Electrical neuromodulatory therapy in female voiding dysfunction

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Female voiding dysfunction such as urge-frequency syndrome, urge incontinence and unobstructive urinary retention are often refractory to conservative management. Electrical neuromodulation with surface electrodes or with implantable systems has become a valuable addition to the therapeutic options in the last two decades. Interstitial cystitis is an emerging indication. The application of these techniques in non-neurogenic patients is reviewed. The techniques using unimplantable electrodes, anogenital electrical stimulation with plug electrodes, transcutaneous electrical nerve stimulation with surface electrodes, and posterior tibial nerve stimulation using needle electrodes are addressed. Several techniques using implantable systems are discussed, e.g. sacral nerve neuromodulation (Interstim™ device), pudendal nerve stimulation (Interstim and Bion™ device) and paraurethral neuromodulation (Miniaturo™ device). The long-term efficacy of neuromodulation for the established indications is more than half, but 20–50% of the patients initially tested do not respond to a test procedure. The disadvantage is the high surgical revision rate and the high cost of treatment. Technical advances will hopefully be able to address these aspects.

KEYWORDS

neuromodulation, incontinence, female, voiding, neurogenic, stimulator

INTRODUCTION

Female voiding dysfunction such as those related to overactive bladder (OAB) syndrome, unobstructive urinary retention and interstitial cystitis (IC) often are refractory to conservative management, including drug therapy, behavioural therapy, pelvic floor muscle exercises, biofeedback and intermittent self-catheterization. Neuromodulation and particularly sacral neuromodulation (SNM) has proved to be valuable in these situations [1]. The currently available methods include: anogenital electrical stimulation, transcutaneous electrical nerve stimulation (TENS), posterior tibial nerve stimulation (PTNS), SNM, pudendal neuromodulation (PNM) and paraurethral neuromodulation.

The precise mode of action of neuromodulation is unknown. Its effects can be explained by modulation of reflex pathways at the spinal cord level [1,2]. However, there are now studies that indicate that supraspinal pathways are also involved [3]. Experimental work in animals, human volunteers and patients shows that at least two mechanisms are important: (i) Activation of efferent fibres to the striated urethral sphincter reflexively causes detrusor relaxation; (ii) Activation of afferent fibres causes inhibition at a spinal and/or

Tanagho and Schmidt [4], who introduced SNM, adhered to the first theory. In agreement with this theory, Shafik [5] showed that electrical stimulation of the external urethral sphincter in human volunteers can inhibit detrusor contraction. Studies supporting the second theory are those in which the dorsal clitoral or dorsal penile nerve, both purely afferent branches of the pudendal nerve, were electrically stimulated. This induced a strong inhibition of the micturition reflex and detrusor hyper-reflexia [6–8]. Thus, pudendal nerve afferents are particularly important for the inhibitory effect on the voiding reflex. Pudendal afferent activity mapping during neurosurgical procedures of the sacral nerve roots has shown that the S1, S2 and S3 roots contribute 4%, 60.5% and 35.5%, respectively, of the overall pudendal afferent activity [9]. Despite that S2 carries more pudendal afferents, the S3 spinal nerve is the preferential site of lead implantation in conjunction with the Interstim™ device (Medtronic, Minneapolis, MN, USA). Stimulation of S3 in comparison to S2 causes less undesired excitation of efferent fibres that innervate leg muscles. However, it was also shown that pudendal afferent distribution is confined to a single level (i.e. S2) in 18% of the subjects [9]. A lack of effect of S3 stimulation can therefore be expected in some subjects and direct pudendal nerve

Experimental work in spinalized rats showed that neuromodulation reduced the degree of hyper-reflexia and the expression of the *c-fos* gene after bladder instillation with acetic acid [10]. (C-fos protein is expressed in the spinal cord after irritation of the lower urinary tract; this expression is mainly mediated by afferent C fibres). This result shows that inhibition of afferent C fibre activity might be one of the underlying mechanisms of neuromodulation. Patients with IC might benefit from this effect.

Paradoxically, neuromodulation also works in patients with urinary retention in the absence of anatomical obstruction. It was postulated that neuromodulation interferes with the increased afferent activity arising from the urethral sphincter, restoring the sensation of bladder fullness and reducing the inhibition of the detrusor muscle contraction [11].

Detailed assessment of the sensory response during lead placement is important for long-term success. This is now possible with a two-stage procedure using tined lead placement under local anaesthesia. In a comparative study between the traditional and the first stage of the two-stage implant, Peters *et al.* [12] reported a re-operation rate of 43% vs 0%, respectively, after a mean follow-up of 5.6 months. It is clear that the mechanisms of

but stimulation of afferent pathways seems to play a crucial role.

ANOGENITAL ELECTRICAL STIMULATION

The first publications on anogenital electrical stimulation as a treatment option in the OAB appeared in the 1970s [2] and the technique can now be considered an established treatment [13]. The method implies the insertion of plugs equipped with electrodes into the anal canal and (or) the vagina. Two modes of this type of therapy can be distinguished. Long-term or chronic stimulation implies a home-treatment programme for several (e.g. 3–12) months. This is mainly used in stress incontinence. In acute maximal stimulation the patient is treated in a limited number (usually 4–20, sometimes much more) of sessions.

It was stated that anogenital electrostimulation has a beneficial effect in about half of the patients [14,15]. However, the reported results vary considerably [16,17]. Most [18–20] but not all [21] authors found that active treatment was superior to sham treatment.

Success rates heavily depend on the selection of patients. As an example, Primus and Kramer [22] obtained a success rate of 64% in a group of patients with idiopathic detrusor instability 2 years after treatment, while all patients with multiple sclerosis, who initially had benefited, relapsed within 2 months. Disappointing results were also obtained in elderly cognitively impaired patients [23].

Geirsson and Fall [13] noted that the results obtained with a routine outpatient procedure were far less good than those obtained in their prospective research series. No data are available on the minimum number of treatments required. Siegel *et al.* [24] found no significant difference between daily and every-other-day treatment.

Few studies reported success rates after a follow-up of >6 months. Of the 17 patients treated by Yamanishi *et al.* [20], 41% remained cured for 9 months on average after stimulation, with no intervention. The success rate of 85% initially obtained by Eriksen *et al.* [16] in 48 idiopathic females fell to 77% after 1 year. No severe side-effects have been

TENS

TENS is used widely in the treatment of pain in various conditions. Fall *et al.* [25] successfully treated patients with IC with surface electrodes stuck over the suprapubic area. In the treatment of the OAB, the electrodes are usually stuck over the S2 and S3 dermatomes (peri-anal region) or over the sacral foramina S2 and S3. Stimulation takes place daily during one or more weeks. Beneficial results of TENS at various sites have been reported [26].

Of patients treated by Walsh *et al.* [27], with sacral dermatome TENS, 76% and 60% reported an improvement in daytime frequency and urgency, respectively, while 56% noted a reduction in nocturia. Hasan *et al.* [28] reported a >50% decrease in the urinary frequency in 37% of 59 patients with an unstable bladder. The number of leakages improved by >50% in 69% of those with urge incontinence. In a group of 55 children aged 6–12 years, 57% and 33% of those with daytime incontinence and bedwetting, respectively, became dry, while the voiding frequency became normal in 67% [29]. Hasan *et al.* [28] saw no urodynamic improvement with TENS over the posterior tibial nerve and the suprapubic region.

Application of TENS is not useful if the patient is not offered the opportunity for re-treatment. The symptoms of all 25 patients who were successfully treated by Walsh *et al.* [27] returned to pretreatment levels within 6 months. Local skin irritation at the site of the electrodes is seen in a third of the patients [28].

PTNS

Intuitively, the pelvic region is the most logical place to seek a site for neuromodulation, but physiological mechanisms permit suppression of bladder overactivity from a more distant location. In PTNS, a thin acupuncture needle is inserted 5 cm cephalad from the medial malleolus and just posterior to the margin of the tibia at the site of the posterior tibial nerve. This is a well-known acupuncture point [30]. Treatment usually takes place weekly for 10–12 weeks. Chang [30] showed statistically significant changes in the maximum cystometric capacity in a group of 26 women immediately after a 30-min treatment session; such changes were absent in a

results, it took some time before Stoller [31] introduced this technique in urological practice (PercSANS™). In an abstract, he described an 81% clinical success rate in 90 patients after a mean follow-up of 5.1 years. More recently, modest results were reported [32]. Clinical success, defined as the wish of the patient to continue treatment after an initial 12-week treatment period, was reported in 60% of 30 patients with urge incontinence and in seven of 12 with retention. In the successfully treated patients with retention, none of the voiding variables were statistically significantly improved. In the patients with urge incontinence the percentage of leaking episodes decreased by 63% in those successfully treated, vs 24% in the unsuccessful group [32]. Only minor side-effects such as pain or bleeding at the puncture site have been reported.

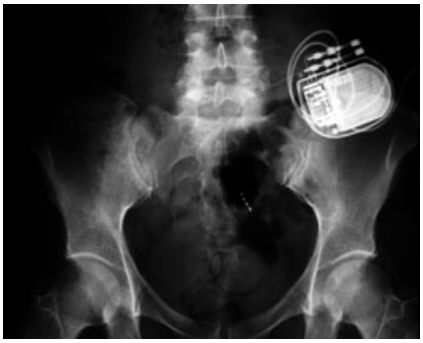
SNM

SNM (Interstim therapy) differs from other types of neuromodulation by its continuous stimulation and close nerve contact. Its characteristic feature is the implantation of a pulse generator and an electrode stimulating one of the sacral nerves, mostly S3. Patients only have a permanent implant if the preceding percutaneous nerve evaluation (PNE) test is successful, or if the effects of the first stage of a two-stage implantation are favourable. In the first stage, only an electrode is implanted but not the pulse generator. Patients in whom the symptoms of the voiding dysfunction are reduced by more than half during testing can receive the permanent implant (Fig. 1).

Established indications for this treatment are urge-frequency syndrome, urge incontinence and unobstructive urinary retention. IC is an emerging indication. It appears that the percentage of patients responding to the traditional test stimulation (PNE) is 60–70% [33]. Recent experience with the staged implant using a tined lead has resulted in a higher implantation rate of up to 80% in patients with various indications [34,35]. It is still unclear how the long-term results in this additional group of responders compare to the long-term results in responders to the traditional PNE test.

The results in patients with urge incontinence were summarized previously [33]. Symptomatically, about half of patients

FIG. 1. Anteroposterior radiograph of the pelvis with the Interstim pulse generator in a buttock position and with the electrode placed in the S3 sacral foramen.



causes have a >90% improvement in their incontinence after the permanent implant; 25% have a 50–90% and another 25% a <50% improvement. In two comparative multicentre studies involving patients with refractory urge incontinence and urgency-frequency, respectively, half of the patients in whom the PNE test was successful were implanted [36,37]. Implantation was delayed for 6 months in the remaining patients, who received standard medical treatment and comprised the control group. The stimulation groups had significantly better symptomatic results than the control groups at 6 months of follow-up.

After the 3-year [38] and 5-year [39] follow-up, respectively, sustained good results were reported, with a reduction of more than half in leaking episodes per day in 53% and 59% of the implanted patients, respectively. Furthermore, 46% and 22%, respectively, were considered dry [38,39]. However, one group reported less good results [40]. These authors reported on the long-term experience (mean follow-up 6.5 years) in a total of 52 implanted patients, of whom 41 were available for evaluation. Of these, six were in the urge incontinence group; there was persistent improvement in only one of the six. It was shown previously that the success rate decreases most rapidly in the first 1.5 years after implantation of the device [41].

In the urge-frequency group, Siegel *et al.* [38] reported that 2 years after implantation, 56% of the patients had a reduction of more than half in voiding frequency. After a mean follow-up of 69.8 months, Van Voskuilen *et al.* [42] reported [illegible] implanted patients with OAB symptoms. Elhilali *et al.* [40] reported persistent improvement in 10 of 22 (45%) patients with urge-frequency after a mean follow-up of 6.5 years.

SNM for treating unobstructive urinary retention is another established indication. Jonas *et al.* [43] reported that 68 of 177 patients in retention responded to traditional PNE with a >50% improvement. Of the implanted patients, 69% eliminated catheterization at 6 months of follow-up and an additional 14% had a reduction of more than half in catheterization volume. At 18 months of follow-up catheterization was completely eliminated in 58% of 24 evaluable patients. Swinn *et al.* [11] reported a 68% success rate to PNE in 38 women, mostly with Fowler's syndrome. The same group reported their long-term results in 26 implanted women. After a mean follow-up of 37 months, 17 of 26 (65%) women voided spontaneously with no need for self-catheterization [44]. After a mean follow-up of 70.5 months, Van Voskuilen *et al.* [42] reported 'good results' in 76.2% of implanted patients with urinary retention.

Several authors used permanent implants of the InterStim device for treating patients with IC. Mixed results were reported with SNM of S3. Some investigators report good results, with up to 75% improvement in symptoms [12,45,46], including a 20% 'cure' rate [45]. The follow-up in these studies was relatively short, at 5.6–14 months. Berman *et al.* [47] could not confirm these results; in 13 patients who were implanted with the Interstim device, only two were pleased or delighted with the results. Elhilali *et al.* [40] reported that of four patients with IC and intractable pelvic pain, only one was improved after a mean follow-up of 6.5 years.

At present, the only way to determine whether a patient is a candidate for implantation is a PNE test or a staged implantation. Attempts to identify factors predicting the success of SNM failed [37,48]. Psychological factors seem to be important [33,49].

The need to reposition the electrode after migration is the most frequently reported adverse event, occurring in ≈20% of the patients [37,41]. Some patients complained of pain at the site of the pulse generator, which [illegible] can often be reduced by decreasing the stimulation amplitude. Van Voskuilen *et al.* [42] reported a re-operation rate of 48.3% (excluding pulse generator replacements) after a mean follow-up of 64.2 months. Dasgupta *et al.* [44] reported an overall adverse-event rate of 51.6%. Siegel *et al.* [38] reported the adverse events for 219 Interstim-implanted patients; the commonest events were pain at the stimulator site (15.3%), new pain (9%), pain at the lead site (5.4%), suspected lead migration (8.4%), infection (6.1%), transient electric shock (5.5%) and adverse changes in bowel function (3%).

Displacement of the electrode during the PNE test might give a falsely negative result. Janknegt *et al.* [50] therefore repeated the test by placing a permanent electrode and an extension cable in patients in whom displacement was suspected, and connected those to an external pulse generator. The permanent pulse generator was placed at a later stage if the patient had a good response (which was so in eight of 10 patients). The two-stage implant has now become the standard, particularly since the introduction of a minimally invasive technique for the placing a tined lead [35]. The pulse generator was traditionally placed in a lower abdominal pocket. Buttock placement has the advantage that the patient need not be repositioned during operation, and it saves ≈1 h of operative time; this has become the standard [51].

PNM

Considerably many patients do not respond to SNM; this has fuelled the interest in the use of PNM. In a single-blind randomized crossover trial of SNM vs PNM in a group of 30 patients it was recently shown that 80% responded to the testing phase and that six had no response to either lead. Of the responders, 79% had chosen the pudendal lead as the superior one. In this study the Interstim device with tined lead, placed either at the pudendal nerve via a posterior approach or the traditional placement in the S3 foramen, was used [52].

Another approach recently reported is implantation of the Bion device (Advanced Bionics Corp., Valencia, CA, USA) [53]. This rechargeable device is a self-contained, battery-powered, telemetrically programmable, current-controlled mini-[illegible]

It is 27 × 3.3 mm and can be implanted adjacent to the pudendal nerve.

Subjects qualify for implantation after a positive percutaneous screening test (PST). A PST is considered positive if stimulation results in an increase of more than half in the bladder volume at the first involuntary detrusor contraction or the maximum cystometric capacity. After a successful PST the Bion can be implanted at its target location, adjacent to the pudendal nerve at Alcock's canal (Fig. 2); it is implanted with a specially developed tool kit.

The results obtained with the Bion in a pilot study of female patients with refractory detrusor overactivity incontinence were reported [53]; six of 14 responded to the PST and received an implant. After 6 months of follow-up the mean number of incontinence episodes decreased from 6.2 to 2.4 per day [53]. Given that five of six patients had failed SNM, this decrease in incontinence episodes is encouraging. Clinical trials of the Bion device involving more patients are underway.

PARAURETHRAL NEUROMODULATION

The Miniaturo-I system (BioControl Medical Ltd., Israel) is a new implantable system for the treatment of painful bladder syndrome and urinary voiding dysfunction [54]. It consists of a battery-powered electrostimulator and a stimulation lead. The stimulation lead is placed paraurethrally in the pelvic floor. The location of the electrode is comparable to the position described by Caldwell [55], who was the first to use chronic electrical stimulation for the treatment of incontinence, in 1963.

Test stimulation is used to assess the patient's suitability for permanent implantation. The Miniaturo Test System consists of an external unit and a stimulation lead. Typically, patients were asked to wear the test system for 6–48 h in the pilot studies and to keep voiding and/or pain diaries during that period. Implantation can be done under local anaesthesia. The electrostimulator is placed in a suprapubic subcutaneous 'pocket'. The stimulation lead is directed towards the urethral sphincter via a small vaginal incision (Fig. 3).

The feasibility study of the Miniaturo-I in patients with IC was planned to determine the safety, objective and subjective efficacy of

pelvic floor for the treatment of this condition [56]. The inclusion criteria were formulated to reflect the clinically based, definition of IC, i.e. the presence of Hunner's ulcers and petechial haemorrhages is not obligatory, and either pain or voiding symptoms are inclusion criteria.

Of 73 enrolled patients (mean age 55.5 years), 22% did not pass the test procedure [56]; 57 were implanted with the Miniaturo-I system. Of these patients, 23% withdrew their consent to participate in the study, at 1–25 months after implantation, and mainly due to a self-perceived lack of efficacy. Of 57 patients, 45 completed a mean (range) follow-up of 18 (1–40 months) and had a considerable improvement in symptoms. The mean (SD) urinary frequency moderately improved from 24.4 (15.1) per day at baseline to 18.2 (12.2) at a mean follow-up of 18 months ($P = 0.02$). The pain score on the visual analogue scale (range 0–10) improved from 6 (1.9) to 3.1 (2.2). The pain score on the Short Form-Minnesota Pain Questionnaire improved from 36.6 (10.7) to 17.4 (11.2) ($P < 0.001$). The O'Leary-Sant IC index improved from 31.4 (3.9) to 20.3 (9.7), representing an improvement in quality of life.

The feasibility study in patients with urgency/frequency and urge incontinence was initiated in August 2002; the results obtained in the first seven patients were reported [54]. Patients completed a mean follow up of 14.5 months after implantation. In one patient the device had to be explanted because of infection after 10 months of follow-up. At the last follow-up visit five women were completely dry and two reported a reduction in the number of leaking episodes from 15 to 6.7, and from 12 to 4 per 24 h, respectively. The degree of urgency, on a scale from 0 ('no urgency') to 3 (severe urgency), significantly improved from 2.0 at baseline to 1.4 at the last follow-up.

Of 79 implanted patients, 34 had 77 device- or therapy-related adverse events [57]; 29 needed surgical intervention (i.e. repositioning or replacement), giving a patient surgical revision rate of 36.7%. The number of events after implantation that required surgical intervention was 46.

The initial results in patients with IC or OAB are encouraging. The implantation procedure

FIG. 2. Anteroposterior radiograph of the pelvis with the Bion in position close to Alcock's canal.

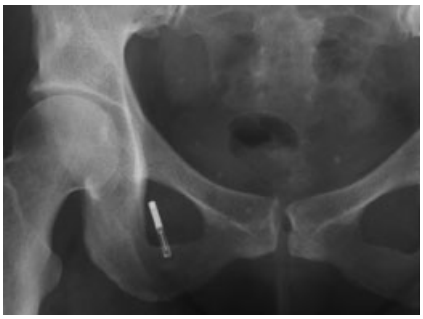
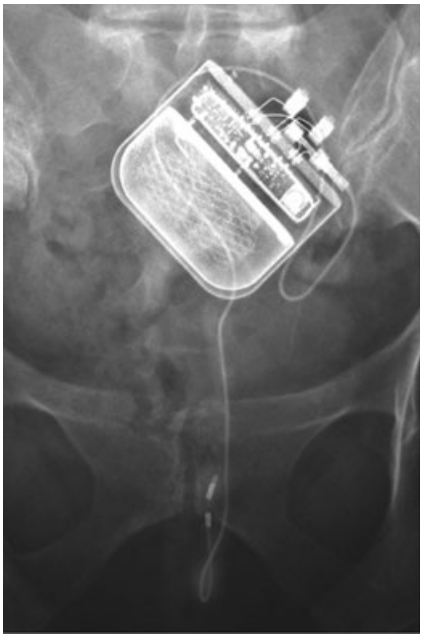


FIG. 3. Anteroposterior radiograph of the pelvis with the Miniaturo-I pulse generator in a suprapubic position and with the electrode situated para-urethrally.



was an improvement in >70% [56]. The long-term results of treatment with the Miniaturo-I device in patients with IC remains to be determined. The preliminary and relatively small experience with the Miniaturo-I device in urge incontinence shows that five of seven patients no longer use pads after a mean follow-up of 14.5 months. Confirmation of these results in a larger patient group with a longer follow-up is awaited.

CONCLUDING REMARKS

Neuromodulation is a valuable treatment

unobstructive urinary retention. The non-surgical techniques can be applied as an alternative to standard conservative treatment. Neuromodulation should be considered before using a more invasive operation such as bladder augmentation. It is unclear to what extent the various techniques are interchangeable.

No variables predictive of success have been identified. The determination of reliable selection criteria would be a major advance. A better understanding of the mechanism of action might contribute considerably to this goal. Discouraging is the high surgical revision rate with the implantable systems; this adds to the costs of this type of treatment, which are already very high. The high costs do not encourage the use of these devices at an earlier stage of the disease, although this might be preferable to treating 'desperate' cases only. Hopefully, some technical advances such as the use of the tined lead, the two-stage implant and the minimally invasive technique, will decrease the need for revision.

CONFLICT OF INTEREST

Ruud Bosch has worked as a study investigator for Biocontrol.

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