Sacral neuromodulation and refractory overactive bladder: an emerging tool for an old problem

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Abstract: Overactive bladder (OAB) syndrome negatively affects the daily life of many people. Conservative treatments, such as antimuscarinics, do not always lead to sufficient improvement of the complaints and are often associated with considerable side effects resulting in treatment failure. In the case of failure or intolerable side effects, sacral neuromodulation (SNM) and botulinum toxin intravesical injections are minimally invasive and reversible alternatives. Currently, both SNM and botulinum toxin injection have FDA approval for use in OAB patients. This mini-review attempts to provide an update on SNM as a second-line management of adults with refractory OAB, based on the available clinical evidence concerning the efficacy and safety.

Keywords: overactive bladder, sacral neuromodulation

Introduction

Overactive bladder (OAB) syndrome is a combination of urinary symptoms and is defined as urgency with or without urge incontinence, usually with frequency and nocturia [Abrams *et al.* 2009]. The estimated prevalence is between 12% and 17% of which one-third of cases experience urgency urinary incontinence [Irwin *et al.* 2006; Milsom *et al.* 2001; Stewart *et al.* 2003; Temml *et al.* 2005]. This syndrome has a significant impact on the patient's health-related quality of life (HRQL) [Coyne *et al.* 2004; Jackson, 1997]. Treatment of patients with OAB is complex and international guidelines suggest lifestyle interventions, pelvic floor muscle training, bladder retraining and medication (antimuscarinics) as first-line treatment options. When conservative treatments fail after 8–12 weeks, alternative therapies should be considered [Abrams *et al.* 2009]. These alternatives used to be invasive and irreversible surgical procedures, such as bladder augmentation or urinary diversion. Currently, new and minimally invasive techniques are available such as sacral neuromodulation (SNM; recommended by ICI, level of evidence A), posterior tibial nerve stimulation (not recommended by ICI, insufficient scientific data) and intradetrusor injection of botulinum toxin (BTX; ICI off-label treatment, level of evidence C) [Abrams *et al.* 2009], although the latter has recently received US Food and Drug Administration (FDA) approval for use in the treatment of urinary incontinence that results from neurological impairments. Nevertheless, SNM is the only minimally invasive option approved for idiopathic OAB patients who are refractory to conservative treatment.

In our center, there is no definitive criteria for therapy selection. We usually offer refractory OAB patients the option between intravesical Botox injection and SNM therapy for them to decide. We guide patients' selection by mentioning therapy features. SNM has the benefit of test trial period at which the patient can judge their therapy selection, the therapy is considered effective in candidate patients and benefit lasts until the battery life ends (average 5–8 years) at the time patient will need to undergo an operation to replace the battery. On the other hand, intravesical Botox injection is a temporary treatment and the benefit lasts for 6–9 months. The risk of urinary retention and the need for catheterization is one of the factors affecting patients' therapy selection. In our center, SNM costs are covered by our national health plans while Botox is not, so we believe that this is another factor affecting some patients' therapy selection.

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In this mini-review, we describe SNM mechanism of action and technique, in addition to surveying published data pertaining to the application of SNM in the management of refractory OAB using a Pubmed/Medline search of contemporary relevant data.

Sacral neuromodulation

SNM comprises the stimulation of the sacral nerves that innervate the bladder, urethral sphincter and pelvic floor muscles. Stimulation electrodes are placed at the level of the third sacral nerve (S3) and connected to an electrical stimulator that is implanted. The implantable pulse generator (IPG) that is being used for SNS therapy uses the Interstim™ technology (Medtronic, Minneapolis, MN, USA). The indications for SNM therapy are OAB symptoms such as frequency urgency syndrome and urge incontinence, in addition to nonobstructive urinary retention, fecal incontinence and chronic constipation.

SNM and OAB

Urge incontinence usually results from an imbalance between inhibitory and excitatory control systems, often causing a 'hyperactive' detrusor, leading to incontinence during the filling phase. Therefore, in OAB SNM devices act to modulate detrusor contractions [Fall and Lindstrom, 1991]. From a chronological point of view, in 1977, Teague and Merrill [Teague and Merrill, 1977] transrectally stimulated the pudendal nerve electrically in dogs which was found to activate pudendal-to-pelvic nerve reflex that depresses or eliminates uninhibited detrusor contractions. Tai and colleagues [Tai *et al.* 2004] were able to show the effectiveness of S2 sacral spinal prominent bladder and urethral sphincter responses in spinal-cord-injured cats demonstrating the potential for using microstimulation techniques to modulate lower urinary tract function in patients with neurogenic voiding dysfunctions. Another publication by the same group showed that in anesthetized chronic spinal-cord-injured cats, impaired storage and voiding functions of the lower urinary tract could be improved by activation of the somatic afferent pathways in the pudendal nerve [Tai *et al.* 2007]. The authors demonstrated that electrical stimulation of the pudendal nerve at 3 Hz inhibited nonvoiding contractions during bladder filling, suppressed reflex voiding, and increased bladder capacity. In a human study, data from 22 patients with OAB, who underwent an ambulant urodynamics investigations (ACM) before and during SNM, were investigated by Scheepens and colleagues [Scheepens *et al.* 2003]. Blind analysis of the ACM was performed, and the detrusor activity index (DAI) was calculated as the degree of detrusor overactivity. The subjective as well as the objective results showed a decrease in bladder over activity during SNM. During SNM, overactivity of the bladder was still present; however, to a lesser extent. A significant correlation was found in DAI reduction of the ACM before and during SNM as compared with the clinical improvement on OAB symptoms. This concept has become popular since it bridges the gap between conservative treatment and highly invasive options. Currently, these devices include SNM via surgically implanted electrodes.

Mechanism of action

The precise mechanism of action of SNM is still not entirely clear. However, a number of theories have been proposed to help explain the effect of electrical neuromodulation and how it can restore normal function in the setting of OAB:

1. It is assumed that SNM affects the 'neuroaxis' at various levels and restores the balance between excitatory and inhibitory regulation at various locations within the peripheral and central nervous system [van der Pal *et al.* 2006].
2. SNM may activate the afferent bladder somatosensors which run to the micturition center in the brain stem, and/or activate the hypogastric sympathic nerves [Chancellor and Chartier-Kastler, 2000].
3. The bladder tends to respond to neural stimulation initially with rapid contraction followed by slow, longer-lasting relaxation. With recurrent, repetitive stimuli produced by the electrical stimulation, there is a decay and downregulation of the bladder's response, thus reducing the detrusor muscle overactivity [Appell and Boone, 2007].
4. Stimulation of afferent sacral nerves in either the pelvis or lower extremities increases the inhibitory stimuli to the efferent pelvic nerve and reduces detrusor contractility [Fall and Lindstrom, 1991]. One proposed theory for the above effect is that there is supra-spinal inhibition of the detrusor [Fall and Lindstrom, 1991]. Another

theory is that, at low bladder volumes, there is stimulation of the hypogastric nerve through activation of sympathetic fibers and at maximal bladder volume direct stimulation of the pudendal nerve nuclei in the spinal cord [Chancellor and Chartier-Kastler, 2000; Zvara *et al.* 1998].

Treatment protocol

Before implanting the SNM, a screening test is performed to assess the clinical effect of sacral nerve stimulation. There are two test protocols: one-stage or two-stage implantation.

One-stage implantation

The percutaneous nerve evaluation (PNE) test uses a nonanchored test lead placed into the S3 foramen and connected to an external stimulator. The test period extends between 5 and 7 days, after which the test lead is removed. The procedure is usually done in an outpatient setting under local anesthesia and prone position. The procedure is done by stimulating the S3 sacral nerves on each side to elicit the desirable response of tingling or vibration-like sensation at the pelvic floor (rectum/vagina/scrotum) and big toe dorseflextion.

The procedure is done bilaterally and the side eliciting the desirable response and comfort for the patient is selected for the nonanchored lead insertion. The patient's electrode will be connected to an external pulse generator that gives the patient the ability to control the stimulation intensity. After the test period the patient will be evaluated in the clinic for 50% or more subjective and or objective response. The objective response will be evaluated on voiding diaries the patient will fill them before insertion which will be compared with the other one filled during the test period. The overall response rate for PNE is around 55% [Schmidt *et al.* 1999; Weil *et al.* 2000]. Lead migration is considered the main factor leading to false-negative results [Everaert *et al.* 2004; Janknegt *et al.* 1997]. If the patient had the desired response they will undergo the permanent implantation of the tined lead and the pacemaker known as an internal pulse generator (IPG). On the other hand, some patients who do not respond to PNE may in fact have an excellent outcome when they undergo two-stage implantation [Janknegt *et al.* 1997].

Two-stage implantation:

If the patient is not a candidate for office-based test stimulation or did not respond to the outpatient PNE test, stimulation may be performed in the operating room (OR) using the tined lead. In fact, the two-stage procedure decreases the technical related test failure.

Immediate implantation of a permanent lead aims to avoid lead migration and allows prolonged patient testing/screening [Kessler *et al.* 2005, 2007]. The definitive lead electrode has self-anchoring tines that reduce the risk of migration. These leads can also be used for testing. The lead is usually placed into the S3 foramen under general anesthesia (although some centers also use local anesthesia in an outpatient setting), correct positioning is guided with fluoroscopy, and the lead is subcutaneously tunneled and connected subcutaneously to a temporary extension lead that exits the skin and is connected to an external pulse generator. This procedure enables test periods of up to 2–4 weeks. If the patient has a good response during the test, the present lead is connected to an IPG. This procedure is performed under local or general anesthesia in the buttock area subcutaneously. Owing to the decreased risk of migration and the longer test duration, this test has a higher response rate. According to a study by Kessler and colleagues [Kessler *et al.* 2007] prolonged screening with the tined lead has a response rate of 67% compared with 43% during PNE testing. The costs for the test protocol with the tined leads are much higher compared with the PNE test. Currently, the use of either one of the two screening options is arbitrary. Postoperatively, the IPG will be turned ON and programming the SNM with different settings that can elicit desirable vibration sensation at the target area (rectum, vagina, scrotum) and the patient will be advised to try different programs to control symptoms [Al-Shaiji *et al.* 2011].

A prospective, randomized study showed that the two-stage implant technique of SNM has a higher success rate compared with the one-stage method, despite prior positive PNE, both in the short term and in the long term [Everaert *et al.* 2004]. Another important study by Borawski and colleagues [Borawski *et al.* 2007] randomized 17 patients to staged implant and 13 patients to PNE. The staged implant group was significantly more likely to proceed to IPG implant than the

Table 1: Results of SNM treatment in OAB patients [Hassouna *et al.* 2000; Hijaz *et al.* 2006; Sutherland *et al.* 2007; van Kerrebroeck *et al.* 2007; van Voskuilen *et al.* 2006, 2007; Weil *et al.* 2000].

Study	General improvement (%)	Void/day (%)	Volume/void (%)	Follow up (months)
Hassouna *et al.* [2000]	88	–46	77	12
Hijaz *et al.* [2006]	75	NA	NA	16
Sutherland *et al.* [2007]	69	–35	NA	22
van Kerrebroeck *et al.* [2007]	NA	–23	79	49
van Voskuilen *et al.* [2006]	80	–38	44	15
van Voskuilen *et al.* [2007]	64	NA	NA	64
Weil *et al.* [2000]	56 (100% continence)	NA	NA	6

PNE group (88% versus 46%). Similar results were shown by Peters and colleagues [Peters *et al.* 2003] who also noted that sensory response assessment at the time of implantation reduced the reoperation rate from 43% to 0%. In addition, increased response rate to SNM was noted when the testing period was extended from 5 to 7 days to 14 days per implanted electrode lead [Kessler *et al.* 2005]. The costs for the test protocol with the tined leads are much higher compared with the PNE test.

Efficacy

There is convincing evidence for the success of SNM with the Interstim technique for refractory OAB. Three randomized, controlled trials (two on patients with urgency incontinence and one on patients with urgency frequency) [Hassouna *et al.* 2000; Schmidt *et al.* 1999; Weil *et al.* 2000] and many articles on long-term observational studies have been published [Hijaz *et al.* 2006; Sutherland *et al.* 2007; van Kerrebroeck *et al.* 2007; van Voskuilen *et al.* 2006, 2007]. Investigators have been used the following parameters to define success versus failure: general improvement, number of voids per day, voided volume, number of incontinence episodes per day, number of pads per day, maximum cystometric capacity, and proportion of subjects with 100% continence rate.

Good clinical response is reported in between 64% and 88% of all patients. All parameters reported showed significant improvement compared with the placebo group: a 23–46% decrease in the number of voids per day, 44–77% increase in the average voided volume (Table 1). A 5-year follow-up study on 121 patients with refractory OAB showed persistence of the clinical success in the long term: 84% of the patients with urgency incontinence and 71% of the patients with urgency/frequency who had a successful outcome 1 year after implantation continued to have a successfully outcome after 5 years [van Voskuilen *et al.* 2007]. A study on the tined lead procedure in 21 patients with OAB showed clinical success after an average of 15.5 months to be around 90% [van Voskuilen *et al.* 2007]. In all reported studies, clinical success is defined as 50% improvement in one of the relevant urinary voiding parameters. Satisfaction and quality of life scores after SNM have also been studied. Cappellano and colleagues [Cappellano *et al.* 2001] showed a significant improvement in the quality of life score in patients with urgency incontinence that underwent SNM from a mean score of 34 to 76. At 18 months of follow up, they were asked whether they would undergo this treatment again: 90% responded yes and 100% would recommend it to a relative or friend. Foster and colleagues [Foster *et al.* 2007] asked 49 patients with urgency incontinence about their satisfaction with SNM treatment. The majority was satisfied (84%).

But is there any reduction of efficacy with time? A multicenter, randomized trial suggests reduction with time in which efficacy dropped from 59% at 6 months to 32% after 2 years in dry OAB patients, although the percentage of patients who had experienced a greater than 50% reduction in the number of daily voids remained unchanged (56%). While in the urgency incontinence group their efficacy was unchanged 46% at 6 months and 3 years but only 59% as opposed to 87% showed a greater than 50% improvement in the number of leakage episodes [Siegel *et al.* 2000]. Further, a multicenter 5-year prospective trial showed reduction of number of leakage episodes and pads used in patients with urgency incontinence and decrease in frequency and urgency and

increase in mean voided volume per micturition episode in OAB dry patients [van Voskuilen *et al.* 2007]. By contrast, the 2-year follow up of a group of OAB patients who had participated in a multicenter randomized trial, had sustained efficacy concerning the improvement in the number of total voids/day, the mean voided volume per micturition and the degree of urgency [Hassouna *et al.* 2000].

Safety

Adverse events are usually related to the implant procedure, the presence of the implant or of undesirable stimulation. The most common adverse event reported is pain at the implant site. The occurrence in most studies varies between 3% and 42% [Hassouna *et al.* 2000; Schmid *et al.* 2006; van Voskuilen *et al.* 2007; Weil *et al.* 2000]. Other adverse events reported are lead migration (1–21%), bowel dysfunction (4–7%) and infection (4–10%). Technical improvements throughout the years have decreased the incidence of adverse events significantly. Two important improvements were the introduction of tined leads (leads with hooks) and the gluteal placement of the SNM instead of abdominal. Ever since, both the incidence of adverse events and the reoperation rate per implanted patient have decreased [van Voskuilen *et al.* 2006].

The majority of adverse events do not require surgical intervention. Decreased efficacy because of electrode migration and undesirable stimulation can easily be solved by reprogramming the SNM. A retrospective analysis among 83 implanted patients with a reduced response or complications, such as pain at the IPG site, showed that 18% of the cases could be helped conservatively [Sutherland *et al.* 2007]. Furthermore, the incidence of adverse events is lower with the new tined leads in comparison with nontined leads (28% and 73%, respectively) [Sutherland *et al.* 2007].

A study among 235 patients confirmed that tined leads migrated less often, which occurred among 5 patients (2.1%) [Deng *et al.* 2006]. The available data indicate that the further development and optimization of SNM limits the risk of adverse events.

Conclusion

SNM is considered as an effective and safe non-invasive therapy for refractory OAB patients. It should be considered before irreversible surgical treatment.

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