WORKSHOP M3 — ELECTRICAL STIMULATION THERAPIES FOR LOWER URINARY TRACT DYSFUNCTION

Chair: Bart Bemelmans

FUNCTIONAL ANATOMY OF THE LOWER URINARY TRACT

Bart L.H. Bemelmans, Unit for Functional Urology, Dept. of Urology, University Medical Centre Nijmegen, The Netherlands

Introduction

The micturition cycle is an ongoing process of filling and emptying of the bladder. Bladder and outlet function have opposite tasks during both parts of the cycle. Complex anatomical and neurological structures and pathways make sure that all processes needed for maintaining urinary continence and enabling prompt and complete evacuation of the bladder contents are possible under voluntary control.

Anatomy

Anatomical knowledge should comprise bladder, bladder base and closing mechanism including mucosal lining, smooth musculature, vascular plexus, striated sphincter and pelvic floor with its ligaments and bony structures. Innervation is composed of peripheral nerves (i.e. pelvic, pudendal and hypogastric nerves) and nuclei and tracts within the sacral/thoracic spinal cord, the pons, midbrain and higher cortical centres. It is postulated that continence is achieved by summation of the function of all aforementioned structures. Gross anatomy of the pelvic floor shows that there is not a circumscript urethral sphincter. Especially in the female it is more the configuration of the pelvic floor muscles with the hammock-like support of the mid urethral portion that preserves continence.

Neuro-Anatomy

During the filling phase mechanoreceptors through A-delta afferent nerves convey information on bladder fullness. Reflex contractions of the pelvic floor governed by somatic pudendal nerve fibres maintain continence. These reflex contractions are mediated by a segmental spinal reflex (i.e. “The Guarding Reflex”) and by spino-pontine-spinal reflexes, which are under volitional control. Sympathetic stimulation of beta-receptors in the bladder dome further enhances bladder relaxation whereas stimulation of alpha-receptors in the bladder outlet causes outlet constriction. Ongoing stimulation of bladder mechanoreceptors urges preparation for voiding. Until a proper place for urination has been reached cortical areas will strongly activate a nucleus situated laterally in the pons (the L-region or continence centre). As soon as voiding may start the L-region is switched off and a more medial nucleus in the pons (the M-region or micturition centre) is switched on. From this M-region the micturition phase is initiated, meaning that sympathetic outflow to the bladder as well as stimulation of the pelvic floor will stop. Next, a parasympathetic nucleus in the sacral spinal cord will be activated, and its outflow through pelvic nerves will induce bladder contraction.

Neuro-Physiology

The most important neurotransmitter in the parasympathetic system is acetylcholine with its muscarinic receptor on the smooth muscle cells of the detrusor. The alpha- and beta-receptors on the bladder wall and outlet are stimulated by (nor)adrenaline. Afferent mechano- and pain receptors are activated by a number of substances of which the vanilloids and neurokines are the most important. Intra-cellular, two routes of calcium shifts should be mentioned. One route (bio-mechanical) is through activation of the muscarinic receptors that finally leads to release of calcium from intracellular stores. A second route (electro-mechanical) is through opening of calcium channels caused by ion-flux over the cell membrane. Proper knowledge of all these processes is indispensable for a clear understanding of modern pharmacologic manipulations of dysfunctions of the lower urinary tract.

THE PHYSIOLOGICAL BASIS OF NEUROMODULATION

Sivert Lindström, Linkoping, Sweden

No abstract available

ELECTRICAL STIMULATION AND REHABILITATION OF THE PELVIC FLOOR

Dr. Barry Berghmans, University Hospital Maastricht, The Netherlands

Introduction

During the last years non-surgical therapy modalities for lower urinary tract dysfunction have increasingly attracted widespread attention. Conservative therapies have become more and more accepted due to good efficacy and few side-effects. Electrostimulation (ES) is one of these treatment modalities, generally performed with a removable device through vaginal or anal stimulation. In this presentation the efficacy of ES as a treatment for women with stress urinary incontinence and bladder overactivity is discussed.

Electrical stimulation for the treatment of stress urinary incontinence

In our review on the efficacy of conservative treatment modalities for stress urinary incontinence (SUI)[1] the included trials of ES showed considerable variation in the types of stimulation used. Trials investigated intravaginal and extravaginal stimulation, interferential and neurotrophic stimulation, maximal and long term stimulation. Not one trial replicated the intervention of another. ES in this patient population is focussed on restoration of reflex activity by excitation of the pudendal nerves in order to create a PFM contraction.[2] Either method of stimulation, when adequately applied, is possible.

Regarding the variability in types, methods and used parameters of ES, results of our review should be interpreted with caution. Trends in the evidence suggest that active stimulation is more effective than sham stimulation, but that ES may be no more effective than pelvic floor muscle exercises (PFME) alone or other physical therapies. Wilson[3] and Luber [4] concluded that the addition of electrotherapy did not offer any significant advantages. It seems that further investigation of ES is required in order to establish its efficacy for SUI; a view also supported by other authors.[5,6] ES for the treatment of SUI is not widely employed as first line management, and is used predominantly in patients where other methods have failed. It may be that ES is particularly appropriate as a biofeedback procedure for patients who are initially unable to contract their pelvic floor muscles, but once active contraction is possible PFME may be more effective.[1]

Electrical stimulation for the treatment of bladder overactivity

Next to SUI, bladder overactivity is the most frequently observed disorder of the storage function in women.[7] The symptoms of bladder overactivity consist of urgency, frequency, nocturia and urge incontinence (UUI). Urgency or urge incontinence has greater impact on quality of life than SUI, probably because it is a highly unpredictable phenomenon[8,9], and has the greatest effect on quality of life in the younger population.[10]

The different physiotherapeutic treatment modalities like ES are still based on hypotheses for the underlying pathologies causing bladder overactivity. However, clinical experience has shown that ES generally will provide some progress in most individuals with bladder overactivity. ES, both external or internal, is suggested to enable an effective reduction or inhibition of detrusor activity by stimulation of afferents of the pudendal nerve.[2] Therefore, in a patient with an overactive bladder refractory to pharmacotherapy, normally the mainstay of therapy, ES should at least be tried before turning to more invasive and irreversible surgery.

Until lately, only a few studies were performed regarding the efficacy of ES for bladder overactivity. Because of the lack of well-designed studies, our review on the efficacy of conservative treatment modalities for women with UUI revealed only insufficient evidence on the efficacy of ES alone or in combination with PFME for women with UUI.[11] However, these findings did not prove the ineffectivity of ES as a treatment modality for urinary incontinence and voiding disorders as a whole. It was our assumption that the lack of efficacy was most likely caused by methodological flaws like heterogeneity of study groups and suboptimal research designs.

Therefore, in a single blind randomized clinical trial (RCT)[12] we assessed the efficacy of various physical therapeutic treatment modalities, i.e. ES, lower urinary tract exercises (LUTE), and a combination of ES and LUTE in women with proven bladder overactivity as indicated by an ambulatory urodynamic investigation. These treatment modalities theoretically stimulate the detrusor inhibition reflex (DIR) and pacify the micturition reflex, resulting in a decrease of overactive bladder dysfunction.[2]

One hundred and twelve women received ambulatory urodynamics (ACM). Based on both urodynamic variables of ACM and the micturition diary, the Detrusor Activity Index (DAI) for each patient was calculated. After randomization, 68 women with a DAI $\exists$ 0.50 were defined as having proven bladder overactivity. Patients were randomized over four treatment groups, i.e. office and home based ES; lower urinary tract exercises (LUTE); office based ES and LUTE; no-treatment. Treated patients received 9 treatment sessions, once weekly, using for ES a special version of the ProSecosystem (Innocept Medizintechnik Inc, Gladbeck, Germany). The primary outcome variable was the DAI, measured before randomization and a.s.a.p. after the end of the study period.

Results of the group of 68 patients showed a statistically significant decrease of DAI-scores in the ES-group (p=0.032) in comparison with no treatment, while this decrease was not statistically significant in the LUTE-group (p=0.105) and the LUTE+ES-group (p=0.672). There were no side-effects or protocol deviations. Our conclusion was that, based on the DAI, only ES seemed to be effective. For the treatment of women with bladder overactivity, this was the first RCT comparing *center and home-based* ES with no treatment. In our review we only could identify four RCTs comparing intravaginal ES vs sham intravaginal ES.[11] Three trials reported results in favor of ES, whereas the low quality study of Sheperd reported that ES was not more effective than sham ES. In the well-designed study of Yamanishi 32 patients in the active group and 28 in the sham group completed the study. Bladder capacity at the first desire to void and the maximum desire to void increased significantly in the active group, but not in the sham group. It was concluded that ES was superior to sham treatment and proved its efficacy for the treatment of UI due to bladder overactivity. The treatment parameters of ES in our study were empirical and in accordance with ES protocols usually employed in studies with the choice for a high intensity treatment. In selected patients with SUI and bladder overactivity ES seems to be a safe and effective treatment modality and should be considered as a first line treatment option.

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INTRAVESICAL ELECTRICAL STIMULATION IN CHILDREN WITH MICTURITION DYSFUNCTION

Gunilla Gladh, Dept. of Molecular and Clinical Medicine, Div. of Paediatrics, Faculty of Health Sciences, Linköping, Sweden

Background

Conflicting results from IVES treatments have been presented over the years since Katona first described the procedure (1). Besides the selection of patients, the used stimulation parameters might be important for the outcome. Experimental studies have shown that IVES involves a direct activation of bladder mechanoreceptor afferents followed by a central modulation of the micturition reflex pathway (2, 3). In addition optimal physiological electrical parameters have been evaluated. It seems clear that the prime role of IVES should be to enhance the micturition reflex in patients with an underactive detrusor.

Looking for alternatives to existing treatments for children with bladder emptying problems, we have been working with electrical stimulation since 1990. The effect of intravesical electrical stimulation (IVES) with physiological parameters in children with weak detrusor contractility has recently been evaluated (4).

Method

Forty-four children were included, 30 girls and 14 boys aged 7-18 years (md 10,5). There were 24 children with idiopathic and 20 with neurogenic bladder dysfunction. Children with neurogenic bladder dysfunction were offered treatment if they had some preserved sensitivity from external genitalia. Treatment with IVES was offered as an alternative to clean intermittent catheterisation (CIC). Nineteen children were already on CIC at start of IVES.

Transurethral intravesical electrical stimulation was given by a special catheter electrode (cathode), surrounded by a small amount (30 ml) of saline in the bladder. The anode was two surface diathermic plates placed just above the symphysis pubis. A battery powered constant current stimulator (Medicon MS 210) with square unipolar pulses, (0.7 ms) was used. The stimulation frequency was 25 Hz continuously. Current intensity was adjusted according to the acceptance of the child. We were always careful not to induce any pain sensation. Initially stimulation sessions of 60 minutes daily for ten days at the clinic was used, the last years 20 minutes twice daily during 5 days have been preferred. If needed, home treatment was suggested. No biofeedback technique was used.

Effect of treatment was followed by urinary flow and residual urine recordings before the start of treatment, before and after each stimulation session and at follow up.

Results

There were 5 drop outs, 3 because of non-compliance to the treatment and two for socio-cultural reasons. The number of stimulations at the clinic were 3 -24 (md 10). Sixteen children continued at home with another 5-114 (md 17) stimulations with exception for one girl with neurogenic problems who stimulated at home in repeated periods together 264 sessions. Twenty-eight children (64 %) had their bladder emptying normalised with a median follow up of 2,5 year. One more girl with neurogenic bladder dysfunction has developed a normalised voiding but needs repeated stimulation periods to maintain a good bladder emptying. Another three children have improved substantially. Eleven of fifteen the children on CIC have terminated their catheterisations, 8 of them with neuropathic bladder. These beneficial results were obtained without severe side effects or complications. Seven children had no remaining benefit of the treatment.

Conclusion

IVES is a promising method to treat weak detrusor contractility in children. Even in a selected group of children with neurogenic bladder dysfunction it is possible to regain a functional micturition reflex. Additional treatment sessions seem to be required for neuropathic cases, but can easily be given at home by the children themselves or their parents. Further experience is needed to select those in the neuropathic group that may benefit from the treatment.

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AN OVERACTIVE BLADDER IS MORE THAN AN UNSTABLE DETRUSOR

Bert Messelink, Hospital OLVG, Amsterdam, The Netherlands

Introduction

In the latest version of the ICS Standardization of Terminology the term Overactive Bladder (OAB) syndrome is used under the term Urgency. The discussion at the time when OAB was introduced focused on the question "overactive bladder" versus "overactive detrusor". When using OAB the terms "motor urgency" and "sensory urgency" loose their sense and in the ICS classification these terms are no longer recommended[1]. One of the advantages of the term OAB is the fact that it is defined on the symptoms reported by the patient. This means that more attention can be given to two aspects. The first one is the role of the pelvic floor muscles and the second is the role of psychological influences.

Theoretical backgrounds

The micturition cycle is regulated from within the **central nervous system**. Recently it has been shown that the pontine micturition centers (PMC) play a major role in this regulatory system. The pons has a strong relation with the PeriAqueductal Gray, which is part of the emotional motor system[2].

In the normal situation **pelvic floor muscles** (PFM) and the bladder are coordinated at the level of the PMC under control of the PAG-region. Voluntary control on the lower urinary tract can be assessed by contraction and relaxation of the PFM. A contraction of the PFM results in prevention of urine loss and in an inhibition of the detrusor contraction[3]. During voiding the PFM must be completely relaxed to minimize the outflow resistance. For the understanding of pelvic floor pathophysiology it is important to realize that the PFM arte involved not only in the lower urinary tract but also play a role in the ano-rectal function and during sexual functioning.

During **potty training** in childhood the desire to void, as a somatic sensation is incorporated into daily life, so that voiding takes place at an appropriate time and place. Conditioning has long ago been recognized as an important psychological mechanism used and mis-used in this training[4]. Respondent conditioning means that anxiety, expectations and other signals are mixed up with the desire to void. Operant conditioning mechanisms can train the individual to postpone voiding because they are rewarded for this action by their social environment. Patients may also benefit from their symptoms by getting special privileges and attention based on their complaints[5].

A history of **child abuse or neglect** may play a role in developing an OAB. In patients with an OAB and comorbidity (like pain and depression) it is necessary to ask for problems during childhood. In retrospective studies among pain patients the percentage of self reported child abuse or neglect is high (up to 50% in a study for GI problems) [6]. In a prospectively study looking at court documented cases of childhood sexual and physical abuse and neglect no relation was found between early childhood victimization and pain symptoms in young adults[7].

Diagnostic needs

Based on the aforementioned theories we can discuss the diagnostic needs for patients with an OAB. In **history taking** it is important to pay attention to the presence of other symptoms: gastro-intestinal, gynecological, sexual and pain. Consultation of another discipline maybe useful in these cases. Furthermore attention must be paid to psychological and sexual influences on the complaints.

On **physical examination** it is important to pay attention to the local situation: the vulvar and vaginal region or the scrotal and perineal region. Special attention is paid to the PFM. The tone and voluntary contraction and relaxation can be tested. When in doubt about the function of the PFM: consult a physical therapist experienced in pelvic floor education.

A **urine specimen** should be tested on the presence of blood and signs of infection; a culture will be needed in case of infection. A **voiding diary** is important to classify the complaints and get insight into the severity of the problem.

Urodynamics will be needed before doing Sacral Nerve Stimulation and before doing surgery.

Therapeutic tools

First line treatment of the OAB consists of **pharmacotherapy** and/or **pelvic floor education**. Psychotherapy should be offered to patients in whom the psychological aspects are thought to play an important role. **Behavioral therapy** can be used to reset the mechanism of wrongly trained bladder behavior. This therapy can only be successful when there is a clear relation between the complaints and psychological aspects. General aspects of this therapy are: toilet behavior, relaxation, stress management or psycho-education. In cases where this therapy does not work a **psychotherapeutic** approach can be used. In this therapy attention is paid to

aspects like a disturbed self-image and a negative attitude towards (parts of) its own body. Therapy is focused on processing earlier experiences and improving autonomy[8].
When conservative therapy fails **neuromodulation** and in special cases **surgery** can be considered.

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SACRAL NERVE STIMULATION FOR TREATMENT OF LOWER URINARY TRACT DYSFUNCTION

Dr John PFA Heesakkers, Dept Urology, University Medical Center, Nijmegen, The Netherlands

Sacral nerve stimulation nowadays is regarded as an efficacies treatment for lower urinary tract disorders like urge incontinence, the urgency / frequency syndrome and chronic urinary retention. The best known therapy to date is provided by the Interstim® device (Medtronic, USA). This device delivers continuously electrical pulses to the sacral nerves by an electrode inserted through one of the sacral foramina and connected to an implantable pulse generator nerve that is implanted subcutaneously.
The classical work-up of a patient who is regarded eligible for the application of the technique consists of three stages: an acute stimulation phase, a subchronic stimulation phase and the phase of the permanent implant. The combined acute and subchronic phase is known as the Peripheral Nerve Evaluation (PNE). During this phase the beneficial effect of sacral nerve stimulation on the disturbing behavior of the lower urinary tract is analyzed.
The acute phase is done on an outpatient basis. Via a percutaneous puncturing technique a test wire is placed adjacent to the one of the sacral nerve on either the left or right side. Most of the time the third sacral nerve is regarding the optimal nerve. The patient is asked to tell what kind of sensation and in what area he or she experiences. The right feeling is a twinkling sensation in the bladder, groin, vaginal or anal area. At the same time specific motor responses like contraction of the pelvic floor muscles (“bellows”) and flection of the ipsilateral great toe are looked for.
If appropriate sensory and motor responses are obtained, the subchronic phase starts. The test wire is connected to an external pulse generator or screener and the patient goes home. During 3 to 7 days the effect of the nerve stimulation on the lower urinary tract is noted in a voiding diary. If a positive effect occurs a reduction in complaints or disturbances is perceived. For patients with urge incontinence this means a reduction in number of incontinence episodes. For patients with urgency / frequency this means a reduction in number of voidings per day. Patients with chronic urinary retention have a positive effect if in the number of catheterizations per day or the volume catheterized is reduced.
When the effect is judged to be good and substantial enough a permanent implant may be offered to the patient. During an operation a permanent electrode is inserted through a the same sacral foramen as he one used during PNE. This electrode has four contact points that can be used for applying currents. The electrode is sutured to the periost of the sacral bone and connected the implantable pulse generator, that is positioned in a subcutaneous pocket. This pulse generator is capable of giving permanent electrical pulses via the electrode to the adjacent sacral nerve. The stimulation parameters can be fine tuned in the clinic. This implies that it is possible to vary the stimulation amplitude, the pulse duration, the contact points used on the electrode, the stimulation frequency, the “on – off” scheme etcetera. It is also possible to check the impedance of the

system or the percentage of the time that the system is used during the last period of time. The patient is able to control the stimulation device with an external remote controller. The pulse generator can be switched on or off and the amplitude can be varied within set limits.
Sacral Nerve Stimulation with the InterStim System for treating urge incontinence got FDA approval in 1997. In 1999 also FDA approval was obtained for the urgency / frequency syndrome and chronic urinary retention. Of those patients that undergo a PNE 30-50% are successful which is defined as ore than 50% improvement in lower urinary tract dysfunction symptoms. These patients can be offered a permanent implant. Worldwide nowadays approximately 4500 patients have been implanted with this system. After implantation the long-term success rate is 70%. To date no predictive demographic or urodynamic parameters have been identified to tell what patient is a good candidate for permanent implant and who will be successful in the long-term. The mainstay in measuring success rates stays the voiding diary. In order to improve the success rates of the patient screening other techniques are being developed. These are developments like two-stage techniques; double-sided current application, percutaneous electrode positioning and adjustable positioning of electrodes.
During this course the classical technique of patient screening, the classical technique of permanent implantation and the new developments in screening and implantation will be shown and discussed.

NEUROMODULATION BY POSTERIOR TIBIAL NERVE STIMULATION FOR TREATING LOWER URINARY TRACT SYMPTOMS AND DYSFUNCTION

Bart L.H. Bemelmans, Department of Urology, University Medical Center, Nijmegen, The Netherlands

Introduction

Urologists are often consulted by patients with lower urinary tract symptoms that are difficult to categorise and quantify. Nevertheless, they seriously interfere with patients' quality of life, and hence deserve all possible care and attention. These symptoms can be divided roughly into four categories: irritative micturition complaints, pelvic pain, involuntary urine loss and urinary retention. If diagnosis is difficult, treatment may be even more of a problem. Therapeutic options vary from conservative treatments such as pelvic floor training, medication (e.g. oxybutynin, tolterodine or imipramine) with or without intermittent self-catheterization through to more invasive procedures such as bladder distension and more radically, bladder neck suspension, ileocystoplasty or urinary diversion. The drawbacks of these therapeutic options are limited success, serious side effects and irreversibility.
For many years it has been known that peripheral electrical stimulation of the pelvic nerves through the skin or by implant can have a beneficial effect in the management of problems of the lower urinary tract, especially urinary incontinence caused by bladder overactivity. These techniques may now provide a very different option for treatment. Stimulation sites have included anal, intravaginal, intravesical, and transcutaneous at several locations on the body surface. Because of varying success rates, most of these methods have never gained widespread application but stimulation of the S_3-nerves at the level of the medial malleolus of the ankle has been made clinically applicable. This type of therapy seems to depend on a physiological process, commonly known as neuromodulation, in which the influence of activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction. Little is known about the actual mechanisms underlying the success of this treatment in man. Many of the modulatory reflex mechanisms controlling normal continence are inhibitory in nature and have been shown to occur throughout the central and peripheral nervous systems. It is probably aberrations in some of these systems, for example, underactive inhibition at the brainstem level from more rostral cerebral structures or loss of descending inhibitory pathways to the sacral segmental reflexes, that causes bladder and sphincter dysfunction in the first place.
This paper reviews therapeutic neuromodulation by Posterior Tibial Nerve Stimulation (PTNS). Furthermore, it describes the technique and clinical results.

Indications, Assessment and Technique

The type of patients who may be suitable for neuromodulation have included those with symptoms of urgency, frequency, involuntary urine loss due to urethral or detrusor instability (sensory and/or motor urge-incontinence); pelvic pain associated with interstitial cystitis, the urethral syndrome or prostatodynia; or bladder evacuation difficulties; in each case when they have failed to respond to standard treatment. In many cases, these patients would have had a long-standing history of medical problems and undergone a multitude of behavioural, pharmacological and other treatments. It is therefore, unlikely that any known and treatable cause for the complaints had been overlooked. However, the work-up for treatment by neuromodulation must include careful history taking with special attention given to the use of drugs that influence bladder function, a thorough physical examination, urinalysis to exclude a urinary tract infection, and a urodynamic evaluation to assess bladder and sphincter function. For some patients, a cystoscopy under general anaesthesia with cold-

cup biopsies to rule out interstitial cystitis or carcinoma *in situ* is indicated. Neurologic disease, once considered to be a contra-indication for neuromodulation, is now known to be a successful group for such treatment following a study in children with neurogenic voiding dysfunction and incontinence.
The PTNS technique is easy. The patient is sitting on the investigation couch in the so called “frog” position, that is: with exorotation of both hips and slight flexion of the knees. Thus, the medial sides of the lower legs are exposed. For PTNS a special treatment kit is available (Urgent-PC, CystoMedix, Anoka, USA) that consists of an acupuncture-like needle, a patch reference electrode and a pulse generator. The needle is inserted approximately 5 cm cephalad to the medial malleolus of the ankle and the reference electrode is plastered to the ankle. Then the pulse generator is attached to the needle and the stimulation current is gradually increased. Proper stimulation of the posterior tibial nerve produces a radiating sensation in the sole of the foot and flexion of the great toe. A PTNS session takes 30 minutes and the sessions are repeated for 12 weeks. Therapeutical benefit can be expected after 6 tot 8 weeks. Patients who consider themselves a therapeutical success (that is: partial or complete cure) can be entered into a tapering protocol. This means patients will be treated on a 2-weekly or 3-weekly schedule, as the situation requires.

Clinical Results
In a multi-centre study on 35 patients with urge-incontinence, a cure rate of 46 percent was found. Of these 35 patients, 24 (69 percent) fulfilled the criteria of objective success. In a series of 39 patients with non-obstructive urinary retention, 16 fulfilled the criterion of objective success (> 50 percent reduction in residual urine per 24 hrs.). Therefore, the success rate in this study was 41 percent. A total of 6 patients (15 percent) was cured. In the treatment of pelvic pain objective successes (i.e. > 50 percent reduction in VAS-score) were disappointing: only 7 out of 33 (21 percent) fulfilled this criterion. Remarkably, 14 patients (42 percent) claimed that they felt cured or improved by the therapy. In thousands and thousands of PTNS sessions this technique proved to be easy to learn and to perform. No lasting harmful side-effects were noted.

Practical Conclusions and Future Perspectives
Urine storage and expulsion depends on the total integrity of the nervous system from brain to bladder. Many different neural pathways are involved integrating autonomic function and proper voluntary control over the reciprocal relationship between the storage function of the bladder and the outlet function of the urethra. When patients present with dysfunctions of the lower urinary tract, such as irritative micturition complaints, pelvic pain syndromes and urinary incontinence or retention, standard treatments are not always successful but neuromodulation of sacral nerve roots by PTNS is proving now to become a useful therapeutic alternative. Patients who seek the benefit of this technique are often the most intractable of cases and for whom surgery may otherwise be the last resort. For this reason neuromodulation should at least be considered in any patient with therapy resistant urge-incontinence or urinary retention before proceeding to mutilating and irreversible surgery.