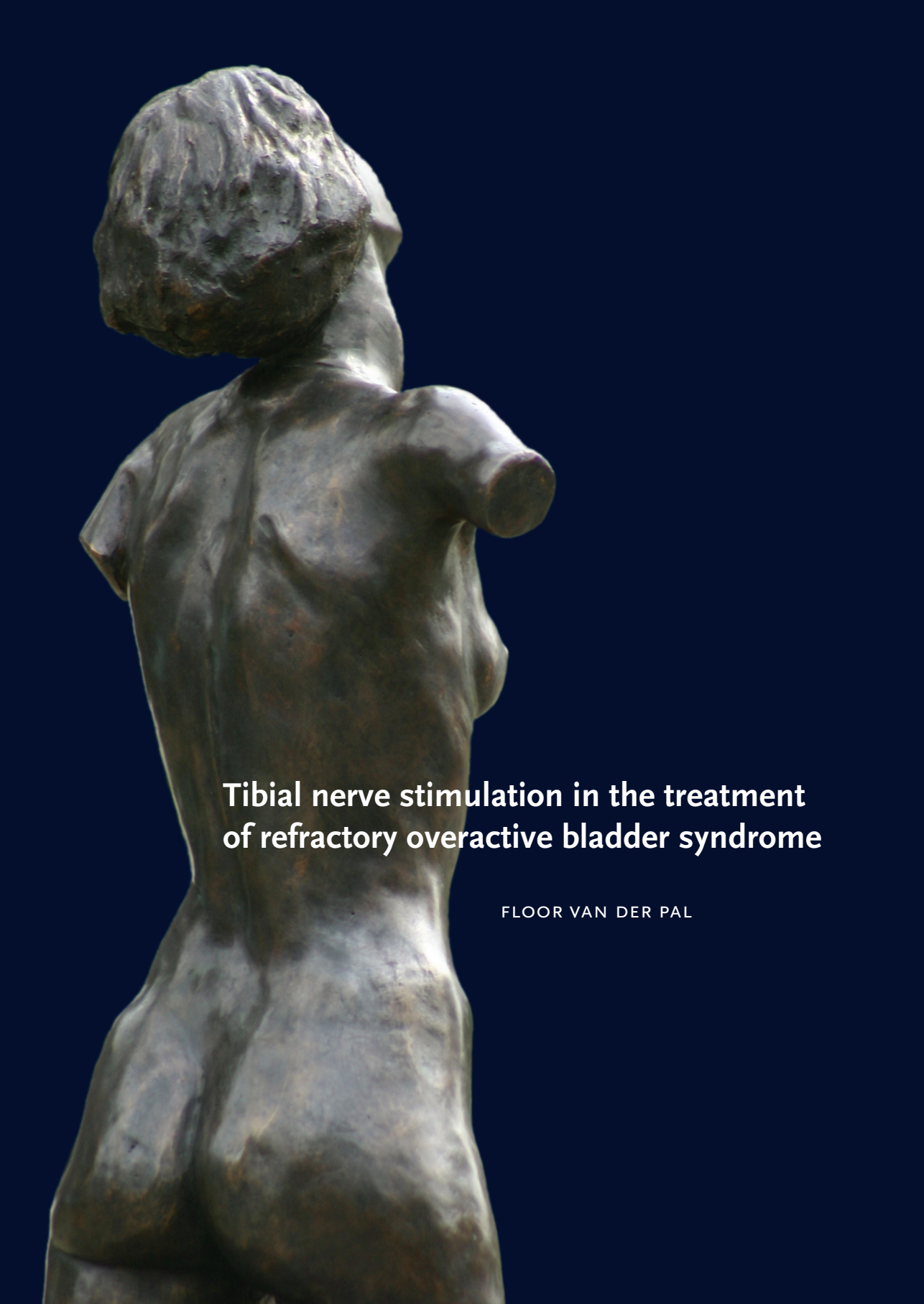

Tibial nerve stimulation in the treatment of refractory overactive bladder syndrome

FLOOR VAN DER PAL

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Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

PROEFSCHRIFT

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aan de Radboud Universiteit Nijmegen
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FLOOR VAN DER PAL

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te Oldenzaal

Promotores
Prof. dr. F.M.J. Debruyne
Prof. dr. B.L.H. Bemelmans, afdeling urologie, VU Medisch Centrum, Amsterdam

Co-Promotor
Dr. J.P.F.A. Heesakkers

Manuscriptcommissie
Prof. dr. G.W.A.M. Padberg
Prof. dr. A.A.B. Lycklama à Nijholt, afdeling urologie, LUMC, Leiden
Prof. dr. M.E. Vierhout

Paranimfen
Elma Gomes Jardin
Maurits Receveur

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CONTENTS

Introduction and outline of the thesis

CHAPTER 1

INTRODUCTION

The symptoms of lower urinary tract dysfunction can vary from chronic pelvic pain to impaired micturition or non-obstructive voiding dysfunction (voiding disorders) or overactive bladder syndrome dry and wet (storing disorders). These disorders can have a large impact on the patient's quality of life[1]. Unlike in neurogenic patients where dysfunction of the peripheral or central nervous system is known to cause these symptoms, the aetiology in non-neurogenic patients is in most cases unknown.

Lower urinary tract dysfunction is a common urological problem. Most is known about overactive bladder syndrome (OAB), which affects approximately 17% of the adult patient population in Europe and the United States[2,3] and has an estimated worldwide prevalence of 50-100 million[4]. The economic costs are high, but can only be estimated since the disorder is often overlooked by physicians and therefore underreported[5,6,7]. The impact of OAB will probably increase even further in the future, since the world population is aging[4] and the prevalence increases with age[8].

Lower urinary tract dysfunction is initially treated with conservative therapy (i.e. behavioural techniques, physiotherapy, clean intermittent catheterisation and pharmacotherapy). When conservative treatment fails, invasive therapy (i.e. bladder augmentation, bladder replacement) can be advocated. However, surgery is not widespread due to complication and remission rates[9]. Neuromodulation has been introduced as an alternative treatment for refractory patients who are not ready for surgical treatment[10].

Neuromodulation is a physiological process, which influences the activity in one neural pathway and modulates the pre-existing activity in another by synaptic interaction[11]. Different neuromodulative therapies, such as pudendal nerve stimulation, sacral nerve stimulation, and lower limb stimulation, have been developed. Their success rates vary[12].

Percutaneous tibial nerve stimulation (PTNS) is a recently introduced neuromodulative treatment[13], with reported success rates of 21-71%[14-19]. The therapy seems to be more effective in patients with storing disorders than in patients with voiding disorders or chronic pelvic pain. The tibial nerve is a mixed nerve containing motor and sensory nerve bundles. The mechanism of action is still unclear, but PTNS is supposed to modulate the signals to and from the bladder (S_2-S_3) via the sacral plexus by afferent stimulation[15].

During PTNS treatment the patient is in the frog position (with soles of the feet together, and knees abducted and flexed). A 34-gauge needle is percutaneously placed approximately 5 cm cephalad to the medial malleolus, between the posterior margin of the tibia and the soleus muscle. Furthermore, a stick electrode is placed on the ipsilateral calcaneus. The needle and electrode are connected to a low-voltage (9 V) stimulator (Urgent-PC®, CystoMedix Inc, Anoka, MN, USA). The stimulator has fixed stimulation parameters: pulse width 200 ms, pulse rate 20 Hz and adjustable stimulation intensity of 0-10 mA. To confirm correct placement of the needle, the amplitude is slowly increased until flexion of the big toe and/or fanning of the other toes occurs (i.e. motor response). Moreover, patients have a sensory response to the stimulation, i.e. a radiating sensation under the sole of the foot and/or in the toes[10]). The efficacy of the treatment is usually determined after 12 weekly 30-minute treatment sessions[10,15-19].

OUTLINE OF THE THESIS

This thesis discusses the basic science and applications of tibial nerve stimulation in the treatment of refractory overactive bladder syndrome.

First of all, in CHAPTER 2, the physiology and innervation of the bladder are discussed. After that, the current opinion on the working mechanism of neuromodulation is presented in CHAPTER 3.

Animal studies have demonstrated that afferent pudendal stimulation and sacral nerve stimulation can suppress the micturition reflex[20-23], but for tibial nerve stimulation contradicting data have been presented[24,25]. CHAPTER 4 investigates whether stimulation of the tibial nerve can modulate the micturition reflex in the female cat. Furthermore, it will be investigated whether the sacral plexus is involved in the mechanism of action.

Voiding variables and quality of life have been described to improve significantly in PTNS treated patients with refractory overactive bladder wet[10,15]. The assumption that the improved quality of life in PTNS treated patients is due to improved voiding parameters is investigated in CHAPTER 5.

Patients with overactive bladder syndrome who have been successfully treated with PTNS are put on maintenance treatment to maintain the effect[15,16]. Most patients are treated every 2-3 weeks at the outpatients' clinic[15]. The effects of pausing the maintenance treatment for a period of 6 weeks on voiding parameters and quality

of life in successfully treated patients are presented in CHAPTER 6. Furthermore, the reproducibility of successful treatment in these patients is determined.

Maintenance PTNS is a heavy burden for both patients and hospital facilities, since each patient put on a maintenance schedule will visit the outpatients' department at least 20 to 30 times per annum. A subcutaneous implant, Urgent-SQ™ (CystoMedix Inc., Anoka, MN, USA), has been developed to enable self-treatment at home. CHAPTER 7 presents the 1-year follow up on feasibility and safety of the Urgent-SQ™ in the treatment of refractory overactive bladder syndrome.

In CHAPTER 8 the summary and conclusions of this thesis are presented. A Dutch translation can be found in chapter 9.

The terminology of lower urinary tract dysfunction has been altered during the period this thesis was formed. The correct term for urge urinary incontinence and urgency/frequency syndrome is now 'overactive bladder wet and dry'. Since at the time these publications were written the new terminology had not been introduced yet, the reader may find differing terminology in various chapters of this thesis.

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Physiology and innervation of the bladder

CHAPTER 2

PHYSIOLOGY AND INNERVATION OF THE BLADDER

To grasp the physiological background of neuromodulation, some understanding of the physiology and innervation of the bladder is essential. The bladder has a physiological biphasic cycle consisting of a filling phase and a micturition phase, which are regulated by parasympathetic, sympathetic, somatic and central nervous systems. The innervation of the bladder is presented schematically in FIGURE 1.

Sympathetic efferent nerves of the hypogastric plexus originate from the spinal levels Th_{11}-L_2[1]. These fibres are active during the filling phase of the bladder, which results in parasympathetic efferent nerve inhibition[2], relaxation of the bladder dome and contraction of the intrinsic sphincter, bladder neck and urethra[3,4].

Afferent information is conducted via A-delta and C-fibres. A-delta fibres conduct sensations of urge to void and bladder distension due to bladder filling; C-fibres conduct sensations of noxious stimuli[5]. Both fibre types project to the same spinal levels, Th_{11} to L_2, via the hypogastric plexus[6,7]. Afferent information can be projected to both the brain stem and diencephalon[8]. C-fibres are activated during pathological circumstances, for instance urinary tract infection and neuropathic conditions[9].

Parasympathetic efferent nerves of the pelvic plexus and pelvic nerve originate from the spinal levels S_2 to S_4. These fibres are active during the micturition phase, which results in contraction of the detrusor muscle and relaxation of the intrinsic sphincter[10].

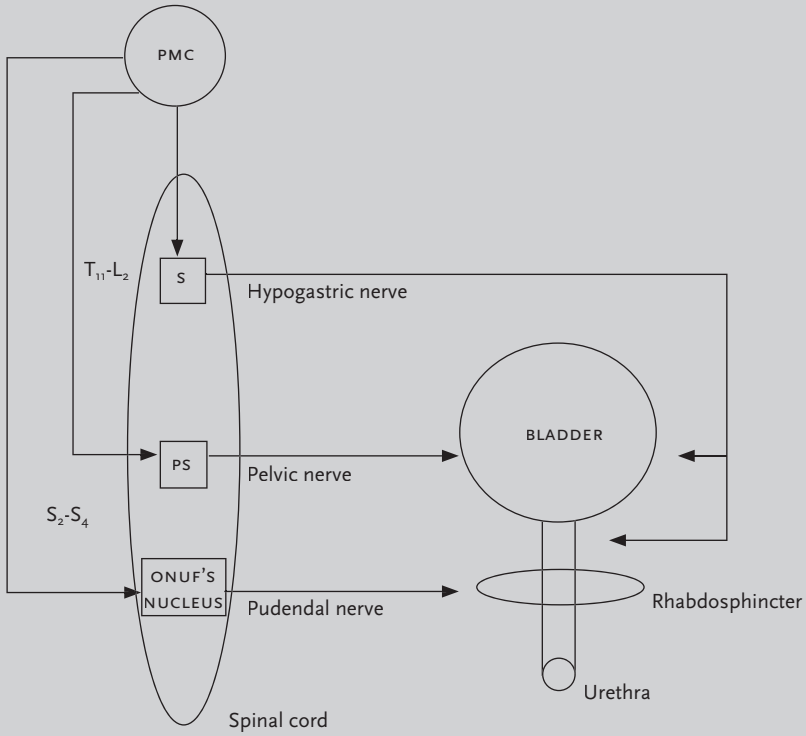
Afferent information via A-delta fibres and C-fibres is transported via the pelvic plexus and pelvic nerve to the spinal cord (S_2-S_4)[6,7,11,12]. These fibres are connected, directly or indirectly via interneurons, to efferent fibres and form a reflex arc[13]. The afferent information can be projected as well to the brainstem and diencephalon[8].

Somatic fibres of the pudendal nerve originate from the nucleus of Onuf at the spinal levels S_2 to S_4 and innervate the rhabdosphincter[14]. Activation of these fibres starts micturition and results in relaxation of the sphincter[15]).

Micturition and continence are centrally controlled by the brainstem and diencephalon and are regulated by the midbrain periaqueductal gray, the hypothalamus, and finally the medial pontine micturition center or M-region, and the lateral pontine continence center or L-region[16]. The M and L-region are together

known as the 'on-off' switch mechanism. The M-region projects to bladder motor neurons in the spinal cord[17] and to inhibitory interneurons in the dorsal gray commissure, which in turn inhibit sphincter motor neurons in Onuf's nucleus during micturition[18-20]. The L-region projects to Onuf's nucleus[21,22]. The periaquaductal gray receives bladder filling information[13] and projects to the M-region[23]. The hypothalamus projects directly to the pontine micturition centre and probably conveys the 'safe' signal to start micturition[16,24,25].

FIGURE 1 The nervous systems involved in controlling the bladder



The bladder is controlled by sympathetic (S), parasympathetic (PS) and somatic nervous systems that are regulated by the pontine micturition center (PMC). The periaquaductal gray, hypothalamus and frontal cortex are not presented in this figure.

Normal voiding is initiated after adequate input from bladder afferents and demand by the frontal cortex. The M-region is then activated (switched to 'on' mode) resulting in a coordinated reflex relaxation of the urethral sphincter muscles, relaxation of the pelvic floor and activation of the detrusor muscle[21,24,26]. This is realized by brainstem nuclei that simultaneously inhibit the somatic motor neurons in the sacral spinal cord (Onuf's nucleus) and activate the sacral parasympathetic motor neurons. After the bladder has been emptied, the pontine continence center (L-region) will be activated and switched to 'off' mode. This induces pelvic floor contraction and an increase in the urethral pressure[21].

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Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction

CHAPTER 3

F. VAN DER PAL
J.P.F.A. HEESAKKERS
B.L.H. BEMELMANS

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ABSTRACT

Purpose

Neuromodulation is a successful treatment for patients with refractory lower urinary tract dysfunction. In recent years, more applications of various types and ways have been developed and put into clinical practice. Therefore, it is important for urologists to know the existing theories on the working mechanisms that explain the effect. Although much research has been devoted to this subject during the past 35 years, the working mechanism is still unknown. This review presents an overview of the different theories and research into the physiological background of neuromodulation during the past 3 decades, with emphasis on recent developments.

Recent findings

Specific receptors in the spinal cord have been identified, which are involved in the working mechanism of neuromodulation. The maximum effect of neuromodulation is not immediately reached, indicating that neuromodulation induces learning changes (i.e. neural plasticity). The carry-over effect could be caused by negative modulation of excitatory synapses in the central micturition reflex pathway.

Summary

Neuromodulation in the treatment of stress incontinence probably induces physiological changes in the sphincter muscles and pelvic floor. In the treatment of overactive bladder syndrome, nonobstructive voiding dysfunction and chronic pelvic pain, the mechanism of action seems to be more complicated. Most likely, it is a combination of the different suggested modes of action, involving the neuroaxis at different levels.

INTRODUCTION

Patients with lower urinary tract dysfunction can have varying complaints from voiding disorders (impaired micturition or nonobstructive urinary retention) to storing disorders (overactive bladder wet and dry) and chronic pelvic pain. Lower urinary tract dysfunction in neurogenic patients is caused by the injury of the peripheral or central nervous system; in nonneurogenic patients, it is usually unknown.

Neuromodulation offers an alternative treatment for patients who are refractory to conservative treatment (behavioural techniques, physiotherapy, clean intermittent catheterization or pharmacotherapy) and not ready for irreversible surgery. Neuromodulation is defined as the physiological process in which the influence of the activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction[1]. Different therapies, like intravesical stimulation, pudendal nerve stimulation, sacral nerve stimulation (SNS) and lower limb stimulation have been developed with varying success rates[2,3]. In recent years, more applications of various types and ways have been developed and put into medical practice[4••12]. As these techniques are put into clinical practice, it is important for urologists to know the existing theories on the working mechanisms that explain the effect. Although much research has been done, the working mechanisms of neuromodulation are still unknown. This review presents an overview of the different theories and research into the physiological background of neuromodulation in the past 3 decades, with emphasis on recent developments.

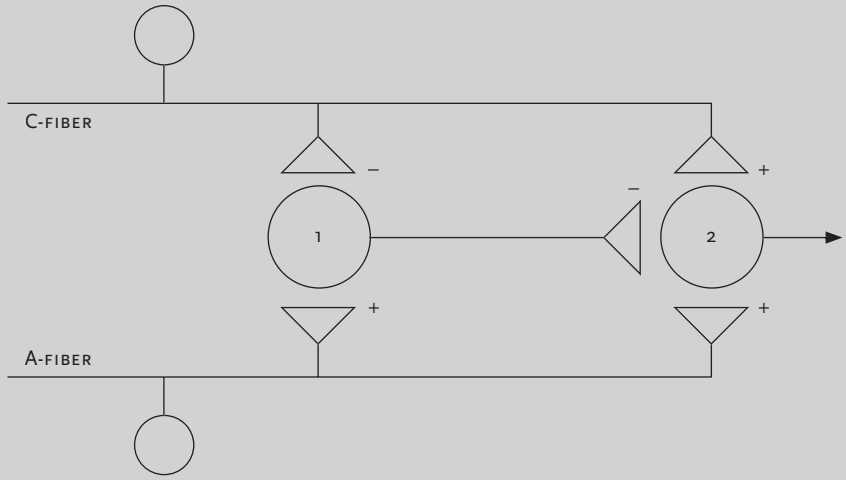
CHRONIC PELVIC PAIN

In the treatment of pain, the working mechanism is believed to be a gate-control mechanism[13]. The gate-control theory states that pain perception does not depend on pain receptors sending information to the brain, but on the pattern of peripheral nervous input[14]. It is believed that a gate-control mechanism is present at the spinal segmental level, which can prevent the sensation of pain and the reaction to it. Interneurons of the substantia gelatinosa of the spinal cord dorsal horn create gating component. Presynaptic inhibition or facilitation of afferent fibres (FIGURE 1) modulates the input to the spinal transmission neurons. Activity in A-fibres excites substantia gelatinosa neurons that, in turn, inhibit synaptic transmission and close the gate, which results in hypoalgesia. Hyperalgesia is caused by C-fibre activity resulting in increased presynaptic transmission. Furthermore, the impulses from the dorsal horn are supposed to be controlled by a des-

cending system containing fibres from the brainstem, thalamus and limbic lobes.

The discussed gate-control mechanism is believed to be the working mechanism for neuromodulation in the treatment of chronic pelvic pain[15-17]. Neuromodulation is supposed to restore the control at the spinal segmental 'gate' as well as at supraspinal sites such as the brainstem and limbic system nuclei. Studies[18,19] using transcutaneous electrical nerve stimulation (TENS) support the existence of descending inhibition, as is supposed in the gate-control theory of Melzack and Wall[14]. The rostral ventral medulla seems to be involved in this and serotonin and opioids are probably used to reduce pain. Finally, it has been suggested that the analgesic effects could be mediated by the modulation of autonomic activity[20] and that adenosine plays a role in the mechanism of action[21,22].

FIGURE 1 Schema of the gate-control theory



[1]*Substantia gelatinosa neuron,* [2]*Spinal cord transmission neuron*

OVERACTIVE BLADDER SYNDROME

Several theories on the working mechanism of the bladder have been proposed. It has been suggested that SNS induces pelvic floor muscle hypertrophy and changes the histochemical properties of the muscle, resulting in improved pelvic floor efficiency[23]. This is supported by animal studies[24] in dogs, which showed hypertrophy of striated external sphincter muscle fibres and increased urethral closure pressure during chronic SNS. Afterwards, it was stated that this theory is more applicable to the treatment of stress urinary incontinence[25]. Direct motor pathway stimulation and retrograde spinal motor neuron stimulation in Onuf's nucleus, or central inhibitory pathway activation via afferent pudendal nerve stimulation could, however, suppress instable bladder contractions. The latter seems to be more logical as neuromodulation is usually applied below the threshold for the motor response. Up till now data supporting this assumption have not been presented.

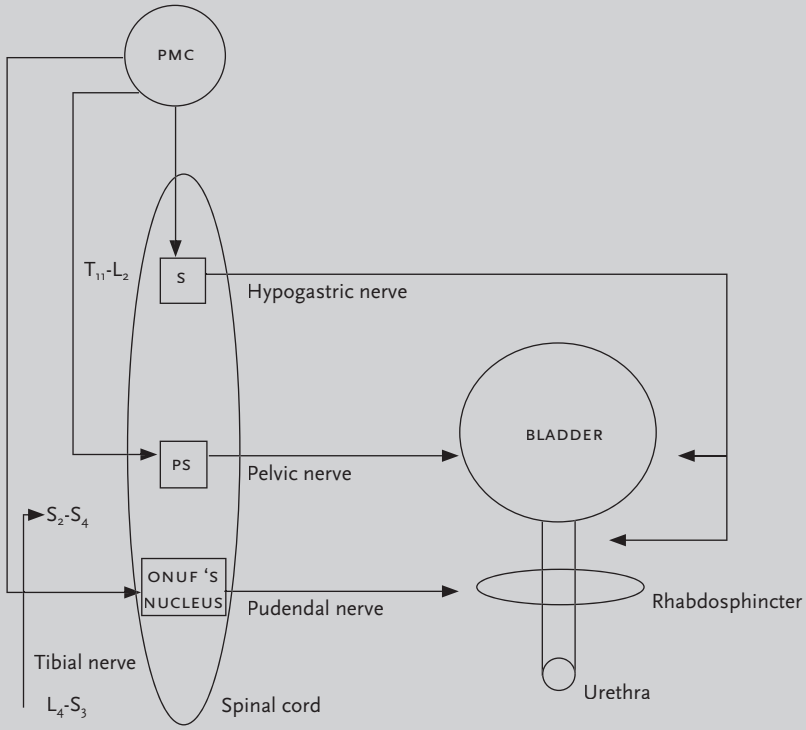
Another theory is activation of sensory nerves[26]. This is supported by research studying the latency of the motor response (i.e. the anal wink) to SNS demonstrating that the latency was approximately 10 times longer than would be expected if the response was mediated by direct motor-nerve stimulation[27]. Moreover, the latency of cortical responses is shortened during chronic SNS, indicating the activation of somatosensory afferent fibres[28].

Activation of the sensory nerves supports the gate-control theory that has been used as the working mechanism of neuromodulation in the treatment of chronic pain. This is supported by animal studies[29] demonstrating that spino-bulbo-spinal pathways are involved in the normal micturition reflex. A-delta bladder afferents project to pontine nuclei in the brainstem, which in turn give rise to inhibitory and excitatory input to lumbo-sacral reflexes controlling bladder and sphincter function. Sensory input from the pelvic floor via large myelinated pudendal fibres may control erroneous bladder input conveyed by A-type or C-type bladder afferents 'at the gate' via sacral segmental interneurons and supraspinally by way of the spino-bulbo-spinal reflex system. When a gate-control system is attributed to the inhibitory influences of interneurons from the somatic pudendal nuclei on parasympathetic pelvic nuclei within the spinal cord and brainstem, the cause of overactive bladder syndrome could be a deficiency of the inhibitory control systems involving the pudendal afferent nerves[30]. Therefore, it has been suggested that neuromodulation treats overactive bladder syndrome by restoring the balance between the inhibitory and excitatory control systems. The latter could be done at various sites in both peripheral and central nervous systems[31]. This is shown in FIGURE 2.

The supraspinal involvement in the 'gate-control' theory is supported by electroencephalogram (EEG) studies during SNS[32]. These studies have demonstrated that both short and long latency cortical potentials can be reproduced with a maximum at the sensory cortical area, indicating a supraspinal-mediated site of modulation, most probably in sensory cortex areas. Moreover, combined photon emission tomography (PET) and magnetic resonance imaging (MRI) studies have demonstrated that SNS has no effect on the brain areas that are important for the micturition itself. The activity of the micturition-dominant right hemisphere is, however, relatively reduced and the activity in brain areas that are important for general arousal, bladder filling sensation and the onset of micturition is decreased[33]. Furthermore, the maximum beneficial effect of SNS is reached after several hours or days, indicating learning changes in the brain (i.e. neural plasticity)[34]. This is supported by PET studies demonstrating that only brain areas important for motor behaviour learning (i.e. lower trunk motor cortex and the cerebellum) are activated during the first hours of SNS. After the initial period, the pelvic floor and abdominal motor cortical areas are more easily excited and the effects of SNS are prolonged and pronounced[34]. Finally, these studies showed that SNS activates the mid cingulated gyrus, which could result in a temporarily increased awareness of bladder filling.

Another mechanism of action of SNS could be the activation of the hypogastric sympathetic nerves, which have an inhibitory effect on the parasympathetic fibres at the pelvic ganglia[35]. Furthermore, recent studies have indicated that non-N-methyl-D-aspartate (non-NMDA) receptors[36••] and proton-sensitive and heat-sensitive vanilloid receptors[37] are involved in the working mechanism of SNS.

FIGURE 2 The nervous systems involved in controlling the bladder and the working mechanism of neuromodulation



The bladder is controlled by sympathetic (S), parasympathetic (PS) and somatic nervous systems that are regulated by the pontine micturition center (PMC). Micturition (bladder contraction) is facilitated by activation of the parasympathetic system through the pelvic nerve (S_2-S_4). Continence is facilitated by both the sympathetic system through the hypogastric nerve (T_{11}-L_2, bladder relaxation and internal sphincter contraction) and the somatic system trough the pudendal nerve (S_2-S_4, rhabdosphincter contraction). It is unclear whether the tibial nerve (L_4-S_3) modulates the bladder function through the pelvic nerve or pudendal nerve or both.

For pudendal nerve stimulation, it has been demonstrated that spinal pathways connect somatic and autonomic reflex circuits, which have mostly an inhibitory mode of action. Two mechanisms have been identified that have their afferent limb in the pudendal nerve and inhibit the bladder directly. At low bladder pressure, bladder contractions are suppressed via sympathetic hypogastric nerves, whereas

at high bladder pressure, parasympathetic pelvic excitatory neurons are activated, resulting in central inhibition[38,39]. Furthermore, pudendal nerve stimulation results in the activation of the sympathetic hypogastric nerves and inhibits the excitatory pelvic efferent outflow to the bladder at the ganglionic level[40]. This could be explained by the presence of a gate-control mechanism at the spinal cord to influence either the hypogastric or pelvic afferents. Data supporting this theory have been presented in patients with a complete spinal cord lesion[41]. The study demonstrated that the latencies of bladder neck responses during pudendal nerve stimulation increase significantly and are sensitive to a-blocking agent phentolamine, suggesting the involvement of sympathetic a-adrenergic fibres. Somatic afferent pudendal nerve fibres project to sympathetic neurons in the thoracolumbar spinal cord and the sympathetic bladder neck outflow travels with the hypogastric nerve maintaining the bladder neck tone via a-adrenergic receptors[42-44].

Another suggested mechanism of action is that the sympathetic system is activated that suppresses bladder activity via the b-adrenergic system or spinal interneurons that release inhibitory neurotransmitters such as enkephalin, glycine or g-aminobutyric acid[45].

Pudendal nerve stimulation in healthy volunteers showed specific activation of the somatosensory and somatomotor cortex[46] on functional magnetic resonance imaging (fMRI). The first has been confirmed by several studies[47,48]. Furthermore, it has been suggested that the amygdala and periaqueductal grey are activated during pudendal nerve stimulation[46]. Pudendal nerve stimulation-induced cortical activation is, however, not identical to SNS-induced cortical activation. A larger similarity was expected as S_2 and S_3 roots contribute 60.5 and 35.5%, respectively, to the overall pudendal afferent activity[49]. The activity of pudendal nerve stimulation was, however, confined to a single level (S_2) in 18% and even to a single root in 8% of the participants. Therefore, direct pudendal nerve stimulation could be more effective as more afferents are stimulated than during SNS[6,50], as has been confirmed by Peters et al.[51•]. To date, no results have been published of a comparative study on cortical activation during SNS and pudendal nerve stimulation in patients with lower urinary tract dysfunction.

A carry-over effect has been shown in animal studies for pudendal nerve stimulation[52] and intravesical stimulation[53], in contrast to SNS where up till now no carry-over effect has been described. For intravesical stimulation, the carry-over effect is supposed to be caused by the long-term potentiation of excitatory synapses in the central micturition reflex pathway[53], analogous as has been described for other central excitatory synapses[54]. It has been suggested that the carry-over

effect of pudendal nerve stimulation could be caused by the negative modulation of excitatory synapses in the central micturition reflex pathway[52]. This is supported by the study of Bear and Malenka[55], which showed that intense activation of inhibitory input to target cells results in a prolonged decrease in synaptic efficacy of excitatory synapses (i.e. long-term depression) in the hippocampus. Long-term depression could be the mechanism of action for the carry-over effect as well for TENS and percutaneous tibial nerve stimulation (PTNS). Although a clear carry-over effect has not been described for both therapies in an animal model, it is to be expected as patients are successfully treated with intermittent therapy[56-61]. The modulatory effect of pudendal nerve stimulation could be prolonged by frequent stimulation sessions[52], as the carry-over effect is reversible and patients are treated with frequent stimulation sessions during a certain period before their symptoms improve. This could be the case as well for TENS and PTNS; however, data supporting this assumption have not been presented yet.

Other suggested central modes of action for pudendal nerve stimulation are activation of tonic inhibitory mechanisms and shifts in firing threshold of involved neurons[62].

The mechanism of action for TENS and PTNS in the treatment of overactive bladder syndrome is supposed to be a gate-control mechanism as well[25,30,63]. It has, however, been demonstrated for TENS that different stimulation frequencies have different effects. TENS at 2 Hz is supposed to activate afferent pudendal nerve fibres and 50 Hz stimulation is considered to activate striated paraurethral muscle fibres[30,38]. TENS at 150 Hz is supposed to influence the anterior cutaneous branch of the iliohypogastric nerve or to inhibit the afferents of the pelvic splanchnic nerves that join the inferior hypogastric plexus, resulting in a decreased bladder contractility[56].

Another suggested mode of action for TENS is that it provides relief from pain, resulting in increased bladder filling and postponed micturition[64].

Tibial nerve stimulation, like SNS[65], reduces fos protein expression after chemical irritation of the bladder[66], indicating decrement of spinal neural cell activity and therefore, neuromodulative action. Fos protein is the third messenger that modulates cell activity and is especially expressed in neurons after external stimulation[66] and in the spinal cord after lower urinary tract irritation[67].

The tibial nerve is a mixed nerve containing sensory and motor nerve fibres. PTNS is supposed to treat overactive bladder syndrome by modulating signals from and

towards the bladder via the sacral plexus by retrograde afferent stimulation[61]. This has been confirmed by studies in anaesthetized female cats[68]. The study has also confirmed the observation that the effect of PTNS is temporary and that maintenance treatment is necessary as PTNS reversibly modulates the micturition reflex in the female cat.

VOIDING DISORDERS

Different theories on the mechanism of action have been proposed. Direct afferent pudendal nerve stimulation resulting in a direct change of pelvic floor behaviour[69], as well as a rebound phenomenon[70], suppression of the guarding reflexes[3] and retuning of the L and M regions or 'on–off' switch mechanism in the brainstem[25], have been suggested.

The guarding reflex is a bladder-to-urethral reflex and is mediated by sympathetic afferent pathways to the urethra. The reflex is excitatory and results in contraction of the urethral smooth muscle during the storage phase of the bladder[71]. The guarding reflex is activated during coughing or exercising resulting in momentarily increased bladder pressure, which prevents stress urinary incontinence by contraction of the external urethral sphincter. The reflex is activated as well by signalling of bladder afferents that synapse with sacral interneurons, which in turn activate efferent neurons of the external urethral sphincter[72]. Animal studies have provided data indicating that the guarding reflexes can be modulated by afferent nerve activation and inhibit bladder activity by spinal or supraspinal pathways [73-78].

The retuning of the 'on–off' switch seems to be a more logical mechanism of action for neuromodulation, as nonobstructive bladder retention is supposed to be caused by a malfunction of the 'on–off' switch mechanism due to urethral sphincter and pelvic floor spasticity[79]. Evidence supporting this theory has been provided by PET studies, which showed pontine activation during SNS in patients with urinary retention[80]. Contradicting data have been presented as well. Single photon emission tomography (SPET) during SNS showed an increase in the regional cerebral blood flow of all brain areas which are activated during micturition[81]. This study was, however, performed in healthy volunteers and not in patients with nonobstructive voiding dysfunction.

Retuning of the 'on–off' switch could be the mechanism of action as well for PTNS. Up till now, no data, however, have been presented that confirm this assumption.

According to Vapnek and Schmidt[82], SNS treats nonobstructive retention by eliminating the spasticity of the urethral sphincter and pelvic floor and not by direct activation of the parasympathetic sacral nerves, as the stimulation intensity of SNS is too low for the depolarization of these unmyelinated nerve fibres.

CONCLUSIONS

Although many hypotheses have been given and much research has been performed, the exact mechanism of action of neuromodulation in the treatment of lower urinary tract dysfunction is still unclear. In the treatment of stress incontinence, it seems likely that neuromodulation induces physiological changes in the sphincter muscles and pelvic floor. In the treatment of overactive bladder syndrome, nonobstructive voiding dysfunction and chronic pelvic pain, the mechanism of action seems to be more complicated. The mechanism is most likely a combination of the different suggested modes of action, involving the neuroaxis at different levels.

ABBREVIATIONS

PET	photon emission tomography
PTNS	percutaneous tibial nerve stimulation
SNS	sacral nerve stimulation
TENS	transcutaneous electrical nerve stimulation

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Tibial nerve stimulation to modulate the micturition reflex: an experimental study in anaesthetized female cats

CHAPTER 4

F. VAN DER PAL
J.P.F.A. HEESAKKERS
F.M.J. DEBRUYNE
B.L.H. BEMELMANS

Submitted

ABSTRACT

Objectives
Tibial nerve stimulation was performed to modulate the micturition reflex in anaesthetized female cats.

Methods
Baseline micturition reflex volume (MRV) was determined in 7 cats by cystometry. Subsequently MRV was determined during continuous tibial nerve stimulation (10 Hz, 100 microsec., mean 2 mA (range 1-4)). Afterwards, cystometries were repeated until baseline values were reached. In 2 cats that responded positively on tibial nerve stimulation (i.e. an increased MRV during tibial nerve stimulation), MRV was also determined during median nerve stimulation (10 Hz, 100 microsec., mean 2 (range 1-2)).

Results
In only 5 cats the reflex was present, with a mean baseline MRV of 54 mL (SD 26). During tibial nerve stimulation mean MRV significantly increased to 71 mL (SD 30, $p< 0.001$). Afterwards, MRV returned to mean 54 mL (SD 27, $p< 0.002$). In 1 cat a carry-over effect of 103 minutes was found. During tibial and median nerve stimulation no increment in heart rate and blood pressure, nor paw retraction occurred. Median nerve stimulation had no effect on MRV.

Conclusions
The cat model is suitable to investigate the effect of tibial nerve stimulation on the micturition reflex. It was demonstrated that tibial nerve stimulation reversibly modulates the micturition reflex in anaesthetized female cats.

INTRODUCTION

Overactive bladder syndrome (OAB dry and wet) is a common urological problem that can strongly affect patients' quality of life[1]. In most cases the aetiology is unknown and symptoms are difficult to treat. If conservative treatment (i.e. behavioral techniques, physiotherapy or pharmacotherapy) fails, patients can be treated with surgery such as bladder distension, augmentation or replacement. Surgical treatment, however, has major drawbacks such as irreversibility, and high recurrence as well as complication rates[2].

Percutaneous tibial nerve stimulation (PTNS) has been introduced as an alternative treatment for patients with refractory OAB who are not ready or fit for surgical treatment[2]. Significant changes in quality of life and parameters on both bladder diaries and urodynamic evaluations have been described in observational studies[2-5]. Up till now it has not irrefutably been proven that PTNS is more than a placebo effect. A randomized double-blinded placebo-controlled trial to investigate the efficacy of PTNS in patients with refractory OAB wet is underway but results are not available yet. In addition animal experiments are needed to shed some light on this matter.

The feline animal model is a frequently used model for studying the modulative effect of neuromodulation on the bladder function[6-9]. It has been demonstrated in these animal studies that both afferent pudendal nerve stimulation and afferent sacral nerve stimulation can inhibit the micturition reflex. There are very strong indications that at brainstem and diencephalic level micturition is organized in the same way in cats and humans[10], which makes it tempting to extrapolate results. For tibial nerve stimulation contradicting data have been presented, concerning the effectivity of micturition reflex inhibition in cats[9,11]. However, tibial nerve stimulation proved to be effective in primates[12]. The present study was designed to investigate whether tibial nerve stimulation can inhibit to micturition reflex in anaesthetized female cats.

MATERIALS AND METHODS

The present study was carried out after approval of the local review board. Between October 2003 and December 2004, 7 female cats (mean weight 3.2 kg, range 2,5-4) were used for this research. Before the study was performed a pilot study was undertaken in 3 female cats (mean weight 3.7 kg, range 3,5-4) to determine the best anaesthesia protocol. All animals were housed at the Central Animal Labora-

tory. Tap water and standard cat chow were freely available, except 24 hours before the study was performed. No control group was used in this study, since the individual cats were their own controls. The protocol was performed twice in the same animal. Between two sessions was a period of one week. The animals were euthanized at the end of the experiment by penthotal, either by an injection in the heart or intravenously.

The primary objective of the study was defined as a significant increase of volume at which the micturition reflex occurs (micturition reflex volume, MRV) during tibial nerve stimulation.

Induction of the cats

7 female cats were anaesthetised with ketamine (10 mg/kg/hour i.v.) and xylazine (2 mg/kg/hour i.v.). A foreleg vein was cannulated for anaesthesia and fluid injections (6-10 mL/hour), for which an infusion pump was used. The infusion rate was continuous and was not altered in any of the cats during the study. The internal carotid artery was cannulated for blood pressure recordings. A pulse oxy meter monitored the heart rate and O_2 saturation. The temperature was kept at 38-39 °C by a heating lamp and mattress. After zero set, a 6 Fr double-lumen micro-tip catheter (MMS, Enschede, the Netherlands) was inserted transurethrally into the bladder and fixated with a ligature. Both lumens of the catheter were separately connected to an infusion pump and a pressure transducer. After zero set, a 6 Fr single-lumen micro-tip catheter (MMS, Enschede, the Netherlands) was inserted into the anal canal and a pressure transducer. The pressure signals were displayed and stored on an urodynamic unit and on a digital chart recorder for off line analysis. The voided urine was collected in a bowl.

Cystometry in anaesthetized cats

After adequate anaesthesia and analgesic depth were reached (i.e. the eyelash reflex was almost absent and absence of paw retraction on moderate pinching), baseline micturition reflex volume (i.e. MRV) was determined by filling the bladder with body warm saline at a constant infusion flow of 1,0 mL/minute. When the micturition reflex occurred, the infusion was stopped immediately and the bladder was evacuated through the catheter. MRV was determined by measuring the collected voided and catheterized residual volume. This was repeated 2 times. Between cystometries there was a resting period of 5 minutes. Electrical stimulation was performed after a resting period of one hour.

Electrical nerve stimulation

To determine the effect of tibial nerve stimulation on the micturition reflex volume,

an acupuncture needle was placed in the vicinity of the tibial nerve at 1-2 centimetres above the medial ankle in 1 leg and a second needle approximately 1 cm proximal to the first. Both needles were connected to a stimulator (Interstim®, Medtronic Inc., Minneapolis, Minnesota). Stimulation was performed continuously during cystometry at 10 Hz, 100 microseconds and at amplitude above the motor response threshold, which did not result in an increment in heart rate and blood pressure[11]. Stimulation was stopped when the micturition reflex occurred and MRV was determined as described above. Cystometry was then resumed and continued until MRV returned to baseline values. This was repeated at least once. Between stimulation sessions was a resting period of 5 minutes. In 2 cats, in which MRV was successfully modulated by tibial nerve stimulation (i.e. a marked increase of MRV), stimulation of the median nerve was performed, using the same parameters as for tibial nerve stimulation. In the vicinity of the median nerve, approximately 1-2 cm's below the elbow joint, an acupuncture needle was placed and a second needle approximately 1 cm proximal to the first. Both needles were connected to the stimulator.

Data analysis

Data are expressed as the mean ± SD. The statistical analyses were performed with commercial software (SPSS version 10, Chicago, Illinois, USA). Comparison of the results at baseline, during PTNS and after PTNS were conducted with the Wilcoxon Signed Ranks Test.

RESULTS

Rhythmic bladder contractions were present during cystometry in all cats as described by Klevmark[13]. These contractions usually occurred in higher frequency and amplitude with increased bladder filling, resulting in a micturition reflex and voiding in 5 out of 7 cats. In 2 cats in whom no such reflex could be determined cystometry was performed until the bladder pressure had gradually increased with 20 cmH_2O or spontaneous urine loss without a recorded bladder contraction (i.e. overflow) occurred, after that the bladder was evacuated. If the micturition reflex had not occurred after 2-3 cystometries, saline at 4 °C was used. This was performed in all cats. It took a mean of 4 hours (range 2-7,5) for the first micturition reflex to occur. In 3 cats the micturition reflex was absent during the first measurement session but present during the second. Since according to the protocol all cats were euthanized after the second measurement session, data of only 1 measurement session could be collected in these cats. The results in the individual cats are presented in TABLE 1.

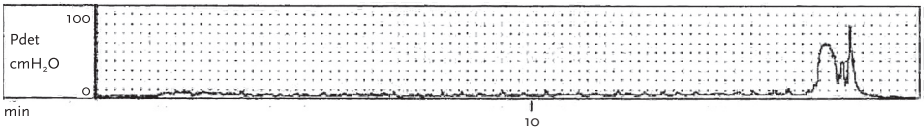
TABLE 1 The micturition reflex volume (mL) at baseline, during and after tibial nerve stimulation in 5 female cats and during median nerve stimulation in 2 cats.

	Micturition reflex volume (mL) Mean (SD)			
	Baseline	During tibial nerve stimulation	After tibial nerve stimulation	During median nerve stimulation
Cat 1	22 (1.2)	31 (1.4)	20 (3.5)	-
Cat 2	47 (2.8)	55 (3.6)	46 (1.4)	-
Cat 3	44 (12.3)	61 (7.1)	47 (12.0)	-
Cat 4	102 (4.7)	116 (1.3)	101 (0.7)	97 (4.2)
Cat 5	56 (7.1)	63 (11.1)	54 (8.4)	55 (9.6)

Mean MRV at baseline was 54 mL (SD 26). Subsequently, tibial nerve stimulation (100 microsec., 10 Hz) was continuously performed during cystometry at a mean stimulation intensity of 2 mA (range 1-4). In all animals tibial nerve stimulation resulted in flexion of the toes. The stimulation amplitude was not adjusted during the measurement, since the motor response was continuously present. No paw retraction or increase in blood pressure and heart rate occurred during stimulation. Stimulating at a higher intensity was painful, since it did result in retraction of the stimulated paw and a rise in both blood pressure and heart rate. During tibial nerve stimulation mean MRV significantly increased to 71 mL (SD 30, $p< 0.001$) and met the primary objective. The rhythmic bladder contractions seemed to occur at a larger volume and with lower amplitude, but not significantly. Moreover, the duration and maximal amplitude of the micturition reflex were not significantly altered by the stimulation. After tibial nerve stimulation mean MRV returned to a baseline value of 54 mL (SD 27, $p< 0.002$). Cystometries directly after the stimulation showed that there was no carry-over effect, except in 1 cat. In animal number 3 it took 103 minutes before MRV had returned to baseline values.

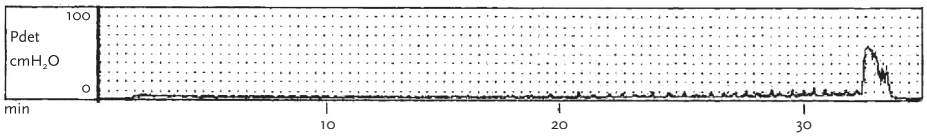
The effects of tibial nerve stimulation on the micturition reflex in the female cat are shown in FIGURES 1 and 2.

FIGURE 1 Baseline cystometry in cat number 1



The detrusor pressure (Pdet) is shown with the time registration (minutes) below. The micturition reflex occurs after 16 minutes with a micturition reflex volume of 17 mL.

FIGURE 2 Cystometry during PTNS in cat number 1



The detrusor pressure (Pdet) is shown with the time registration (in minutes) below. The micturition reflex occurs after 32 minutes with a micturition reflex volume of 32 mL.

In 2 cats, in which MRV was successfully modulated by tibial nerve stimulation (i.e. a marked increase of MRV), median nerve stimulation was performed (mean 2 mA (range 1-2), 100 microsec., 10 Hz). Stimulation resulted in flexion of the toes of the foreleg and stimulation amplitude was not adjusted during the measurement, since the motor response was continuously present. During stimulation of the median nerve no paw retraction or rise in blood pressure and hearth rate occurred. Median nerve stimulation had no effect on MRV.

DISCUSSION

The primary objective (i.e. a significant increase of MRV during tibial nerve stimulation) was achieved in the present study, demonstrating that afferent tibial nerve stimulation suppresses and modulates the micturition reflex, as has been demonstrated for pudendal nerve stimulation and sacral nerve stimulation[6-9]. This corroborates the urodynamic data that have been presented on PTNS treated patients with refractory urge urinary incontinence[3,4].

The present study demonstrates also that the feline animal model is useful to investigate the effects of neuromodulation techniques, since a micturition reflex could be observed and tibial nerve stimulation could be performed. However, the

use of this model is challenging, since the micturition reflex was present in 5 out of the 7 cats, in 3 cats the micturition reflex was only present during the second measurement and it took a mean of 4 hours (range 2-7,5) before the first reflex occurred.

Female cats were used in this study since it was easier to insert a 6 Fr transurethral catheter into a female cat than in a male. Anaesthesia with kematine and xylazine has been used successfully before[11]. The anaesthesia was continuous, since an infusion pump was used with a fixed infusion rate that was not altered during the measurement. Furthermore, the anaesthesia depth was checked at regular intervals by testing the presence of the eyelash reflex. The reflex was almost absent and had not altered during the measurements. Therefore it is unlikely that the anaesthesia did influence the results of the study and nor does it explain the observation that the micturition reflex was present in 5 out of 7 cats and that in 3 cats the reflex was only present in the second measurement. The use of saline for cystometry at 4 °C in stead of body temperature seemed not to influence the occurance of the reflex either. Furthermore, there seemed to be no difference in the biometric parameters (blood pressure, heart rate, temperature, anaesthesia depth, analgesic depth) of the cats and all were acclimatized a week before the first measurement of the study was performed.

The 5-minute resting period between the cystometries is short, since it is known from patient studies that repeated cystometries can influence the results[14]. However, the 5-minute resting period is similar to the resting period that has been used by Jiang and Lindstrom[7]. Furthermore, the 5-minute resting period seemed not to influence MRV in this study since the standard deviation in the individual cats is very small (TABLE 1). Cat number 3 and 5 were the only cats that had a micturition reflex during both measurements. There was a difference between baseline MRV during the first and second measurement, resulting in a larger standard deviation. This could be explained by a varying urine production rate during the two sessions. The ureters were left intact, and therefore any urine produced during the study was collected in the bladder. The urine production did vary despite the continuous intravenous fluid injection. This did not influence MRV, since it was determined by measuring the voided volume collected in a bowl, together with the catheterized residual volume.

It has been demonstrated in animal studies that the effect of afferent nerve stimulation is reversible and that a carry-over effect is present. The first observation has been confirmed by our data, since the volume at which the micturition reflex occurred returned to baseline values after cessation of tibial nerve stimulation. This

confirms the notion that maintenance treatment is necessary in successfully treated patients[15]. The second observation being that of a carry-over effect was only confirmed in 1 out of 5 cats. It was expected from our clinical data, since patients have been successfully treated with 12 weekly sessions[2,4,5]. A distinct carry-over effect has been described after pudendal nerve stimulation, which was present in all cats[16]. Moreover, it has been described in rats that it took more than an hour before the micturition reflex volume returned to baseline values[7]. Nevertheless, a satisfying explanation for the absent carry-over effect in our experiment in 4 out of 5 cats cannot be provided.

The tibial nerve (L_4-S_3) is a mixed nerve that contains sensory and motor nerve bundles. The mechanism of action of PTNS is still unclear, but it is supposed to modulate the signals to and from the bladder (S_2-S_3) via the sacral plexus by afferent stimulation[5]. This suggests neuromodulative action, as has been confirmed by Chang et al.[17]. The present study indicates that the sacral plexus is involved in modulating the micturition reflex by stimulation of the tibial nerve (L_4-S_3), since median nerve stimulation (C_6-C_8) did not change the micturition reflex volume in the anaesthetized female cat model. Further research is needed to investigate whether for instance increased sympathetic activity is involved in the mechanism of action, or suprasacral (i.e. pontine and/or cortical) areas as has been suggested in the literature[18,19].

CONCLUSIONS

This anaesthetized cat model is useful to investigate the effect of tibial nerve stimulation. It was demonstrated that tibial nerve stimulation reversibly modulates the micturition reflex and increases the volume at which the reflex occurs.

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CONFLICT OF INTEREST

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Correlation between quality of life and voiding variables in patients treated with percutaneous tibial nerve stimulation

CHAPTER 5

F. VAN DER PAL
M.R. VAN BALKEN
J.P.F.A. HEESAKKERS
F.M.J. DEBRUYNE
L.A.L.M. KIEMENEY
B.L.H. BEMELMANS

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ABSTRACT

Objectives
It is assumed that improvement of voiding variables will lead to improved quality of life in patients with lower urinary tract dysfunction. The present study was performed to investigate the relationship between quality of life and voiding variables in percutaneous tibial nerve stimulation (PTNS) treated patients.

Methods
30 patients with urge urinary incontinence were treated with PTNS. 24-hour bladder diaries and quality of life questionnaires (SF-36 and I-QoL) were filled out at baseline and after PTNS.

Results
A significant correlation ($p<0.05$) was present between number of used pads and SF-36 domains physical and vitality, between number of incontinence episodes and SF-36 domains physical and role physical, between nocturia and SF-36 domains general and mental health, between mean voided volume and the SF-36 domain role physical and finally, between mean voided volume and the I-QoL score.

Conclusions
PTNS has a useful place in the treatment of refractory urge Incontinence and should at least be considered as a therapeutic alternative before turning to aggressive surgery, since voiding and quality of life variables do significantly and quantifiably correlate in PTNS treated patients with refractory urge urinary incontinence. Patients must have a reduction of at least 2 used pads before their quality of life improves. This could be the best definition of successful therapy for patients with urge urinary incontinence.

INTRODUCTION

Percutaneous tibial nerve stimulation (PTNS) has been used to treat patients with complaints of lower urinary tract dysfunction, since its introduction in 1999[1]. Moreover, PTNS has been presented as an alternative treatment for refractory non-neurogenic patients who are not ready for surgical treatment[2].

Significant improvements documented on bladder diary, quality of life questionnaires and urodynamic evaluations have been reported[2-8]. It is generally assumed that improved voiding variables will lead to improved quality of life[9]. However, the correlation between these variables has not been investigated. The present study was performed to quantify the correlation between voiding variables and quality of life in PTNS treated patients with refractory urge urinary incontinence.

PATIENTS AND METHODS

Between November 2002 and January 2004, 4 male and 26 female patients were enrolled in a clinical trial. No control group was used for the present study. The use of a delayed implant group[10] was not possible, since an implantable device was not available when the present study was carried out. All patients were evaluated at the urology outpatients clinic for refractory urge urinary incontinence by history, physical and urological examination, including urodynamic evaluation and 24-hour bladder diaries[11-13]. Methods, units and definitions used in this study conform to the standards recommended by the International Continence Society (ICS)[14], except for the 24-hour bladder diaries[15]. Data suggesting that such diaries are sufficient to evaluate the patients' micturition complaints have been presented[11-13]. Moreover, 24-hour bladder diaries have been used previously[2,5,7].

Since there is no ICS definition of urge urinary incontinence that is based on the outcome of bladder diaries, we defined urge urinary incontinence as urgency leading to urinary leakage occurring at least 3 times per 24 hours on bladder diary. All medication that could influence bladder function was stopped at least 2 weeks before treatment or continued without dose changes during the entire study. Specific exclusion criteria as described by van Balken et al. were used[2].

30 patients with a mean age of 51 years (range 20-72) were treated for complaints of urge urinary incontinence. The patients had complaints for a mean period of 10 years (range 1-28). All were treated with conservative therapy without result. 28 patients were unsuccessfully treated with oral medication. Patients had had

a mean of 2.2 (range 0-8) prescriptions for their complaints; anticholinergics, (oxybutynin, tolterodine, flavoxate hydrochloride), alpha-blockers, antidepressants, antibiotics, oestrogens and desmopressin were prescribed mostly. 14 patients were treated with physiotherapy or bladder training, 7 with the test stimulation phase of sacral nerve stimulation and 6 with other treatments, all without success. 13 patients had had unsuccessful surgical treatment (range 0-2 operations). These surgical therapies included colposuspension, urethra dilatation, urethrotomy, bladder distension with or without bladder biopsies, intravesical Botulinum toxin injections, bulk injections, and transurethral resection of the prostate.

PTNS was performed as described by van Balken et al.[2]. A low-voltage (9 V) stimulator (Urgent-PC®, CystoMedix Inc., Anoka, MN, USA) was used. The stimulator has an adjustable stimulation intensity of 0-10 mA and fixed stimulation parameters: pulse width 200 microseconds, and pulse rate frequency 20 Hz. The amplitude was slowly increased until flexion of the big toe and/or fanning of the other toes occurred, to confirm correct placement of the needle. If the motor response did not occur, the needle placement procedure was repeated. All patients had a sensory response to the stimulation, i.e. a radiating sensation under the sole of the foot and/or in the toes. Ongoing stimulation at the intensity of the motor response was too painful for nearly all patients, so the current was set at a well-tolerable level resulting in the sensory response. If the patients adapted to the stimulation the intensity was adjusted. Patients were treated with 30-minute sessions 3 times a week during a period of 4 weeks. PTNS was performed on Monday, Wednesday and Friday of each week.

At baseline patients were evaluated by having them fill out a 24-hour bladder diary, as well as general and disease specific quality of life questionnaires. This procedure was repeated after PTNS treatment. In the bladder diaries the micturition frequency, voided volume (cc), number of incontinence episodes, and the number of pads were recorded. General and disease specific quality of life questionnaires were evaluated with the 36-item short-form health survey (SF-36)[16] and the incontinence-specific quality of life assessment (I-QoL)[17]. The SF-36 consists of 36 items regarding distinct health status concepts. The specific domains are physical health, role physical, role emotional, social function, pain, mental health, vitality and general health. The maximum score for each domain is 100, and higher scores relate to better quality of life. The I-QoL questionnaire consists of 22 items, each with a 5-point response scale. As with the SF-36 questionnaire a high score means a good quality of life.

Changes in the voiding and quality of life variables after treatment were tested on

statistical significance using the Wilcoxon Signed Ranks Test. Correlation between change in voiding and quality of life variables were statistically tested on significance using the Spearman's Correlation Test. The statistical analysis was performed using commercial software (SPSS version 10, Chicago, Illinois, USA).

RESULTS

Of the 30 included patients 29 could be evaluated. One patient did not complete follow up. Patients were treated with a mean pulse intensity of 3.2 mA (range 1.0-6.5). Complications of the therapy – minor bleeding or a temporary painful/numb feeling at the insertion site or under the sole of the foot – occurred rarely.

After PTNS, 4 out of the 5 voiding variables changed significantly on bladder diary compared to baseline (TABLE 1). Concomitantly, 5 out of the 8 domains of the SF-36 questionnaire changed significantly, as well as the I-QoL score (table 2). Significant correlations could be detected between voiding and quality of life variables (table 3). A reduction of number of used pads did correlate with an increase in the SF-36 domain physical function. Results of linear regression suggested that a reduction of 1 used pad would result in a 5-point increase of the physical function domain of the SF-36 questionnaire (FIGURE 1A). Furthermore, a reduction of number of used pads did correlate with an increase in the SF-36 domain vitality. Results of linear regression suggested that a reduction of 1 used pad would result in a 3-point increase of the physical function domain of the SF-36 questionnaire (FIGURE 1B). No other suggestions of linear regression between voiding variables and SF-36 domains were found.

TABLE 1 Voiding variables and QoL scores at baseline and after PTNS in 29 patients

Variable	Mean (SD) at baseline	Mean (95% CI) change	p
Voiding			
Number of voids	13.0 (6.5)	-1.3 (-2.7, +0.1)	0.070
Nocturia	2.2 (1.5)	-0.8 (-1.3, -0.2)	< 0.01
Mean voided volume (mL)	128.6 (55.4)	+51.8 (+17.0, +86.5)	< 0.01
Number of incontinence episodes	8.0 (7.7)	-4.1 (-6.2, -2.0)	< 0.01
Number of used pads	3.9 (3.6)	-1.3 (-2.3, -0.4)	< 0.01
QoL			
SF-36 domains:			
Physical	66.0 (24.9)	+10.0 (+0.6, +19.4)	< 0.05
Role physical	49.1 (47.4)	+19.8 (+2.9, +36.8)	< 0.05
Role emotional	62.1 (46.9)	+21.8 (+4.5, +39.2)	< 0.05
Social function	57.8 (28.6)	+12.0 (+1.0, +23.0)	< 0.05
Pain	62.5 (25.5)	+10.5 (+4.5, +16.5)	< 0.01
Mental health	66.3 (14.9)	-3.2 (-10.6, +4.1)	0.375
Vitality	53.4 (21.5)	+2.8 (-3.7, +9,2)	0.386
General health	56.9 (25.4)	+4.6 (-1.4, +10.7)	0.128
I-QoL	61.0 (17.4)	+11.8 (+4.5, +19.1)	< 0.01

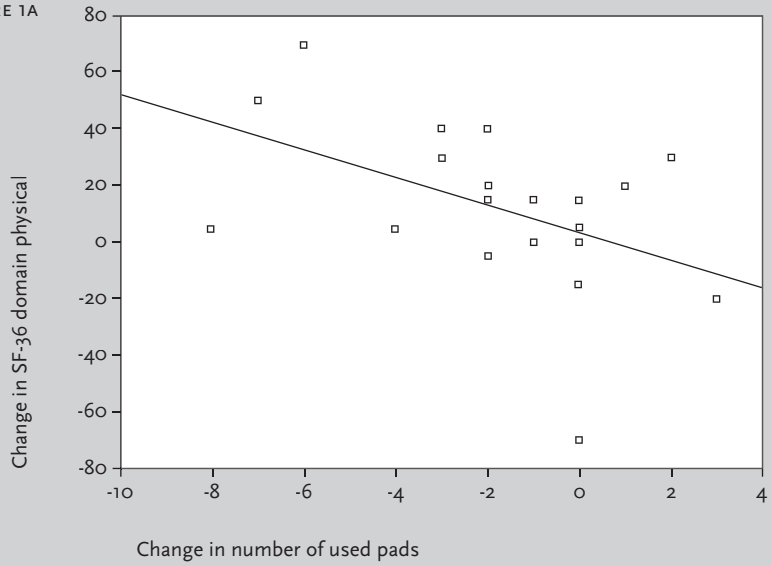
TABLE 2 Correlation between changes in voiding and quality of life variables in 29 patients

	Physical	Role physical	Role emotional	Social function	Pain	Mental health	Vitality	General health
Void[1]	-0.21	0.06	0.10	0.06	-0.21	-0.27	-0.16	-0.02
Mvv[2]	0.19	0.37*	0.21	0.14	0.11	0.20	0.34	-0.02
Noct[3]	-0.24	-0.08	-0.26	-0.28	-0.21	-0.43*	-0.34	-0.39*
Inco[4]	-0.39*	-0.54*	-0.28	-0.32	-0.11	-0.08	-0.35	-0.15
Pad[5]	-0.46*	-0.08	-0.26	-0.34	-0.11	0.07	-0.44*	0.02

**p < 0.05, [1]number of voids, [2]mean voided volume (mL), [3]nocturia, [4]number of incontinence episodes, [5]number of used pads*

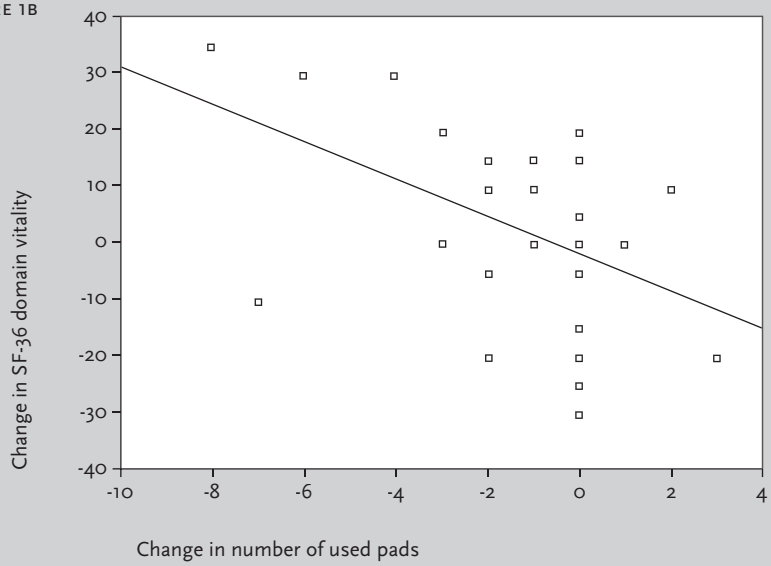
FIGURE 1 Linear regressions between voiding and QoL variables in 29 patients treated with PTNS

FIGURE 1A



Linear regression coefficient -4,91 (Standard Error 1.68), R square 0.24, p<0.01

FIGURE 1B



Linear regression coefficient -3,29 (Standard Error 1.16), R square 0.23, p<0.01

The I-QoL score did also significantly correlate with the voiding parameter mean voided volume. Results of linear regression suggested that a 100 cc increase of mean voided volume should result in a 10-point increase of the I-QoL score.

DISCUSSION

Concerning the primary objective, a quantifiable correlation between voiding and quality of life variables could be determined at baseline (data not shown). This confirms data presented by O'Conor et al.[9]. However, in the O'Conor study the effect of treatment on the quality of life was not investigated, nor was the correlation between the change in quality of life and voiding variables. Moreover, the results at baseline confirm the statement that overactive bladder syndrome can strongly affect the patient's quality of life[18]. At baseline, the quality of life of the patient population was very poor compared to the national Dutch values of healthy persons (i.e. a difference of at least 10 points in all SF-36 domains), even compared to patients with migraine[19]. Various authors have confirmed the poor quality of life in patients with overactive bladder syndrome[9,20], indicating the necessity of treatment.

The present study has demonstrated that PTNS has an effect on the patient's quality of life. A significant correlation has been demonstrated between number of used pads and the SF-36 domains physical and vitality, between mean voided volume and the SF-36 domain role physical, between number of incontinence episodes and the SF-36 domains physical and role physical, between nocturia and SF-36 domains mental health and general health and finally between mean voided volume and the I-QoL score. This confirms the assumption that improvement of the voiding variables results in an improved quality of life[9].

It was not possible in the present study to determine whether the effect that PTNS had on the patient's quality of life was placebo or therapy induced. This will be investigated in a designed randomized double-blinded placebo-controlled trial, which is being conducted. However, no data are available yet.

Up till now different definitions of successful PTNS treatment have been used by various authors[3,4,7], which makes it difficult to compare the studies with each other. All definitions were based on the clinical outcome on bladder diaries. The present study has demonstrated that PTNS has an effect on the patient's quality of life. Therefore, a definition of successful treatment based on quality of life improvement would be more appropriate. The I-QoL quality of life questionnaire seems

not suited for the efficacy evaluation, since the I-QoL score only correlated with the voiding parameter mean voided volume. The SF-36 quality of life questionnaire is suited, since several domains did correlate with various voiding variables (TABLE 3).

According to Norman et al.[21] the threshold of discrimination for changes in health-related quality of life for chronic diseases appears to be approximately half a standard deviation. Extrapolating this to PTNS treated patients, the SF-36 domains should change approximately half a standard deviation SD at baseline before a change in quality of life is detected. In the present study similar results were described for all significant changes (TABLE 2). Because of this we have set the cut off value for successful treatment at a minimal increase of 10 point in the SF-36 domains physical and/or pain. The corresponding voiding parameter is number of used pads, which has a significant ($p<0.01$) linear regression coefficient of -4.91 (Standard Error 1.68). Therefore, in order to detect a quality of life improvement and to be successfully treated, patients must have a decrease of at least 2 used pads.

CONCLUSIONS

PTNS has a useful place in the treatment of refractory urge incontinence and should at least be considered as a therapeutic alternative before turning to aggressive surgery, since there is a quantifiable correlation between voiding and quality of life variables in PTNS treated patients with refractory urge urinary incontinence. The best definition of successful PTNS therapy based on quality of life improvement for patients with urge urinary incontinence is a reduction of at least 2 used pads on bladder diary.

CONFLICT OF INTEREST

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Percutaneous tibial nerve stimulation (PTNS) in the treatment of refractory overactive bladder syndrome: is maintenance treatment necessary?

CHAPTER 6

F. VAN DER PAL
M.R. VAN BALKEN
J.P.F.A. HEESAKKERS
F.M.J. DEBRUYNE
B.L.H. BEMELMANS

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ABSTRACT

Objectives
To determine the effect of pausing percutaneous tibial nerve stimulation (PTNS) in successfully treated patients and the reproducibility of successful treatment.

Methods
11 patients (mean age 51 years) with refractory overactive bladder syndrome (> 7 voids and/or ≥ 3 urge incontinence episodes per day) were successfully treated with PTNS and continued treatment. Patients filled out bladder diaries and quality of life questionnaires (SF-36 and I-QoL) before (T1) and after a 6-week pause (T2) of maintenance PTNS and again after re-treatment (T3). The first objective was defined as a ≥ 50% increase of the number of incontinence episodes and/or micturition frequency on bladder diary after the 6-week pause of maintenance PTNS. The second objective was defined as a ≥ 50% reduction of the number of incontinence episodes and/or micturition frequency on bladder diary after re-treatment.

Results
At T2, 7/11 patients (64%) had a ≥ 50% increase of the number of incontinence episodes and/or micturition frequency on bladder diary after the 6-week pause of maintenance PTNS. Mean voided volume, nocturia, number of incontinence episodes and incontinence severity had significantly ($p<0.05$) deteriorated. At T3, 9/11 patients (82%) had a ≥ 50% reduction of the number of incontinence episodes and/or micturition frequency on bladder diary after re-treatment. Nocturia, number of incontinence episodes, incontinence severity, mean voided volume and quality of life had significantly ($p<0.05$) improved.

Conclusions
Continuous therapy is a necessity in successfully PTNS treated patients. The efficacy of PTNS can be reproduced in formerly successfully treated patients.

INTRODUCTION

Percutaneous tibial nerve stimulation (PTNS) is an alternative therapy for refractory non-neurogenic lower urinary tract dysfunction[1]. After successful treatment patients are put on maintenance therapy[2]. So far there have been no reports on long-term results in treatment of patients with overactive bladder syndrome (OAB), nor are any data available on the effect of prolonged interruption of the maintenance treatment, nor concerning the question if the efficacy of the therapy can be reproduced.

The present study was performed to evaluate the effect of prolonged interruption of the maintenance therapy on the complaints of patients with overactive bladder syndrome. A second goal was to investigate whether the efficacy of the therapy can be reproduced.

PATIENTS AND METHODS

Between November 2003 and January 2004, 11 patients were enrolled in a clinical trial. Patients were evaluated at the outpatients' clinic for overactive bladder syndrome (OAB) by history and physical and urological examination, including urodynamic evaluation. Methods, units and definitions used in this study meet the standard recommended by the International Continence Society[6], except for the 24-hour bladder diaries[7]. These bladder diaries are sufficient to evaluate the patients' micturition complaints[3-5].

OAB was defined as more than 7 voids per day and/or a sudden insuppressibly urge to void, culminating in urinary leakage at least 3 times per day on bladder diary. All medication that could influence bladder function was stopped at least 2 weeks before treatment or continued without dosage changes during the entire study. Specific exclusion criteria for PTNS as described by van Balken et al. were used[1] (TABLE 1).

All patients, 5 men and 6 women with a mean age of 51 years (range 33-66), were diagnosed with OAB (2 patients had urgency/frequency syndrome and 9 had urge urinary incontinence). All patients were refractory to conservative treatment. Oral medication was unsuccessful in all and patients had had mean 3 prescriptions (range 1-8) for their complaints. Mostly anticholinergics, alpha-blockers, antidepressants, antibiotics, and desmopressin were prescribed. 6 patients were treated with physiotherapy or bladder training, 5 with sacral nerve stimulation and

4 with other therapies, all unsuccessfully. 4 patients had had unsuccessful surgical treatment (range 1-2 operations). The performed surgical therapies were colposuspension, urethra dilatation, bladder distension, bulk injections and transurethral resection of the prostate.

All patients were prioryly successfully treated with PTNS (≥ 50% reduction of incontinence episodes and/or micturition frequency on bladder diary) and had continued treatment. 5 patients had maintenance PTNS in an outpatients' setting, and all were diagnosed with urge urinary incontinence. 6 patients performed self-administered home treatment, either by transcutaneous stimulation with 2 surface electrodes (5 patients) or percutaneous tibial nerve stimulation (1 patient). Of these patients 4 were diagnosed with urge urinary incontinence and 2 patients with urgency/frequency syndrome. Maintenance therapy was performed during a mean period of 13 months (range 1-36 months).

TABLE 1 Exclusion criteria

Exclusion criteria
Younger than 18 years
Symptoms existing for less than 6 months
Pregnancy or intention to become pregnant during the course of the study
Active urinary tract or recurrent urinary tract infection (5 or more recurrent infections during the last 12 months), carcinoma in situ, bladder malignancy, interstitial cystitis
Bladder or kidney stone
Severe cardiopulmonary disease
Use of pentosan polysulfate sodium or bladder installations, including dimethyl sulfoxide, bacillus Calmette-Guerin, Chloropectin or heparin
Uncontrolled diabetes
Diabetes with peripheral nerve involvement
Neurological disease like multiple sclerosis, Parkinson's disease, cerebrovascular accident, bifid spine or spinal cord lesion
Physiotherapy during the study
Bladder outlet obstruction (Abrams-Griffiths nomogram)
Transurethral instrumentation 4 weeks or less before or during the study

All patients paused maintenance PTNS for a 6-week period, and were re-treated after this period in outpatients' setting. PTNS was performed as described by van Balken et al.[1]. A low-voltage (9V) stimulator (Urgent-PC®, CystoMedix Inc, Anoka, MN, USA) was used. The stimulator had an adjustable stimulation intensity

0-10 mA and fixed stimulation parameters: pulse width 200 microseconds, pulse rate 20 Hz. All patients had a sensory response to the stimulation: a radiating sensation at the sole of the foot and in the toes. Stimulation at the intensity of the motor response was too painful for almost all patients, so the current was set at a well-tolerable level resulting in the sensory response. If patients had adapted to the stimulation the current was adjusted, usually as soon as the sensation faded away. Patients were treated with 30-minute treatment sessions 3 times a week during a 4-week period. PTNS was performed on Monday, Wednesday and Friday of each week.

At baseline (before the 6-week pause of maintenance PTNS, T1) patients were evaluated by 24-hour bladder diaries, as well as general (36-item short-form health survey, SF-36)[8] and disease specific quality of life (incontinence-specific quality of life assessment, I-QoL) questionnaires[9]. This procedure was repeated after the 6-week pause (T2), and after PTNS re-treatment (T3). In the bladder diary micturition frequency, voided volume (cc), number of incontinence episodes, severity of urine loss and the number of used pads were recorded. The severity of urine loss was described on a scale of 0-3 (i.e. 0– no urine loss, 1– loss of some drops, 2– loss of small amount and 3– change of clothes due to urine loss).

The first objective was defined as a $\geq$50% increase of the number of incontinence episodes and/or number of voids on bladder diary after the 6-week interruption of the maintenance PTNS. The second objective was defined as a $\geq$50% reduction of the number of incontinence episodes and/or number of voids on bladder diary after PTNS re-treatment. Comparison of the results before and after pausing maintenance PTNS and re-treatment were conducted with the Wilcoxon signed Ranks Test; the statistical analysis was performed with commercial software (SPSS version 10, Chicago, IL, USA).

RESULTS

At T1 (before the 6-week interruption of maintenance PTNS), the patients who performed self-administered home treatment (i.e. self-treatment group, 6 patients) tended to have lesser voiding parameters and quality of life compared to the patients who received maintenance treatment in an outpatient setting (i.e. outpatient group, 5 patients) (TABLE 2 and 3). However statistical significance could not be determinated since the patient groups were too small.

At T2 (after 6-week pause of maintenance PTNS) 7 out of the 11 patients (64%)

met the first objective and had ≥ 50% increase of the number of incontinence episodes and/or number of voids on bladder diary. 2 patients, who performed self-administered home treatment, had a deterioration of their symptoms but did not meet the first objective and 2 patients had no change of their symptoms on bladder diary, of which 1 performed self-treatment and another had maintenance treatment in an outpatient setting. All patients experienced a subjective deterioration of their symptoms. There was an objective significant deterioration ($p<0.05$) of nocturia, mean voided volume, and number of incontinences episodes and the SF-36 domain pain (TABLE 2 and 3).

The self-treatment group tended to still have slightly lesser voiding and quality of life parameters, compared to the outpatient group. However, statistical significance could again not be determinated due to the small patient groups.

During PTNS a mean pulse intensity of 3.8 mA (range 1.6-7.8) was used. Complications of the therapy – minor bleeding or a temporary painful/numb feeling at the insertion site or under the sole of the foot – rarely occurred.

At T3 (after PTNS re-treatment) 9 out of the 11 patients (82%) met the second objective and had a ≥ 50% reduction of the number of incontinence episodes and/or number of voids on bladder diary. 2 patients had no improvement on bladder diary, of which 1 patient performed self-treatment and another had maintenance PTNS in an outpatient setting. 8 patients (73%) did again subjectively improve and wanted to continue the treatment. There was a significant ($p<0.05$) improvement of nocturia, mean voided volume, number of incontinence episodes, incontinence severity, I-QoL score and the SF-36 domains physical, role emotional, social function, pain and mental health (TABLE 2 and 3).

At T3 (after PTNS re-treatment) the difference with the data at T1 (before the 6-week interruption) tended to be the largest in the self-treatment group. Again statistical significance could not be determinated due to the small patient groups.

TABLE 2 Voiding parameters at T1 to T3 in 11 patients

Parameters per 24 hours	Mean (SD)		
	T1·	T2··	T3···
Number of voids			
Home[1]	12.5 (7.3)	13.0 (8.3)	8.5 (1.9)
Clinic[2]	9.2 (2.9)	10.8 (4.1)	10.0 (3.9)
All patients	11.0 (5.8)	12.0 (6.5)	9.2 (2.9)
Nocturia			
Home[1]	1.7 (1.4)	3.7 (4.2)	0.7 (0.5)
Clinic[2]	1.0 (0.7)	2.2 (1.3)	0.6 (0.9)
All patients	1.4 (1.1)	3.0 (3.2)*	0.6 (0.7)*
Mean voided volume (mL)			
Home[1]	190.3 (123.3)	95.8 (62.0)	222.0 (124.2)
Clinic[2]	174.0 (60.1)	121.6 (37.1)	146.0 (45.4)
All patients	182.9 (95.5)	107.6 (51.5)*	187.5 (100.6)*
Number of incontinence episodes			
Home[1]	1.3 (2.4)	3.5 (4.5)	1.0 (1.5)
Clinic[2]	2.6 (2.7)	12.0 (16.8)	5.6 (6.4)
All patients	1.9 (2.5)	7.4 (12.0)*	3.1 (4.9)*
Incontinence severity[3]			
Home[1]	0.3 (0.5)	1.2 (1.2)	0.8 (0.5)
Clinic[2]	1.0 (0.7)	1.4 (0.5)	0.6 (0.5)
All patients	0.6 (0.7)	1.3 (0.9)	0.6 (0.5)*
Number of used pads			
Home[1]	1.5 (2.0)	2.2 (2.9)	0.7 (1.5)
Clinic[2]	2.0 (1.0)	3.6 (2.4)	2.6 (1.5)
All patients	1.7 (1.6)	2.8 (2.6)	1.6 (1.5)*

*·Baseline, ··After 6-week pause of maintenance PTNS, ···After PTNS-retreatment, *p<0.05, [1]6 patients who performed self-administered maintenance PTNS at home, [2]5 patients who had maintenance PTNS in an outpatient setting, [3]0= no urine loss, 1= loss of some drops, 2= loss of small amount and 3= change of clothes due to urine loss*

TABLE 3 Quality of life parameters at T1 to T3 in 11 patients

Parameters per 24 hours	Mean (SD)		
	T1·	T2··	T3···
SF-36 domains			
Physical			
Home[1]	80.8 (16.9)	75.8 (28.4)	96.7 (4.1)
Clinic[2]	79.0 (21.0)	70.0 (22.1)	81.0 (19.5)
All patients	80.0 (5.4)	73.2 (7.4)	89.5 (4.5)*
Role physical			
Home[1]	62.5 (49.4)	45.8 (51.0)	95.8 (10.2)
Clinic[2]	55.0 (51.2)	55.0 (51.2)	70.0 (44.7)
All patients	59.1 (14.4)	50.0 (14.7)	84.1 (9.7)
Role emotional			
Home[1]	94.5 (13.6)	61.1 (39.0)	94.5 (13.6)
Clinic[2]	73.3 (43.5)	66.8 (40.8)	93.3 (14.9)
All patients	84.9 (9.4)	63.6 (11.4)	93.9 (4.1)*
Social function			
Home[1]	66.7 (20.4)	58.3 (30.3)	81.3 (19.0)
Clinic[2]	75.0 (23.4)	50.0 (15.3)	80.0 (14.3)
All patients	70.5 (6.4)	54.5 (7.2)	80.7 (4.9)*
Pain			
Home[1]	79.5 (27.9)	64.3 (30.7)	82.8 (18.8)
Clinic[2]	73.4 (30.6)	51.2 (16.8)	75.0 (25.4)
All patients	76.7 (8.4)	58.4 (7.6)*	79.3 (6.4)*
Mental health			
Home[1]	61.3 (12.08)	58.0 (18.5)	72.0 (13.4)
Clinic[2]	72.0 (17.2)	69.6 (16.4)	80.0 (14.7)
All patients	66.2 (4.6)	63.3 (5.4)	75.6 (4.2)*
Vitality			
Home[1]	60.0 (23.2)	46.7 (24.2)	67.5 (12.9)
Clinic[2]	65.0 (25.5)	67.0 (20.8)	71.0 (20.4)
All patients	62.3 (7.0)	55.9 (7.3)	69.1 (4.8)
General health			
Home[1]	61.8 (27.8)	56.0 (24.1)	66.3 (12.6)
Clinic[2]	64.4 (14.1)	58.4 (26.5)	66.2 (20.5)
All patients	63.0 (6.5)	57.1 (7.2)	66.3 (4.7)
I-QoL			
Home[1]	67.3 (19.7)	61.0 (15.9)	88.0 (15.7)
Clinic[2]	80.2 (14.7)	67.0 (23.7)	77.8 (18.3)
All patients	73.2 (18.1)	63.7 (19.0)	83.4 (16.9)*

*·Baseline, ··After 6-week pause of maintenance PTNS, ···After PTNS-retreatment, *p<0.05, [1]6 patients who performed self-administered maintenance PTNS at home, [2]5 patients who had maintenance PTNS in an outpatient setting*

DISCUSSION

The present study stresses that maintenance treatment is a necessity in successfully PTNS treated patients. All patients had subjective and 9 out of 11 patients an objective deterioration of complaints after the 6-week pause of maintenance therapy. Moreover, there was a significant deterioration of mean voided volume, nocturia, number of incontinence episodes and quality of life (TABLE 2 and 3). The observation that not all parameters did significantly change is obviously caused by the small patient population. Furthermore, 2 patients did not respond to the interruption of maintenance PTNS or re-treatment. In retrospect, PTNS was probably not effective in these patients in the first place.

Another explanation could be that 6 out of the 11 patients who performed self-administered home therapy – either percutaneous or transcutaneous tibial nerve stimulation – could have done this suboptimally. This is supported by the tendency that the voiding and quality of life parameters of the self-treatment group seemed to be lesser than the outpatient group. Moreover, the difference between the voiding and quality of life parameters at T1 and T3 seemed to be larger for the self-treatment group than for the outpatient group, however not significant.

The difference between both groups was to be expected, since all patients of the self-treatment group, except one, performed transcutaneous maintenance PTNS. Up till now, no comparing study has been performed to determine whether transcutaneous stimulation is as effective as percutaneous treatment. PTNS seems to be more effective, since the electrical field is created between a stick-electrode and a needle, which is close to the tibial nerve. Low currency is needed for the motor response (flexing the big toe and/or fanning of the other toes) and sensory response (a radiating sensation at the sole of the foot and in the toes) to occur. In the case of transcutaneous stimulation, the electrical field is created between two surface stick-electrodes. The current has to overcome the impedance of the skin before it has its effect on the tibial nerve. Therefore, in theory, for transcutaneous stimulation a larger current is needed to evoke the motor and sensory responses compared to the percutaneous needle stimulation. When larger amplitude is applied, more afferent nerves located in the skin are recruited and stimulated, which can lead to a painful sensation. This could result in suboptimal stimulation when patients stimulate themselves at a well-tolerable level.

Our results do not only support the notion that maintenance therapy is indispensable to keep up positive clinical results. Obviously, such maintenance programs put great strains on caregivers and hospital facilities. Each patient that is put on a

maintenance schedule will visit the outpatients' department at least 20 to 30 times per annum. This problem was the basis for new developments in the field of tibial nerve stimulation. Currently clinical work is undertaken to develop an implantable device that allows a patient to stimulate himself at home as frequently as the individual situation requires. In prospect, this implantable device will lessen the burden on medical professionals and institutions.

CONCLUSIONS

Maintenance treatment is a necessity in successfully PTNS treated patients, since they experience a subjective an objective deterioration of their complaints when it is not provided. The efficacy of PTNS is reproducible in these patients.

CONFLICT OF INTEREST

None declared. The study was supported by an unrestricted grant from CystoMedix Inc., Anoka, MN, USA.

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Tibial nerve stimulation by implant in the treatment of refractory overactive bladder syndrome: 12-month follow up

CHAPTER 7

F. VAN DER PAL
M.R. VAN BALKEN
J.P.F.A. HEESAKKERS
F.M.J. DEBRUYNE
B.L.H. BEMELMANS

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ABSTRACT

Objectives
To investigate feasibility and safety of implant driven tibial nerve stimulation.

Methods
8 patients with refractory overactive bladder syndrome were successfully treated with percutaneous tibial nerve stimulation and implanted. Patients were evaluated with bladder diaries, quality of life questionnaires, and physical examination before implantation, and at 3, 6 and 12 months of follow up. The primary objective was a $\geq$ 50% reduction of the number of incontinence episodes and/or voids on bladder diary. The Wilcoxon Signed Ranks Test was used.

Results
At 3, 6 and 12 months respectively 5, 6 and 4 patients met the primary objective. At 3 and 6-month follow up voiding and quality of life parameters had significantly ($p<0.05$) improved. Urinary tract infection, temporarily walking difficulties, and spontaneous radiating sensations were reported as adverse events but no local infection, erosion or dislocation.

Conclusions
Implant driven tibial nerve stimulation seems to be feasible and safe.

INTRODUCTION

Overactive bladder syndrome (OAB, overactive bladder wet and dry) is a common urological problem in many countries. It has been estimated that OAB affects approximately 17% of the adult population in Europe and the United States[1,2], with an estimated worldwide prevalence of 50-100 million[3]. The economic burden of OAB can only be estimated since the disorder is underreported and often overlooked by physicians[4]. Total annual costs, including treatment and diagnosis, absorbent products, related medical conditions, assisted living or nursing home care, lost wages and cleaning expenses are estimated to range from $16 billion to $26 billion each year in the United States, depending on the studied age group[5,6]. In the future the impact of OAB will probably increase even further, since the world population is aging[4] and the prevalence increases with age[7]).

OAB is initially treated with conservative therapy. If refractory, irreversible surgery can be advocated. However, this is not widespread due to high recurrence and complication rates[8]. Percutaneous tibial nerve stimulation (PTNS) is an alternative therapy in the treatment of refractory OAB, with reported clinical success rates of 63-71%[8-10]. It is known that PTNS maintenance therapy is a necessity in successfully treated patients[11], usually once every 2-3 weeks[9]. This is demanding for both patients and outpatient departments. Therefore, it would be advantageous if the patients themselves at the location and time of their choice could perform maintenance therapy. Surface electrodes can be used for tibial nerve stimulation, as has been demonstrated by Andrews[12]. However, there are indications that transcutaneous tibial nerve stimulation may be less effective than percutaneous stimulation[13]. There are no randomized studies to confirm this yet, nevertheless surface electrodes were not considered for self-administrated maintenance treatment.

Ongoing research has led to the design and development of an innovative subcutaneous implant – Urgent-SQ™ (CystoMedix Inc., Anoka, MN, USA) – that enables self-treatment. This pilot study presents results concerning the feasibility and safety at 12 months of follow up in 8 patients with refractory OAB.

METHODS

With the approval of the institutional review board 8 patients with refractory OAB were enrolled in a prospective pilot study between November 2002 and January 2004. All patients gave written informed consent to the study. Implantations were performed in either November 2003 or January 2004.

Methods, units and definitions used in this study all conform to the standards recommended by the International Continence Society[14], except for the 24-hour bladder diary[15]. A 24-hour bladder diary is sufficient to evaluate the patients' micturition complaints[16-18]. OAB was defined as more than 7 voids and/or a sudden compelling urge to void, culminating in urinary leakage at least 3 times per 24 hours on bladder diary. All medication that could influence bladder function was stopped at least 2 weeks before treatment or continued without dose changes during the entire study. For this study specific exclusion criteria as described by van Balken et al.[8] were used.

The primary objective of the study was defined as $\geq$ 50% reduction of the number of incontinence episodes and/or voids on bladder diary after implant driven tibial nerve stimulation. Apart from feasibility a secondary objective was to evaluate the safety of the implant.

Patients

2 male and 6 female patients (mean age 56 years, range 46-66) had had OAB complaints for a mean period of 10 years (range 1-30) and were enrolled in the study. Prior to enrolment, patients were evaluated for OAB by history, physical examination and urological examination, including urodynamic investigation. All patients had an urodynamic evaluation without abnormalities, except for one patient who showed late onset detrusor overactivity. All patients had been unsuccessfully treated with conservative treatment. 3 patients had had unsuccessful surgery (range 1-2 operations) for their symptoms. Colposuspension, Botulinum toxin A injections in the bladder and urethral dilatation were performed. All patients had been successfully treated with PTNS ($\geq$ 50% reduction of the number incontinence episodes and/or voids on bladder diary).

Method of treatment

PTNS was performed as described by van Balken et al.[8]. Patients were treated with 30-minute sessions, 3 times a week during a 4-week period. Until implantation no maintenance PTNS was provided for a mean period of 8 months (range 3-12).

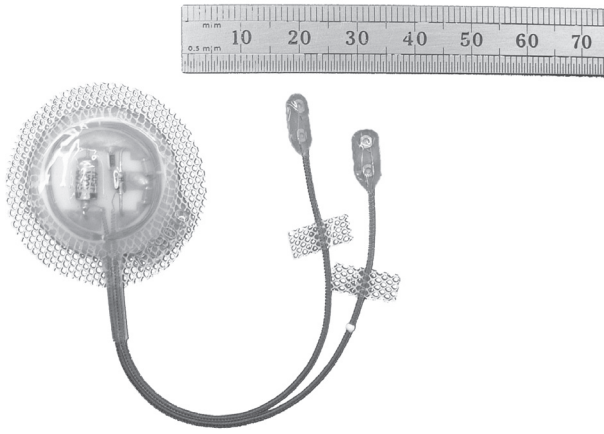
The Urgent-SQ™ consists of an external electromagnetic pulse generator with radio-frequency (RF) transmission capability (FIGURE 1) and an internal electromagnetic pulse receiver, the body, with two leads and monopolar electrodes, which are covered by medical grade silicones with the leads having platinum electrodes (FIGURE 2). The electrodes are approximately 1 cm2. The body has a diameter of approximately 4 cm and receives RF electromagnetic pulses from the generator transforming them into current pulses. Stimulation parameters are: 0-19 mA am-

plitude, 12 or 20 Hz pulse rate and 200 msec pulse width. The maximum amplitude was not altered during follow up. The pulses are biphasic and symmetrical. The 12 Hz pulse rate was chosen, since 1 patient did only respond to PTNS at 12 Hz. The external stimulator has to be placed directly on the skin over the internal body in order to activate it. Therefore, the amplitude will not be influenced by the coil position and the internal body will not be activated by other high frequency devices, such as mobile telephones.

Pre- and postoperatively prophylactic oral antibiotics (500 mg amoxicillin) were given. Patients were implanted in the supine position and were covered with sterile drapes after an antiseptic scrub of the lower leg. After spinal or general anaesthesia an incision of 5-7 cm was made approximately 5 cm above the medial malleolus, parallel to the tibia. Muscle relaxants were avoided in order not to blur a motor response of the foot musculature. After incising the fascia of the flexor tendons the electrodes were placed near the neurovascular bundle that contains the tibial nerve, without exposing it. The electrodes were parallelly placed and the distance between them was approximately 1 cm. The internal body was placed in a subcutaneous pocket overlying the tibia. During the procedure the implant was activated at regular intervals to confirm correct functioning and placement. Similar to percutaneous stimulation, hallux flexion can be observed when positioned correctly. If correct placement was confirmed the implant was fixed, and the wound was closed.

FIGURE 1 The External stimulator

FIGURE 2 The internal body with 2 leads and monopolar electrodes



Motor and sensory responses were evaluated postoperatively at day 10 and at follow up at 3, 6 and 12 months. The responses were tested by a physician, who correctly placed the external stimulator and slowly increased the amplitude until the sensory response was present. The amplitude was further increased until the motor response occurred or to maximum amplitude (19 mA), which was not painful for the patients. There were no limitations to test the responses. Therapy was started at home postoperatively at day 10, each session lasting 30 minutes 3 times a week. The stimulation was performed at the amplitude resulting in the sensory response and adjusted when it had faded, as has been described for PTNS[8].

Patients were evaluated by 24-hour bladder diaries, and quality of life questionnaires: SF-36 social function[19] and I-QoL (index of quality of life)[20] before implantation and at follow up of 3, 6, and 12 months of implant driven tibial nerve stimulation. Physical examination and urinalysis were performed at all visits. X-rays in 2 directions of the medial ankle were made 1 day and 1 month postoperatively to verify the position of the implant. During follow up no urodynamic evaluations were performed, nor was sham stimulation performed, nor were the stimulators turned off. Furthermore, it was not possible to determine whether the patients had actually treated themselves, nor changed the stimulation frequency and amplitude.

Changes in the voiding and quality of life parameters were tested on statistical significance using the Wilcoxon Signed Ranks Test.

RESULTS

After cessation of the PTNS treatment in all patients voiding and quality of life parameters returned to baseline values as before PTNS.

The surgical procedure was straightforward without complications. Mean operating time was 25 minutes (range 20-30). Patients were discharged after 2 days of bed rest and leg elevation. The implant was not visible from the outside.

The individual results during follow up are presented in TABLE 1 and 2. The motor responses were present intra-operatively in all patients and in none at postoperative day 10. The sensory response (i.e. a radiating sensation at the sole of the foot and toes) was present 10 days postoperatively in 6 patients. 7 patients were treated with a frequency setting at 20 Hz and 12 Hz in 1 patient.

TABLE 1 The individual results during follow up in 8 patients

	Patient							
	1	2	3	4	5	6	7	8
Sex	M[1]	F[1]	F[1]	F[1]	M[1]	F[1]	F[2]	F[1]
Age (years)	49	65	66	46	50	48	62	64
Postoperative day 10	*		*	*				
Responses	m-	m-	m-	m-	m-	m-	m-	m-
	s+	s+	s+	s+	s-	s+	s-	s+
Stimulation frequency	b	c	a	b	a	b	c	c
3 months of STNS								
Responses	m+	m+	m+	m+	m+	m-	m+	m-
	s+	s+	s+	s+	s+	s+	s+	s+
Successful treatment	-	+	-	-	+	+	+	+
6 months of STNS			‡					
Responses	m+	m+	m+	m+	m+	m-	m+	m-
	s+	s+	s+	s+	s+	s+	s+	s+
Successful treatment	+	+	-	+	+	- †	+	+
12 months of STNS								
Responses	m+	m+	m+	m+	m+	**	m+	m-
	s+	s+	s+	s+	s+		s+	s-
Succesful treatment	-	+	-	+	+	-	+	-†

*+present, -absent, [1]20 Hz pulse rate, [2]12Hz pulse rate, [M]male, [F]female, *walking difficulties, ‡urinary tract infection, †unexplainable loss of efficacy, **dropped out of the study, [a]daily stimulation, [b]stimulation 3 times a week, [c]weekly stimulation, [m]motor response, [s]sensory response*

At the 1-month follow up, X-rays showed no dislocation of the implant and no cable breach in any of the patients. For home-based stimulation, patients adjusted the stimulation schedule to their individual needs.

At the 3-months follow up, 5 patients met the primary objective and were considered a success. There was a significant improvement in number of voids, incontinence episodes and I-QoI score (TABLE 3). The motor and sensory responses were respectively present in 6 and 8 patients. 3 patients still performed implant driven tibial nerve stimulation 3 times per week, 2 patients once per week and 3 patients daily.

TABLE 2 Individual voiding and quality of life parameters in 8 patients at baseline, 3 and 6 months of follow up and in 7 patients at 12 months of follow up

Parameters per 24 hour	Patient							
	1	2	3	4	5	6	7	8
Number of voids								
Baseline	16	9	15	12	23	14	8	18
3-month follow up	10	9	9	8	9	13	6	11
6-month follow up	7	13	13	9	11	17	8	9
12-month follow up	9	12	16	10	9		10	15
Nocturia								
Baseline	5	1	3	3	3	2	1	5
3-month follow up	5	1	0	0	2	3	0	3
6-month follow up	3	2	1	0	1	3	1	2
12-month follow up	3	3	2	2	2		1	2
Mean voided volume (cc)								
Baseline	104	209	120	170	17	90	127	153
3-month follow up	135	242	233	123	27	65	117	145
6-month follow up	114	174	133	206	32	49	114	133
12-month follow up	156	158	222	190	44		167	142
Number of incontinence episodes								
Baseline	0	3	0	12	0	40	6	13
3-month follow up	0	1	0	5	0	17	2	6
6-month follow up	0	0	0	6	0	21	0	2
12-month follow up	0	1	0	4	0		0	8
Incontinence severity[1]								
Baseline	0	2	0	2	0	1	2	2
3-month follow up	0	1	0	1	0	1	2	2
6-month follow up	0	0	0	1	0	1	0	2
12-month follow up	0	1	0	1	0		0	2
Number of used pads								
Baseline	0	3	2	4	0	6	6	2
3-month follow up	0	2	1	2	0	5	2	3
6-month follow up	0	2	2	0	0	6	1	2
12-month follow up	0	2	2	2	0		2	7
I-QoL score								
Baseline	69	88	68	62	51	47	80	48
3-month follow up	84	97	98	71	96	61	101	52
6-month follow up	84	105	89	80	96	52	105	81
12-month follow up	82	99	76	81	97		99	51

[1]*0= no urine loss, 1= loss of some drops, 2= loss of small amount, 3=change of clothes due to urine loss*

At the 6-month follow up, 6 patients met the primary objective. Compared to the 3-month follow up, voiding and quality of life parameters had not significantly changed except for the SF-36 domain general health ($p<0.05$). Compared to before implantation, number of incontinence episodes, I-QoL score (TABLE 3), and SF-36 domains social function and vitality had significantly ($p<0.05$) improved. Compared to the results after PTNS, voiding and quality of life parameters were similar, except for mean voided volume, which had significantly decreased ($p<0.05$). Patients had not changed their treatment schedule.
At the 12-month follow up, 5 patients had improved on bladder diary and 4 of these patients met the primary objective. Compared to the data before implantation and at 6-month follow up there were no significant changes in the voiding and quality of life parameters. Compared to the results of PTNS, voiding and quality of life parameters were similar and without significant differences. The motor response was present in 6 and the sensory response in 7 patients. Patients had not changed their treatment schedule. All patients who completed the 1-year follow up were satisfied with the results of the implant.

TABLE 3 Voiding and quality of life parameters before implantation, at 3 and 6 months of implant driven tibial nerve stimulation in 8 patients, and at 12 months in 7 patients

Parameters per 24 hours	Mean (SD)			
	Before implantation	3-month follow up	6-month follow up	12-month of follow up
Number of voids	14.4 (4.9)	9.4 (2.1)*	10.9 (3.3)	11.6 (2.9)
Nocturia	2.9 (1.6)	1.8 (1.8)	1.6 (1.1)	2.1 (0.7)
Mean voided volume (cc)	123.8 (57.6)	135.9 (73.9)	119.4 (58.0)	154.1 (55.3)
Number of incontinence episodes	9.3 (13.5)	3.9 (5.8)*	3.6 (7.3)*	1.9 (3.0)
Number of used pads	2.9 (2.4)	1.9 (1.6)	1.6 (2.0)	2.1 (2.3)
I-QoL score	64.1 (15.1)	82.5 18.9)*	86.5 17.1)*	83.6 (17.2)

**compared to before implantation and p<0.05*

Directly after the operation 3 patients reported difficulties when walking or standing on the operated leg due to wound pain. Two of these patients received physiotherapy for their complaints, which had disappeared within 2-3 weeks without

further intervention. Moreover, these patients had not used the prescribed analgesics. Postoperatively, 7 patients reported spontaneous radiating sensations (i.e. sensory response without activation of the implant), which disappeared without any intervention within 3 months in all patients except one. Before the 3-month follow up and at 6 months one patient had a urinary tract infection, which was treated with antibiotics. During follow up no other adverse events were reported, such as local infection, dislocation or erosion. The adverse events are summarised in TABLE 4.

TABLE 4 Reported adverse events in 8 implanted patients during 12 months of follow up

Adverse events	Number of patients
Walking difficulties	3
Spontaneous sensory response	7
Urinary tract infection	2

At 6 months of implant driven tibial nerve stimulation, one patient had an unexplainable loss of efficacy while still having the sensory response (the motor response had been present only intra-operatively). Technical problems like lead dislocation were ruled out on X-ray. However, lead wire breach can not be ruled out since no surface mapping was performed. Switching the stimulation frequency to 12 Hz had no result; neither had PTNS re-treatment. Afterwards the patient dropped out of the study and the treatment was considered unsuccessful.

At 12-month follow up, another patient had an unexplainable loss of efficacy. This patient had lost the sensory response to the implant driven tibial nerve stimulation (the motor response had only intra-operatively been present). Technical (dislocation) and physical causes were ruled out on respectively X-ray and physical examination, including neurological examination. However, since no surface mapping was performed, therefore lead wire breach can not be ruled out. The patient was successfully re-treated with PTNS. Afterwards, the Urgent-SQ™ was explanted at the patients' request. During explantation the implant was activated, which did not result in a motor response. The device was examined; however no results are available yet.

DISCUSSION

Implant driven tibial nerve stimulation seems to be feasible, since both sensory and motor responses were present postoperatively. The occurring loss of the motor response at maximal amplitude (temporarily in 6 and lasting in 2 patients) may have been caused by edema and/or fibrosis around the electrodes, since after the edema had disappeared the response occurred in 6 out of the 8 patients.

At 3, 6 and 12 months of follow up, respectively 5, 6 and 4 patients were successfully treated. The fact that not all voiding and quality of life parameters improved significantly at follow up can most probably be explained by the small number of patients included in this pilot study, the fact that at the 6-month evaluation one patient had a urinary tract infection (the patient was not re-evaluated after treatment) and by the unexplainable loss of stimulation efficacy in 2 patients at 6 and 12 months of follow up. Moreover, when the data at 6 months of implant driven tibial nerve stimulation are corrected for the urinary tract infection and the unexplainable loss of efficacy, these are similar to the data after PTNS.

Due to the small patient population it was impossible to determine whether the preoperative urodynamic outcome correlates with the efficacy of the implant. However, it is to be expected that patients with urodynamic stable bladders or late onset detrusor overactivity are the best candidates for implant driven tibial nerve stimulation, as has been described for PTNS[21].

Also, because of the small patient population, it was impossible to determine whether the presence of the motor and/or sensory responses correlates with the efficacy of the implant. To date this has not been determined for PTNS either. Percutaneous tibial nerve stimulation is performed at an amplitude resulting in the sensory response with adjustment of the amplitude when the response has faded[8,9]. Moreover, stimulation at amplitude resulting in the motor response is too painful for most patients. Therefore, implant driven tibial nerve stimulation was performed similar to PTNS. As with PTNS, implant driven stimulation at the level of the motor response is too painful for most patients.

The observation that not all patients who respond well on percutaneous stimulation do the same on subcutaneous stimulation, is known from studies concerning sacral nerve stimulation; the same goes for loss of efficacy[22-24]. The difference between percutaneous and implant driven tibial nerve stimulation could be that for implant driven stimulation it was impossible to determine whether the patients had actually treated themselves or not. Moreover the stimulation amplitude was

not recorded, so it is possible that the patients had treated themselves at too low amplitude. Another possibility is that the placebo effect is larger for implant driven tibial nerve stimulation than for PTNS. For the latter a randomized double-blinded placebo-controlled study is being performed to determine whether PTNS is more than a placebo effect; however results are not available jet. It seems likely that the PTNS placebo effect is similar to that of pharmacotherapy in the treatment of OAB. Pharmacotherapeutic placebo-controlled trials have reported placebo effects of 28-43% in patients with urge urinary incontinence[25-27]. A larger study is needed to make conclusions concerning the efficacy of the implant.

Patients were discharged after 2 days, which is a relatively long period for such a procedure. This was caused by the fact that these patients were the first to be operated on, which led to increased caution. Probably we were too careful and we anticipate that future patients will be discharged at the same day.

During the 12-month follow up implant driven tibial nerve stimulation proved to be safe. No local infection, spontaneous dislocation or erosion of the Urgent-SQ™ had occurred during follow up. Postoperatively, 3 patients had walking difficulties due to pain caused by the surgery. These complaints had disappeared completely within 2-3 weeks. Moreover, these patients used no the prescribed analgesics. During the 12-month follow up 2 patients had a urinary tract infection. These patients were known to have had some recurrent urinary tract infections in the past. 7 patients postoperatively mentioned a sudden radiating sensation, which disappeared without intervention within 3 months in all patients except one. In this patient the sudden radiating sensations are still present, but occur rarely. Long-term follow up is needed to determine the safety of the implant during chronic use.

Other implantable devices are available for neuromodulative treatment of lower urinary tract dysfunction[28-30]. For all devices a pre-operative eligibility test is performed to determine whether the patient is a deemed candidate. Of these implantable devices sacral nerve stimulation (SNS) has proven to be effective and safe[30-33]. Side effects have been reported such as pain in the buttocks, pelvic area, lower extremities and at the pulse generator (Interstim®, Medtronic, Minneapolis, Minnesota, USA) site, lead migration, infection at test stimulation lead site, transient electric shock, re-operations due to technical problems and adverse change of urinary, bowel or sexual function[30-36]. For pudendal nerve stimulation by the Bion® microstimulator (Advanced Bionics Corp., Valencia, CA), vaginal fungus infection, allergic reaction, vaginal dryness during intercourse, mechanical irritation during bicycle riding and altered bowel functions[28] have been reported. Skin erosion at the connection site between lead and extension cable for pudendal

nerve stimulation by definitive quadripolar tined lead, as is used for SNS[29]. For PTNS minimal hematoma and transient pain at the insertion site have been described[9,37]. The Urgent-SQ™ could be an alternative. Implant driven tibial nerve stimulation is minimal invasive and adverse events like infection or dislocation did not occur in this study. Furthermore, the internal body contains no internal battery that has to be replaced in time, as is the case with SNS and the devices for pudendal nerve stimulation. Patients experience no mechanical problems due to the implant, which is invisible at the outside. Finally, during the 12-month follow up only urinary tract infection, transient walking difficulties and spontaneous sensory responses were reported as adverse events. All patients who completed the 1-year follow up were satisfied with the result. In order to define the proper place of the Urgent- SQ™ in the treatment of lower urinary tract dysfunction, comparative studies are needed.

CONCLUSIONS

Implant driven tibial nerve stimulation with the Urgent-SQ™ device seems to be feasible and safe during short-term follow up in patients with refractory OAB. A study with a larger population and long-term follow up has to be performed to determine the efficacy and long-term safety of the implant.

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CONFLICT OF INTEREST

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Summary and conclusions

CHAPTER 8

SUMMARY AND CONCLUSIONS

CHAPTER 1 provides the introduction to the present thesis, which contains a description of lower urinary tract dysfunction and the different therapies. Furthermore, the aims of this thesis are presented.

CHAPTER 2 discusses the physiology and the innervation of the bladder, as well as the continence and micturition processes.

CHAPTER 3 presents the current opinion on the working mechanism of neuromodulation. An overview is presented of the different theories and research into the physiological background of neuromodulation in the last 35 years, with emphasis on recent developments. It can be concluded that in the treatment of stress incontinence neuromodulation probably induces physiological changes in the sphincter muscles and pelvic floor. In the treatment of overactive bladder syndrome, non-obstructive voiding dysfunction and chronic pelvic pain the mechanism of action seems to be more complicated. Most likely it is a combination of the different suggested modes of action, involving the neuroaxis at different levels.

CHAPTER 4 investigates whether PTNS can modulate the micturition reflex in an anaesthetised female cat model. Moreover, it is determined whether the sacral plexus is involved in the working mechanism of PTNS. It can be concluded that the cat model is suitable to investigate the effect of PTNS on the micturition reflex. It was demonstrated that PTNS modulates the micturition reflex, since the volume at which the micturition reflex occurred (micturition reflex volume, MRV) had increased from 54 ml (SD 26) at baseline to 71 ml (SD 30, $p= 0.001$) during stimulation. This effect was reversible, since mean MRV returned to 54 ml (SD 27, $p= 0.002$) in the continued cystometries. The effect of median nerve stimulation on the micturition reflex was investigated to determine the involvement of the sacral plexus in the working mechanism of PTNS, since both the median nerve (C_{6-8}) and the tibial nerve (L_4-S_3) contain sensory and motor nerve fibres. Stimulation of the median nerve had no effect on MRV, indicating that the sacral plexus seems to be involved in the modulation process of tibial nerve stimulation.

CHAPTER 5 investigates the assumption that the improved quality of life in PTNS treated patients is due to improved voiding parameters. It can be concluded that the improved voiding parameters do result in an improved quality of life in PTNS treated patients with refractory urge urinary incontinence. There was a significant ($p<0.05$) correlation between several quality of life parameters and voiding parameters. This indicates that PTNS has a useful place in the treatment of refractory

urge urinary incontinence (overactive bladder wet) and should at least be considered as a therapeutic alternative before turning to aggressive surgery. Patients must have a reduction of at least 2 used pads before their quality of life improves. This could be the best definition of successful therapy for patients with urge urinary incontinence.

CHAPTER 6 investigates whether maintenance treatment is necessary in successfully PTNS treated patients and whether successful treatment can be reproduced. It can be concluded that maintenance PTNS is a necessity in successfully treated patients with refractory OAB and that the efficacy of PTNS can be reproduced in formerly successfully treated patients. After pausing the maintenance treatment for a period of 6 weeks 7/11 patients (64%) had a $\geq$ 50% increase of the number of incontinence episodes and/or micturition frequency on bladder diary. Mean voided volume, nocturia, number of incontinence episodes and incontinence severity had significantly ($p<0.05$) deteriorated. After re-treatment 9/11 patients (82%) had a $\geq$ 50% reduction of the number of incontinence episodes and/or micturition frequency on bladder diary. Moreover, nocturia, number of incontinence episodes, incontinence severity, mean voided volume and quality of life had significantly ($p<0.05$) improved.

CHAPTER 7 investigates whether implant driven tibial nerve stimulation is feasible and safe in the treatment of refractory OAB. It can be concluded that implanted driven tibial nerve stimulation is feasible and safe during 1-year follow up. The implantation of the Urgent SQ™ itself was straightforward and without complications. Urinary tract infection, temporarily walking difficulties, and spontaneous radiating sensations were reported as adverse events during follow up, but no local infection, erosion or dislocation. Moreover voiding and quality of life parameters had significantly ($p<0.05$) improved. At 3, 6 and 12 months of implant driven tibial nerve stimulation, respectively 5, 6 and 4 patients out of the 8 implanted patients had a $\geq$ 50% reduction of the number of incontinence episodes and/or voids on bladder diary.

GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

PTNS seems to be effective since there is a correlation between the significantly improved voiding parameters and quality of life (CHAPTER 5). Moreover, these parameters deteriorate significantly when maintenance treatment is not provided, and successful treatment can be reproduced (CHAPTER 6). Furthermore, animal studies in cats demonstrate that the micturition reflex can be modulated by PTNS

(CHAPTER 4). It is tempting to extrapolate these results, since there are strong indications that at the brainstem and diencephalic level micturition is organized in the same way in humans[1]. However, to provide irrefutable proof that PTNS is more than a placebo effect randomized studies are needed. A randomized double-blinded placebo-controlled trial is being performed, but results are not available yet. When these results come available, the proper place of PTNS in the treatment of lower urinary tract dysfunction can be determined.

The first results of implant driven tibial nerve stimulation seem to be promising (CHAPTER 7). However, studies with a larger population and long-term follow up are needed to determine the efficacy and long-term safety of the implant. Moreover, the Urgent-SQ™ is not the only available implant for neuromodulative treatment[2-4]. Comparative studies should be performed to define the proper place of the Urgent- SQ™.

Until it has been determined whether tibial nerve stimulation has a place in the treatment of lower urinary tract dysfunction, PTNS should be at least considered before irreversible surgery is advocated. The treatment is safe, minimal invasive and not costly. When the proper place of PTNS has been established a consensus should be made on treatment indications, patient selection and treatment protocol (i.e. stimulation parameters, treatment schedules, evaluation methods and definition of successful treatment). And final, further research should be performed on the mechanism of action to investigate whether for instance increased sympathetic activity is involved or suprasacral (i.e. pontine and/or cortical) areas, as has been suggested by several authors[5;6].

The future directives of neuromodulation in general are very similar to those of tibial nerve stimulation. A consensus is needed on treatment indications, patient selection and treatment protocol. Further research is necessary to determine the mechanisms of action, the efficacy and the proper place of neuromodulation in the treatment of lower urinary tract dysfunction. Final, more selective or event-driven (detrusor overactivity or desire to void) stimulation should be investigated at more peripheral sites and with less invasive devices[7].

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Dutch summary and conclusions

CHAPTER 9

SAMENVATTING EN CONCLUSIES

HOOFDSTUK 1 vormt de inleiding van dit proefschrift. Hierin wordt beschreven wat disfunctie van de lagere urinewegen en de behandeling ervan inhouden. Tot slot worden de doelstellingen van het proefschrift beschreven.

HOOFDSTUK 2 geeft beschrijvingen van de fysiologie en de innervatie van de blaas. Daarnaast worden de processen van continentie en mictie besproken.

HOOFDSTUK 3 geeft een overzicht van de diverse theorieën over en het onderzoek naar de fysiologische achtergrond van neuromodulatie van de afgelopen 35 jaar. Hierbij ligt de nadruk op recente ontwikkelingen. Neuromodulatie in de behandeling van stress-incontinentie induceert zeer waarschijnlijk fysiologische veranderingen in de spiercellen van de blaassluitspier en de bekkenbodem. Bij de behandeling van de overactieve blaas, niet-obstructieve blaasretentie en chronisch bekkenpijn-syndroom lijkt het werkingsmechanisme ingewikkelder te zijn. Het betreft naar alle waarschijnlijkheid een combinatie van de verschillende veronderstelde werkingsmechanismen waarbij de neuroaxis op verschillende niveaus betrokken is.

In HOOFDSTUK 4 wordt onderzocht of het kattenmodel een geschikt diermodel is om het effect van PTNS op de mictiereflex te bepalen. In de eerste plaats wordt nagegaan of PTNS de mictiereflex kan moduleren. Tevens wordt onderzocht of de sacrale zenuwplexus betrokken is bij het werkingsmechanisme. De studie laat zien dat PTNS inderdaad de mictiereflex van de kat kan moduleren, aangezien het volume waarop de mictiereflex optreedt (mictiereflex volume, MRV) toenam van gemiddeld 54 ml (SD 26) in de uitgangssituatie naar gemiddeld 71 ml (SD 30, p= 0.001) tijdens stimulatie. Dit effect is omkeerbaar, aangezien in de daaropvolgende cystometrieën het MRV gemiddeld 54 ml (SD 27, p= 0.002) was. Het effect van de nervus medianus stimulatie werd onderzocht om te bepalen of de sacrale zenuwplexus betrokken is bij het werkingsmechanisme van PTNS, aangezien zowel de nervus medianus (C_{6-8}) als de nervus tibialis (L_4-S_3) sensorische en motorische zenuwvezels bevat. Stimulatie van de nervus medianus had geen effect op het MRV, wat betekent dat de sacrale zenuwplexus zeer waarschijnlijk betrokken is in het modulatieproces van PTNS.

HOOFDSTUK 5 gaat in op de veronderstelling dat verbetering van de mictieparameters leidt tot een verbeterde kwaliteit van leven bij patiënten die met PTNS zijn behandeld. Deze studie bevestigt die veronderstelling. Er is een significante ($p<0.05$) correlatie tussen verscheidene mictieparameters en de kwaliteit van leven. De

studie geeft dan ook aan dat PTNS een plek heeft in de behandeling van urge-incontinentie die niet reageert op de conservatieve behandeling (refractaire urge-incontinentie) en op zijn minst overwogen moet worden voordat wordt overgegaan op agressieve chirurgie. De kwaliteit van leven van deze patiënten verbetert indien ze minimaal 2 verbandjes per dag minder gebruiken. Dit zou wel eens de beste definitie van succesvolle therapie kunnen zijn.

In HOOFDSTUK 6 wordt onderzocht of een onderhoudsbehandeling noodzakelijk is voor patiënten met een refractaire overactieve blaas die succesvol zijn behandeld met PTNS. In de studie komt naar voren dat een onderhoudsbehandeling inderdaad noodzakelijk is en dat de effectiviteit van de behandeling reproduceerbaar is. Na onderbreking van de onderhoudsbehandeling voor een periode van 6 weken bleken 7 van de 11 patiënten (64%) een $\geq$ 50% toename te hebben van de mictiefrequentie en/of het aantal incontinentie episodes op de mictielijsten. Het gemiddeld geplaste volume, nycturie, het aantal incontinentie episodes en de ernst hiervan waren significant ($p<0.05$) verslechterd. Na herbehandeling hadden 9 van de 11 patiënten (82%) een $\geq$ 50% afname van de mictiefrequentie en/of het aantal incontinentie-episodes op de mictielijsten. Daarnaast waren het gemiddeld geplaste volume, nycturie, het aantal incontinentie-episodes en de ernst hiervan en, tot slot, de kwaliteit van leven significant ($p<0.05$) verbeterd.

In HOOFDSTUK 7 wordt onderzocht of stimulatie van de nervus tibialis met behulp van een implantaat, Urgent-SQ™, mogelijk en veilig is. Na een follow up van 1 jaar kan worden geconcludeerd dat stimulatie van de nervus tibialis met behulp van het implantaat inderdaad mogelijk en veilig is. De implantatie van de Urgent-SQ™ verliep eenvoudig en zonder complicaties. Tijdens follow up werden urineweginfectie, tijdelijke loopproblemen en spontane tintelingen onder de voetzool gemeld als bijwerkingen. Lokale infectie, erosie of dislocatie van het implantaat deden zich niet voor. Er was een significante ($p<0.05$) verbetering van de kwaliteit van leven en de mictieparameters. 3, 6 en 12 maanden na implantatie hadden respectievelijk 5, 6 en 4 van de 8 geïmplanteerde patiënten een $\geq$ 50% afname van de mictiefrequentie en/of het aantal incontinentie-episodes op de mictielijst.

ALGEMENE CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Percutane stimulatie van de nervus tibialis lijkt effectief te zijn, aangezien er een correlatie is tussen de significant verbeterde mictieparameters en de kwaliteit van leven van de behandelde patiënten (HOOFDSTUK 5). Bovendien verslechteren deze parameters significant als de onderhoudsbehandeling wordt gestopt en kan het

effect van de behandeling worden gereproduceerd (HOOFDSTUK 6). Verder toont het dieronderzoek met katten aan dat PTNS de mictiereflex inderdaad moduleert. Het is zeer verleidelijk om deze resultaten naar de mens te vertalen, aangezien er sterke aanwijzingen zijn dat bij katten en mensen de mictie op het niveau van de hersenstam en het diencephalon op dezelfde wijze wordt gereguleerd[1]. Er zijn echter gerandomiseerde studies nodig om onweerlegbaar aan te tonen dat PTNS meer is dan een placebo-effect. Een gerandomiseerde dubbel-geblindeerde placebo-gecontroleerde studie wordt momenteel uitgevoerd, maar de resultaten zijn nog niet beschikbaar. Wanneer deze beschikbaar komen, kan de juiste plaats van PTNS in de behandeling van refractaire disfunctie van de lagere urinewegen worden bepaald.

De eerste resultaten van nervus tibialis stimulatie met behulp van een implantaat zijn veelbelovend (HOOFDSTUK 7). Er zijn echter studies met een grotere patiëntenpopulatie en een langere follow up nodig om de effectiviteit en de veiligheid op de lange termijn te bepalen. Bovendien is de Urgent-SQ™ niet het enige beschikbare implantaat voor neuromodulatieve behandeling van lagere urineweg disfunctie[2-4]. Vergelijkende studies zijn dan ook nodig om de juiste plaats van de Urgent-SQ™ te bepalen.

Totdat duidelijk is of nervus tibialis stimulatie een plaats heeft in de behandeling van lagere urineweg disfunctie, moet PTNS op zijn minst overwogen worden voordat wordt overgegaan tot onomkeerbare chirurgie. De behandeling is immers veilig, minimaal invasief en niet duur. Als duidelijk is dat nervus tibialis stimulatie inderdaad een plaats heeft in de behandeling van deze klachten, moet er eenduidigheid komen ten aanzien van de behandelindicaties, patiëntenselectie en behandelprotocollen (stimulatieparameters, behandelschema's, evaluatiemethodes en de definitie van een succesvolle behandeling). Tot slot is meer onderzoek nodig naar het werkingsmechanisme; bijvoorbeeld naar verhoogde sympatische activatie en suprasacrale gebieden in de hersenen (hersenstam en cortex), zoals door diverse auteurs wordt gesuggereerd[5,6].

De toekomstverwachtingen voor neuromodulatie in algemene zin zijn vrijwel gelijk aan die van nervus tibialis stimulatie. Er is consensus nodig ten aanzien van de behandelindicaties, patiëntenselectie en behandelprotocollen. Tevens is meer onderzoek nodig naar het werkingsmechanisme, de effectiviteit en de plaats van neuromodulatie in de behandeling van refractaire lagere urineweg disfunctie. Tot slot is onderzoek nodig naar meer selectieve stimulatie of het stimuleren tijdens het optreden van blaasoveractiviteit of drang tot mictie. Daarbij moet ook gekeken worden naar stimulatie op meer perifere plaatsen en met behulp van minder invasieve apparatuur[7].

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CURRICULUM VITAE

Floor van der Pal werd geboren op 27 januari 1975 te Oldenzaal. In 1993 behaalde zij het VWO-diploma aan het Thij-college in diezelfde plaats. Daarna begon zij aan de studie Geneeskunde aan de Faculteit der Medische Wetenschappen van de Katholieke Universiteit Nijmegen, waar zij in 1998 met goed gevolg het doctoraal examen aflegde. Tijdens de daaropvolgende co-schappen werd haar interesse voor de urologie gewekt, wat bevestigd werd door haar keuze-co-schap op de afdeling urologie in het Bosch Medicentrum te 's-Hertogenbosch (begeleider Dr. J.W. Hoekstra) en haar wetenschappelijke stage op de afdeling urologie van het UMC St. Radboud ziekenhuis (begeleider Dr. J.A. Witjes). In 2001 behaalde zij het artsexamen en ging zij als AGNIO aan de slag op de afdeling urologie van het Bosch Medicentrum te 's-Hertogenbosch (Opleider Dr. J.W. Hoekstra). Tijdens deze periode werkte zij mee aan onderzoek naar de effectiviteit van nervus tibialis stimulatie in de behandeling van interstitiële cystitis. De resultaten van dit onderzoek werden gepresenteerd tijdens een bijeenkomst van de SANS-usersclub: hier werden tevens de eerste bouwstenen voor dit proefschrift gelegd. Van 1 april 2002 tot en met december 2005 was zij als arts-onderzoeker verbonden aan de afdeling urologie van het UMC St. Radboud ziekenhuis te Nijmegen. Tijdens deze periode verrichtte zij het onderzoek dat tot dit proefschrift heeft geleid en werd zij aangenomen voor de opleiding urologie (cluster Nijmegen, opleider Prof. Dr. F.M.J. Debruyne). Op 1 januari 2006 is zij gestart met de vooropleiding op de afdeling chirurgie van het Rijnstate ziekenhuis te Arnhem (opleider: Dr. J.H.G. Klinkenbijl).