatment modality, minimally invasive and with a simple accessible stimulation site. However, in daily practice some logistic problems appeared, PTNS is a time consuming procedure both for clinicians as for patients. Positive responders need to have PTNS on a regular basis, hereby occupying precious out patient clinical time to treat new patients. Most investigators limit the number of sessions for this reason. In our clinic we started to train positive responders how to insert the needle themselves and how they can apply the stimulator at home. Besides more basic research investigating optimal parameters, development of an implantable stimulator might be very useful. In conclusion, PTNS is an attractive young treatment modality for patients with minor chronic voiding disorders, requiring further research to establish optimal stimulation parameters.

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CHAPTER 11

Summary, conclusions and future perspectives

11.1 SUMMARY

The aim of this thesis was to demonstrate that PTNS is a useful alternative treatment option for patients with overactive bladder complaints or voiding dysfunction (**chapter 1**).

In **chapter 2** a concise overview of the lower urinary tract anatomy and its innervation is given. In a brief but comprehensible way the process of micturition is illustrated.

Detrusor overactivity is commonly seen in neurological disease or after neurological injury. Diseases at or above the brain stem, involving the spinal cord or distal to the spinal cord often results in detrusor overactivity. Aging, inflammation, bladder outlet obstruction or irritation of the bladder wall can induce overactivity. Furthermore gender and depression can predispose to overactive bladder complaints. When no specific cause is found the overactivity is defined as idiopathic. Storage failure can also occur in the absence of detrusor overactivity, secondary to pain or hypersensitivity. Interstitial Cystitis or painful bladder syndrome is a classic example of this [Wein, 1998]. Causes of OAB or voiding dysfunction are summarized in **chapter 3**. A rough sketch of the main ideas about pathophysiology of OAB and voiding dysfunction is also drawn. Years of research resulted in new insights, and thus definitions changed once in a while. In 2002 the International Continence Society changed and adjusted a number of old terms and definitions. Therefore a summation of the newest terms relevant to comprehend this thesis was added in this chapter. Also all terms in the published articles were adapted to conform to the ICS recommendations.

Chapter 4 presents the results of the Boxmeer study. In 1998 a Dutch national postal questionnaire survey asked 1460 spouses to participate. They had to complete Urinary Incontinence UI specific and quality of life questionnaires. 1071 women returned their questionnaires: 34% of them were regarded as minimally and 12% as severely incontinent. The self-reported UI rate was 40%. Disease specific and general quality of life was significantly lower for women with UI than for those with minimal or no urine loss. 38% of incontinent respondents had consulted a physician for their urinary incontinence and among respondents with minimal complaints this was 28%. We concluded that 46% of the married population to some degree suffered from incontinence, and severe UI significantly compromised their quality of life. It was clear that the prevalence heavily depended on the definition used. We also found that the self-reported percentage was quite high (40%) compared to the percentage of UI divided in different clinical relevant groups. An important factor is the patient's request for help. Even in our view the relevance of the complaints is classified as "only" clinically minimal relevant, whereas the patients' bother and quality of life can be seriously affected.

Behavioral techniques, bladder re-education, biofeedback combined with e.g. anticholinergics or antispasmodics are primary options for overactive bladder complaints. For voiding dysfunction pelvic floor relaxation, self-catheterisation or permanent catheterisation can bring a solution for some patients. Electrostimulation has also gained an important place in the treatment flow chart.

In **chapter 5** a brief synopsis illustrates the evolution from ancient electrotherapy to the newest modalities; the history from electrical eels to PTNS therapy. It informs about the Users Club, the group effort of more than 25 urologists in the Netherlands, the inclusion and exclusion criteria used in the studies and about the PTNS procedure and its equipment.

Chapter 6 contains the very first results published in 2001. PTNS was used as neuromodulative treatment for lower urinary tract dysfunction. 37 patients with OAB complaints and 12 patients with voiding dysfunction, defined as chronic non- obstructive urinary retention, received 12 weekly sessions. An overall response rate was 60%. 18 out of 37 patients with OAB and 7 out of 12 patients with voiding dysfunction declared that the therapy was successful. Analysis of the responder groups showed that their voiding characteristics improved significantly.

Stimulated by these promising results, PTNS was applied in the Netherlands. Under the coordination of the Users Club and in cooperation with the Italian university of Rome more patients were included and treated.

In **chapter 7** the data of 35 patients with OAB complaints with incontinence are presented. In a prospective multicentre design patients received 12 weekly sessions and completed bladder diaries, quality of life and SF-36 questionnaires. Subjective success was defined as the willingness to continue treatment, 63% of the patients received a maintenance treatment schedule. Objective success in this group was defined as a significant decrease (>50%) in total number of leakage episodes. Bladder diaries showed that in 24/35 (70%) patients the number of episode was reduced to more than 50%. 16/35 (46%) patients was even dry after the 12 sessions. Quality of life parameters increased significantly.

In **chapter 8** the results of the voiding dysfunction group are given. 39 patients necessitating clean intermittent catheterisation were enrolled in a prospective multicentre study. After 12 weekly sessions, questionnaire scores and data from the bladder diaries were analyzed. Also here subjective success was defined as the wish to continue, whereas the objective primary outcome was defined as a reduction of 50% or more in total catheterised volume. 59% of the participants asked for continuation of PTNS sessions. 41% of the participants showed a 50% decrease in total catheterised volume. Additionally 10/39 (26%) showed a 25-50% decrease. For all patients the total catheterised volume decreased by a mean of -228ml (range: -49;-528ml) Also in this study group quality of life and SF-12 parameters improved significantly.

It was clear that a high percentage of the participants demanded maintenance therapy. This subjective success was nearly always illustrated by the improved bladder diary data. In our study participants were also asked to undergo an urodynamic investigation, at baseline and after 12 weekly PTNS sessions. These data provided us even more information and a possible guideline for selecting the right candidates. In **chapter 9** the urodynamic figures of the overactive bladder patients are presented. At that time 90 patients with OAB complaints were enrolled. In this group the subjective

success was 64%, a figure not very different from previous studies. 56% had more than 50% reduction in incontinence episodes, 38% of the participant patients were dry. Before and after treatment, urodynamic data from 46 participants were available. Detrusor overactivity could be abolished in only a few cases, but increments in cystometric bladder capacity and in volumes at first detrusor overactivity were significant. Subjects that had no detrusor overactivity at baseline were 1.7 times more prone to respond to PTNS. A bladder with strong and early onset detrusor overactivity was found to fail to PTNS therapy.

In **chapter 10** the urodynamic data of the voiding dysfunction disorders are listed. 39 patients were enrolled and received 12 PTNS sessions. Surprisingly more detrusor overactivity was found after 12 sessions (from 17 to 34%). Although the presence of detrusor overactivity was not requested to have a successful PTNS therapy, the awareness of bladder activity might help to re-educate the bladder. Detrusor pressure at maximal flow, cystometric residuals and bladder indices improved significantly for all patients. Patients with only minor voiding dysfunction were more prone to notice success.

11.2 CONCLUSION

PTNS is a cheap treatment modality, minimally invasive and with an easily accessible stimulation site. The majority of participants asked for continuation of the treatment and received an individual based maintenance schedule. Not only subjective success was clear, also objective data were observable: episodes of urinary leakage decreased dramatically, total volume of catheterised volume decreased. Quality of life and disease specific scores improved significantly. Urodynamic results confirmed the bladder diary figures. Influencing factors on the outcome were searched for, but the data were somewhat disappointing. The worst cases were mostly not sufficiently treated. Perhaps these subjects with such disabled bladders or micturition control, suffered from their disorder for too long with irreversible damage. Or they might have had an unknown or unfound neurological cause for their bladder complaints.

11.3 FUTURE PERSPECTIVES

Logistical problems on the outpatient ward appeared. Positive responders needed to have PTNS on a regular basis, claiming clinical time to treat or enroll new patients. In our clinic, we started to educate responders on performing self-administered home-based PTNS. Meanwhile an implant device was developed (Subcutaneous Tibial Nerve Stimulation). The first results of this device are presented and will soon be published [van der Pal, 2006]. Many factors seem to influence the outcome of

PTNS. Presumably, complex interaction of several factors, such as bladder retraining by frequently completed bladder diaries, release of enkephalines or other neurotransmitters through needling, decreased c-fos expression by tibial nerve stimulation and attribution of a placebo-effect, will play an important role and finally add up resulting in a successful outcome. This thesis does not intend to reveal electrostimulations' mystery. More basic research is needed to answer these questions. Hopefully future research will be able to distinguish different subgroups in this heterogeneous patient population so that each individual can receive a specific efficient treatment. Is there a high placebo-effect included? The urodynamic results refute the hypothesis of a placebo-effect being the only explanation for the positive results found in this study. The placebo-effect is thought not to be stronger than in any other treatment given to a patient with OAB or dysfunctional voiding complaints. Excluding a strong placebo-effect, a randomized placebo-controlled study should of course be performed, keeping in mind that this is difficult to execute using 34 gauge needles and electrical current. More research, new insights and new developments are necessary.

Recent investigation of the suburothelium and its function will result in future targets. Resiniferatoxin intravesically or botulinum toxine submucosally are new treatment modalities. In the clinical setting botulinum toxin has gained a place in treatment of patients with detrusor overactivity. A method that takes minimal time for the urologist and that gives maximum effect for the patient. Unfortunately this is often a temporary effect and in time it seems that the patient becomes refractory for the toxin. It might be that these botulinum refractory patients still will be treated by neurostimulation. Functional brain imaging examins how the regions interact in order to achieve urinary continence. Similar to the recent development investigation of brain stimulation to overcome for example obesitas or parkinson, a development of such an electrode at the exact micturition area would not be science fiction anymore. Not to mention the hottest topic in urology: tissue engineering techniques. These techniques will be able to modulate stem cells to reinforce weak urethral sphincters or even create a normal contractile bladder. An exciting research time awaits us.

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CHAPTER 12

Samenvatting, besluitvorming en toekomstperspectieven

12.1 SAMENVATTING

Deze studie was opgezet om na te gaan in hoeverre PTNS een waardevol alternatief kon bieden voor patiënten met klachten van een overactieve blaas (OAB) of blaasledigingsstoornissen (**hoofdstuk 1**).
In **hoofdstuk 2** wordt een bondig overzicht gegeven over de anatomie van de lagere urinewegen en zijn bezenuwing. Op een beknopte maar duidelijke manier wordt het ingewikkelde proces van mictie geïllustreerd. OAB wordt vaak gezien bij neurologische aandoeningen of na een neurologische trauma. Afwijkingen ter hoogte van of boven de hersenstam, ruggenmergletsels of afwijkingen distaal hiervan, kunnen aanleiding geven tot detrusor overactiviteit. Ook leeftijd, onstekingsverschijnselen, blaashalsobstructie of irritatie van de blaaswand kan overactiviteit veroorzaken. Daarnaast spelen geslacht en depressie eveneens een rol. Wanneer geen specifieke oorzaak kan gevonden worden, spreekt men van idiopathische overactiviteit van de blaas. Incontinentie kan echter ook plaatsvinden zonder de aanwezigheid van detrusor overactiviteit, bijvoorbeeld tengevolge van pijn of hypersensitiviteit van de blaas. Interstitieel cystitis of pijnlijk blaassyndroom is hier een klassiek voorbeeld van [Wein, 1998].
De verschillende oorzaken van detrusor overactiviteit en blaasledigingsstoornissen zijn samengevat in **hoofdstuk 3**. Daarnaast worden ook enkele denkpistes over de pathofysiologie geschetst.
Overactieve blaasklachten en blaasledigingsstoornissen worden al decennia aan onderzoek onderworpen, en dit deed de terminologie veranderen. In 2002 paste de International Continence Society (ICS) een aantal definities en termen aan. Een kort overzicht van de nieuwste termen en definities die relevant zijn om de thesis op een duidelijke manier te kunnen begrijpen werd aan het hoofdstuk toegevoegd. Alle oude termen in de al gepubliceerde artikels werden overigens vervangen om zo een uniform boekwerkje te creëren.
In **hoofdstuk 4** worden de resultaten van de Boxmeer studie gepresenteerd. In 1998 werd middels een Nederlandse schriftelijke rondvraag 1460 echtgenoten gevraagd deel te nemen aan de studie. De levenskwaliteit van deze deelnemers werd door middel van Urine Incontinence specifieke vragen en vragenlijsten betreffende de levenskwaliteit gescoord. De prevalentie van urineverlies werd bepaald op twee manieren. Allereerst verdeelde de totale score de ondervraagden in drie groepen, te weten geen symptomen (score 0-2), minimale symptomen (score 3-6) en ernstige symptomen (score 7-14). Vervolgens werd een zelfrapportage cijfer berekend door de ondervraagden te vragen of zij urineverlies hadden of niet. 1071 vrouwen beantwoordden de vragenlijst: 34% werd ingedeeld als minimaal incontinent en 12 % als ernstig incontinent. Het zelfrapportage cijfer was 40%. De ziektespecifieke en algemene levenskwaliteit scores waren significant lager voor vrouwen met urineverlies. 38% van de incontinente vrouwen had een duidelijke hulpvraag naar de huisarts toe. Voor vrouwen met minimale klachten was deze 28%. We konden uit deze studie concluderen dat 46% van de getrouwde vrouwen een of andere vorm van urineverlies hadden, en dat ernstig urineverlies significant hun levenskwaliteit

beïnvloedde. Tijdens de analyse van deze data werden we geconfronteerd met de moeilijkheid om deze score juist, naar klinische relevantie, te interpreteren. Het was duidelijk dat de definitie het prevalentiecijfer beïnvloedde. Daarnaast was het zelfrapportage cijfer vrij hoog (40%) in vergelijking met de percentages van de klinisch relevante indelingen. Een belangrijk element is de hulpvraag van de patiënt. Zelfs, in onze ogen minimale klachten, kunnen voor de patiënt voldoende frustraties en een aangetaste levenskwaliteit opleveren.

Leefstijl aanpassingen, blaastrainingen, biofeedback, eventueel gecombineerd met anticholinergica of antispasmodica, zijn de eerste keuze behandelingsopties voor OAB-klachten. Voor de blaasledigingsstoornissen kunnen bekkenbodemrelaxatie-oefeningen, intermittente zelfcatheterisatie of een continue catheter een oplossing bieden. Electrostimulatie heeft ondertussen zijn plaats in het behandel-stroomdiagram verdiend. In **hoofdstuk 5** wordt een korte synopsis gegeven over de evolutie van klassieke electrotherapie tot de nieuwste behandelingen; van het gebruik van de electrische aal tot het gebruik van PTNS. Het ontstaan van de User Club, een groepswerk van meer dan 25 urologen over heel Nederland, alsook de in- en exclusie criteria en de PTNS procedure worden geïllustreerd in het hoofdstuk.

In **hoofdstuk 6** worden onze eerste resultaten gepubliceerd (2001). 37 patiënten met OAB en 12 deelnemers met dysfunctionele mictieklachten, gedefinieerd als chronische niet-obstructieve urineretentie, ondergingen de neuromodulatieve PTNS in 12 wekelijkse sessies. Het succespercentage bedroeg 60%. 18 van de 37 patiënten met OAB-klachten en 7 van de 12 patiënten met blaasledigingsstoornissen verklaarden de therapie als succesvol. Hun mictiepatroon verbeterde significant.

Geïnspireerd door deze resultaten werd onder coördinatie van de SANS User club en in samenwerking met de Universiteit Tor Vergate in Rome een prospectieve studie opgezet in Nederland en Italië.

In **hoofdstuk 7** worden de data van 35 patiënten met een OAB met of zonder incontinentie beschreven. In een prospectieve multicentre studie ondergingen deelnemers 12 wekelijkse sessies en vervolledigden plasdagboekjes, levenskwaliteit vragenlijsten alsook de SF-36 vragenlijsten. Subjectief succes werd gedefinieerd als de vraag om de behandeling voor te zetten. 63% van de deelnemers kregen dan ook een individueel aangepast onderhoudsschema. Objectief succes werd gedefinieerd als de significante vermindering in aantal lekkages (>50%). Plasdagboekjes illustreerden dat dit het geval was voor 24/35 deelnemers (70%). 16/35 (46%) was zonder urineverlies na de 12 sessies. De levenskwaliteit verbeterde aanzienlijk.

In **hoofdstuk 8** worden de resultaten van de groep met dysfunctionele mictieklachten gegeven. 39 patiënten die dagelijks aan intermittente zelfcatheterisatie deden, werden geïncludeerd in deze multicentre studie. Na de 12 wekelijkse sessies werden de vragenlijsten en plasdagboekjes geanalyseerd. Ook hier werd het subjectieve succes gedefinieerd als de wens van de patiënt om PTNS te continueren, terwijl het objectieve succes gehaald werd als het volume van het totaal gecatheteri-

seerd met minstens de helft verminderde. 59% van de deelnemers vroegen om een onderhoudsschema. 41% van de patiënten reduceerden hun residu met minstens de helft. Aanvullend vertoonden 10/39 (21%) een vermindering in totaal gecatheteriseerd volume met 25-50%. Voor alle patiënten verminderde het totale residu met een mean van 228ml (range: -49;-528ml). Ook hier gingen de scores op de SF-36 en levenskwaliteit er significant op vooruit.
Het was duidelijk dat een groot aantal deelnemers een onderhoudsbehandeling behoefde. Hoewel deze subjectieve succespercentages werden geïllustreerd aan de hand van de analyse van plasdagboekjes, werden er aanvullend urodynamische onderzoeken verricht om het objectieve succes data meer te kunnen bijstaan. Daarnaast kan urodynamisch onderzoek meer informatie kunnen verschaffen waaruit selectiecriteria zouden kunnen voortvloeien.
In **hoofdstuk 9** worden de urodynamische resultaten van de OAB-groep voorgesteld. 90 patiënten met OAB-klachten werden geïncludeerd. Het subjectieve succes was 64%, wat goed overeenstemde met de eerdere gepubliceerde succespercentages. 56% van deze deelnemers had 50% of meer reductie in het aantal episodes van urineverlies. 38% van deze patiënten konden als "droog" worden bestempeld. Van 46 patiënten waren er vergelijkende urodynamische onderzoeken beschikbaar, namelijk van voor en na de PTNS-behandeling. Detrusor overactiviteit verdween bij slechts enkele patiënten. De toename in cystometrische capaciteit en het volume waarop de eerste detrusor activiteit verscheen was significant verbeterd. Deelnemers die geen urodynamische detrusor overactiviteit vertoonden in het begin van de studie, hadden 1.7 meer kans om succesvol te reageren op PTNS. Een blaas met sterke en vroegtijdige detrusor overactiviteit echter had meer kans om PTNS resistent te zijn.
In **hoofdstuk 10** worden de urodynamische data van de patiënten met blaasledigingsstoornissen gepresenteerd. Hiervoor werden 39 patiënten geïncludeerd die een 12-wekelijkse PTNS-behandeling volgden. Opvallend was de bevinding dat meer detrusor overactiviteit werd gezien in de urodynamische analyse na 12 weken behandeling (van 17 naar 34%). Hoewel de aanwezigheid van detrusor overactiviteit niet een vereiste was om succesvol te reageren op PTNS, kan dit gegeven wel suggeren dat de gewaarwording van blaasactiviteit een vorm van blaas-educatie gaf. De detrusordruk op het moment van maximale flow, de blaasresiduen en blaasindicatoren verbeterden bij alle patiënten. Patiënten met slechts een milde afwijking hadden meer kans op succes.

12.2 CONCLUSIE

PTNS is een goedkope behandelingsoptie, minimaal invasief en toe te passen op een gemakkelijk bereikbare plaats van het lichaam. Het overgrote deel van de patiënten vroeg om de behandeling voort te zetten en ontving een individueel aangepast stimulatieschema. Niet alleen het subjectief succes was groot, maar ook de objectieve maatstaven spraken duidelijke taal: het aantal episodes van

urineverlies waren verminderd, het totaal volume dat gecatheteriseerd diende te worden verminderde aanzienlijk. De levenskwaliteit van de deelnemers verbeterde, alsook ziektespecifieke scores. Urodynamisch onderzoek bevestigde de data uit de plasdagboekjes. Voorspellende factoren werden bestudeerd, maar de resultaten hiervan waren enigszins teleurstellend: weinig factoren konden het effect op succes voorspellen. Patiënten met een zeer ernstige blaashandicap waren vaak slecht te behandelen door PTNS. Waarschijnlijk gaat het hier om een groep patiënten die reeds lang gestoorde blaasfunctie hebben en dus een onherstelbare schade hebben opgelopen. Misschien hebben enkele onder hen een nog niet ontdekte neurologische aandoening.

12.3 TOEKOMSTPERSPECTIEVEN

Toen de langdurige PTNS-behandeling een logistiek probleem werd, werd naarstig naar een oplossing gezocht: de implanteerbare stimulator, de Subcutaneous Tibial Nerve Stimulator. In afwachting van de eerste productielijn, werden sommige patiënten aangeleerd de naaldjes zelf te prikken en konden ze met een gehuurde stimulator zichzelf thuis behandelen. In 2004 werden de eerste stimulators subcutaan geïmplanteerd en spoedig volgden de resultaten [van der Pal et al., 2006].

Vele factoren lijken de uitkomst van PTNS te beïnvloeden. Waarschijnlijk resulteert de complexe interactie van verschillende factoren, zoals blaastrainingen, het regelmatig invullen van plasdag-boekjes, de vrijstelling van enkephalines of andere neurotransmitters door acupunctuur, de verminderde c-fos expressie na stimulatie van de nervus Tibialis en de bijdrage van placebo-effect, tot een succesvolle behandeling. De grote hamvraag is natuurlijk: hoe werkt PTNS eigenlijk? Dit proefschrift is niet opgezet met de illusie om het mysterie van electrostimulatie eens eindelijk te onthullen. Basaal onderzoek kan ons een eind verder helpen in de zoektocht naar antwoorden. Zo divers als deze patiëntenpopulatie is, zo divers is ook hun onderliggend lijden. In de toekomst moet onderzoek voor elk individu kunnen uitmaken wat de onderliggende oorzaak is van hun blaasklachten en welke behandeling voor deze patiënt de meest efficiënte oplossing zal zijn.

Hoe groot is het placebo-effect? Niet meer dan bij eender welke andere therapie, maar een gerandomiseerde placebo-gecontroleerde studie is hier natuurlijk op zijn plaats. Alleen is deze moeilijk uitvoerbaar als er gewerkt wordt met een naald en electrische stroom.

Verder onderzoek, ontwikkelingen en inzichten zijn noodzakelijk.

Recent onderzoek naar het suburothelium en zijn functie zal resulteren in specifieke therapeutische targets. Resiniferatoxin of botulinum toxine zijn voorbeelden van zulke nieuwe behandelingen. In de klinische praktijk heeft botulinum toxine een plaats veroverd in de behandeling van patiënten met detrusor overactiviteit. Het is een methode die de uroloog een minimum aan tijd kost en een maximum aan resultaat oplevert voor de patient. Helaas betreft het hier vaak een tijdelijk effect

en de patient lijkt in tijd echter refractair voor het toxine te worden. Misschien dat in de toekomst deze botox refractaire patiënten alsnog met de meer arbeidsintensieve neurostimulatie behandeld kunnen worden. Functionele beeldvorming van de hersenen onderzoekt onder andere hoe delen van de hersenen samenwerken om tot continentie te komen. Net zoals bij het recente onderzoek naar neurostimulering om bijvoorbeeld obesitas of parkinsonisme te genezen , zou het ontwikkelen van een electrode ter plaatste van het mictiegebied geen science fiction meer zijn, om nog maar te zwijgen van het meest besproken onderwerp van de urologie: de weefsel engineering technieken.
Deze technieken transformeren stamcellen zodat zwakke sluitspiercellen van de plasbuis versterkt kunnen worden of er zelfs een normaal contractiele blaas kan gemaakt worden. Er staan ons nog boeiende onderzoekstijden te wachten!

LIST OF ABBREVIATIONS

5-HT: 5-hydroxytryptamine or serotonin
ATP: Adenosine triphosphate
BCI: Bladder Contractility Index
BVE: Bladder Voiding Efficacy
CC: Cystometric Capacity
CI: confidence Interval
CVA: Cerebro Vascular Accident
DO: Detrusor Overactivity
GABA: Gamma-amino butyric acid
Hz: Hertz
ICS: International Continence Society
I-QoL: Incontinence Quality of life questionnaire
L region: Lateral region in the pons
LUTS: Lower Urinary Tract Symptoms
mA: milliampère
M receptors: Muscarinic receptors
M region: Medial region in the pons
NGF: Nerve Growth Factor
NO: Nitric Oxide
OAB: Overactive Bladder
OR: Odds Ratio
PAG: Periaquaductal Grey
PMC: Pontine Micturition Centre
PNE: Pelvic Nerve Evaluation
PTNS: Percutaneous Posterior Tibial Nerve Stimulation
PVR: Post-voidal Residual
SF-36: MOS 36-items Short-Form Health Survey
SF-36: MOS Short Form 36 items questionnaire
SNS: Sacral Nerve Stimulation
SPSS: Statistical Package for the Social Sciences, version 9.0
SSRI: Selective Serotonin Re-uptake Inhibitors
UI: Urine incontinence
VDO: Volume at first DO

DANKWOORD

Na vele electrostimulaties van tibiale zenuwen, interviews met patiënten en urodynamische onderzoeken in de eerste 2 onderzoeksjaren, kon het verwerken van de resultaten beginnen. Eindelijk kan ik met trots het boekje presenteren. Het onderzoek en de verwerking van de data zijn natuurlijk het resultaat van de samenwerking met veel bijzondere mensen. Allen die hieraan meewerkten wil ik alvast bedanken. Een aantal personen wil ik graag nog even in de schijnwerpers zetten.

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CURRICULUM VITAE

Vera Vandoninck werd op 12 februari 1974 geboren in Antwerpen. Tot haar twaalfde vertoefde ze in het Antwerpse Kapellen tot ze in 1986 verhuisde naar Mol, gelegen in de Vlaamse Kempen. Daar vervolgde ze de middelbare schoolopleiding aan het Koninklijk Athenuem Mol waar ze in 1999 afstudeerde.

In 1991 begon ze haar artsenopleiding aan het Rijksuniversitair Centrum Antwerpen- Universitaire Instelling Antwerpen, in 1999 behaalde ze haar artsendiploma met onderscheiding. Tijdens haar opleiding heeft ze een half jaar in Stockholm, Zweden co-schappen gelopen. In 1997 was zij secretaris van het Erasmus Student Network Antwerpen.

Van 1999 tot januari 2002 verrichtte Vera Vandoninck haar promotieonderzoek aan het Universitair Medisch Centrum St Radboud, Nijmegen onder begeleiding van Prof. Dr. B. Bemelmans en Prof. Dr. F. Debruyne.

In 2002 startte ze met haar opleiding tot uroloog. Haar chirurgische vooropleiding genoot ze in het Maxima Medisch Centrum Eindhoven onder begeleiding van Dr. W. Prakken. Haar academische opleiding werd voortgezet aan het Academisch Medisch Ziekenhuis te Maastricht onder supervisie van Prof. Dr. Ph. Van Kerrebroeck. In 2006-2007 wordt ze opgeleid in het Catharina Ziekenhuis Eindhoven onder begeleiding van Dr. A. Hendrikx.

Vera Vandoninck is getrouwd met Joeri El Hazimi. In 2003 werd hun dochter Emma geboren en in 2006 hun zoon Benjamin.

PTNS

a new treatment option for lower urinary tract dysfunction

Vera Vandoninck