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SACRAL NEUROMODULATION – A NOVEL THERAPY FOR REFRACTORY OVERACTIVE BLADDER

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Overactive bladder syndrome encompasses a series of symptoms that are both bothersome for the patient and, in most cases, serious from a medical perspective. The investigations protocol ranges from basic to very complex, yet, the treatment alternatives are limited, mainly due to insufficient efficacy or poor tolerability. Sacral neuromodulation promises to do for the bladder what a peacemaker does for the cord, which is regulating normal activity and preventing abnormal behavior. Our paper reviews the current state of the art regarding the overactive bladder, focusing on neuromodulation, its principle, indications, and known limits. Data from the literature is analyzed and presented in an analytical fashion. We conclude that this is a promising treatment alternative although limited by price, difficult implantation technique, and unpredictable efficacy.

1. **INTRODUCTION**

Overactive bladder (OAB) is a urological condition that encompasses urgency, frequency, with or without urge incontinence, in the absence of an obvious trigger. Urgency, the hallmark of the OAB syndrome, is defined as the sudden and intense desire to urinate, difficult to ignore or delay. We define urinary frequency as a minimum of 8 episodes of voiding per 24 hours, while nocturia is characterized by a minimum of 1 voiding per night.

The impact of this pathology is significant in the patient's comfort of everyday life. The relentless searches for bathrooms in every new location, the continuous fear of embarrassment at the thought of having public urinary accidents leads to psychological effects that transform people. They deal with fear, frustration, low self-esteem and self-worth, anxiety, and even certain degrees of depression.

It is easy to understand why this bladder pathology has a significant individual impact on quality of life and imposes limitations to common activities, which makes it not just a medical problem, but also a social and economic one.

1.1 THE PREVALENCE OF OVERACTIVE BLADDER

There is no clear data and there is no consensus on how the incidence of the overactive bladder (OAB) syndrome should be assessed. However, there are two major epidemiologic studies that shed a light in the prevalence and incidence of this pathology. The National Overactive Bladder Evaluation (NOBLE) program was conducted in the United States to evaluate its prevalence and burden [1]. In total, 16.5 % of the participants met the criteria for OAB, divided in two groups – 6.1 % had associated urgency incontinence, while the remaining 10.4% did not. There was no significant difference in the prevalence of OAB between women and men (16.9 % and 16%, respectively), although more women than men reported associated urinary incontinence (9.3 % women with incontinence and 7.6 % women without incontinence compared to 2.6% of men with incontinence and 13.4 % men without incontinence). Other parameters studied showed a direct correlation between greater age and prevalence of OAB for both genders, and between high body mass indexes (BMI) and OAB, although only in women.

The European population was analyzed by Milsom et al in 2001, who relied on telephone surveys and direct interviews of 16,776 people with ages greater than 40 years old [2]. A similar prevalence of the OAB syndrome was found – 16.6 %. People reported frequency (85 %), urgency (54 %) and urge incontinence (36 %). No significant differences were found between women and men, and the direct link between age and OAB was also established.

1.2 CURRENT THERAPY FOR OAB SYNDROME

The current therapy lines include noninvasive treatment, such as fluid intake management, lifestyle changes, Kegel exercises, and medical therapy consisting of anticholinergic medication. Most frequently patients are refractory to the first-line treatment, including various pharmacological agents. In these cases, minimally invasive treatment can be considered, consisting of Botulinum Toxin A endoscopic injections in the detrusor.

When everything fails, surgical treatment might offer a solution, but it is not at all an easy one. For example, augmentation enterocystoplasty is offered traditionally as a last-resort treatment. This intervention bears major risks of complications on both short-term and long-term and is not accepted by the patient in many cases. Even successful interventions might imply the disadvantage of requiring intermittent bladder catheterization for the rest of their lives [3].

1.3 THE PLACE OF SACRAL NEUROMODULATION IN THE THERAPY OF OAB

Sacral neuromodulation has been around for more than 15 years as an FDA approved therapy and for almost 30 years as an experimental technique. The first procedure of sacral nerve stimulation was performed by Tanagho from the University of San Francisco in 1982. The idea behind this technique is that the intermittent electrical stimulation of the sacral neural roots will act as a pacemaker that is able to restore close to normal physiology. Despite this relatively long history of the procedure and a total number of over 70,000 procedures already performed worldwide, the actual mechanism of action is poorly understood.

Most of the existing theories argue that its functioning relies on targeting the sacral nerve and subsequently the pathways in the central nervous system that control both the voiding and the storage phases. Studies point to targeting the afference of the somatic nerve in the spinal root since the therapeutic intensity of stimulation does not result in efferent effects, *i.e.*, muscle contraction.

In treating detrusor hyperreflexia two mechanisms can be targeted – either inhibition of the bladder preganglionic

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neurons or inhibition of the interneuronal transmission in the micturition reflex afference. Most commonly in sacral nerve stimulation (SNM) seems to be involved the second mechanism, targeting the afferent interneuronal transmission [4].

Other authors consider a multifactorial mechanism that targets different levels of the neuraxis. Griebling [5] brings forward a theory that suggests an indirect stimulation of the pudendal nerve and direct inhibition of the preganglionic neurons. The result is a reduction in bladder overactivity and, subsequently, its symptoms.

A more recent theory states that neuromodulation might inhibit involuntary reflex voiding by altering the sensitive signal from the bladder to the micturition center located in the pontine region. By this mechanism, the ascending afferent pathway is inhibited, while the descending pathway has a normal function. If the patient did not develop urinary retention, neuromodulation will inhibit the guarding reflex. leading to a reduction in the overactivity of the sphincter, thus reducing the outlet resistance below the bladder.

1.4 INDICATIONS FOR TREATMENT AND PATIENT SELECTION

SNM has been widely used since 1997, following the Food and Drug Administration (FDA) approval for urinary conditions such as urge incontinence and nonobstructive urinary retention. At that time Tanagho and Schmidt were reporting the successful method that led to achieving continence and promoted bladder evacuation in their enrolled patients [6]. As a result of further research, FDA widened the indications of this therapy in 1999, adding to the list: significant urgency, frequency, and idiopathic urinary retention [7]. Today, due to results reported by studies in terms of safety and efficacy, there is a large market for SNM therapy, with more than 150,000 devices implanted so far.

Before implantation, rigorous history of the patients and their urinary symptoms should be acquired for a precise diagnosis and therapeutic indication. The consultation should also include a physical exam and instructions for completing a bladder diary for three or five days.

Current contraindications focus on the cognitive ability of the patient to understand and comply with the treatment, as well as on the physical ability of the patient or of the caregiver to operate the device. An older contraindication before 2012 regarded imminent lumbosacral magnetic resonance imaging scans (MRI), but more recent studies showed that it can be safely performed in patients with SNM [8]. Other contraindications consider anatomical particularities that could imply technical difficulties in mounting the device, such as sacral deformations with challenging transforaminal access. Cases of spinal cord injury with intact lumbar and sacral spine could benefit from this therapy at present. Existing cardiac pacemakers and other stimulating devices demand additional precautions and counseling. Finally, an unsatisfactory result after the test period prompts against permanent stimulation.

Briefly, the indications are:

- overactive bladder – patients without neurologic conditions and with normal anatomy of the bladder;
- neurogenic disorders – a wide, but not very researched area of interest. It includes preponderately multiple sclerosis, Parkinson's disease and partial spinal cord injury;
- interstitial cystitis and pelvic pain – depending on the symptoms, patients who are diagnosed with these conditions may benefit from this therapy. While it is not a straightforward indication, their urinary symptoms make them eligible for SNM;
- pelvic floor muscle dysfunction – these patients benefit from this treatment since they present with urgency-frequency, urge incontinence, and idiopathic urinary retention. They usually present with bowel dysfunction and pelvic pain as well;
- failed prior conservative therapy – patients usually go through a multistep approach before having an SNM indication. A first-line approach includes lifestyle changes, pelvic floor exercises and EMG biofeedback. They usually fail conservative medication (antimuscarinics, tricyclic antidepressants, or muscle relaxants) and even closely related therapies such as transvaginal or transanal pelvic floor stimulation, percutaneous tibial nerve stimulation, or extracorporeal magnetic therapy;
- non-obstructive urinary retention – it is theorized that these patients might suffer from Fowler's syndrome, characterized by an abnormally functioning urethral sphincter and an underactive detrusor. This leads to voiding difficulties, dribbling, chronic pelvic pain, urgency, and frequency [9].

Encouraging results obtained from clinical trials led to FDA approval of InterStim therapy for chronic fecal incontinence in addition to OAB symptoms and non-obstructive urinary retention. In clinical trials, it improved the bowel control in 80% of the participants and it is now considered to be a safe and efficient treatment option for this condition [10].

2. THE INTERSTIM DEVICE

According to the manufacturer, the InterStim II device is comprised of the Model 3058 neurostimulator, and a specialized lead to which it is connected. In addition, the system requires a smart programmer used by the health provider to activate and program it, and a controller which will be used by the patient for minor adjustments not requiring reprogramming or revision visits.

Briefly, the neurostimulator delivers electrical pulses within set ranges to the lead, that will then stimulate the sacral nerves in its vicinity. No direct access to the device is needed to program and tune the neurostimulator – the technology includes radio frequency telemetry between the device and the external controllers.

The neurostimulator has either continuous or cycling operating modes, delivering amplitudes from 0 V to 8.5 V with 100 mV resolution or 0 V to 6.35 V with 50 mV resolution, at frequencies ranging from 2.1 Hz to 130 Hz. The pulse width ranges from 60 μs to 450 μs, in increments of 30 μs. The stimulator has a titanium shield measuring 44/51/7.7 mm, it weighs 22 grams, and it is equipped with a 3.2 V built-in battery made from a lithium silver vanadium oxide hybrid that does not require recharging. On the external shield there is also a radio-opaque insert reading NJY followed by the serial number for identification purposes.

For the InterStim II device, the model 978B1 tined lead should be used. It comes in three sizes (28 cm, 33 cm or 41 cm in length) and is only 1.27 mm thick. The materials used include polyurethane for lead body and ends, platinum-

iridium for the electrodes, titanium for the rings. A nickel cobalt alloy (MP35N) is used for wires and connectors, which are also wrapped in fluoropolymer insulation.

The model 978B1 lead is a quadripolar in-line lead with tines which secure it to the tissues and with marker bands that allow proper installation (the A and B bands can be directly visualized, while the C and D bands will show up during fluoroscopic imaging). The electrodes are 3 mm long and are strategically spaced at 3 mm in between. The conductor resistance ranges from 87 to 130 Ω, depending on the length of the lead.

The lead is inserted using the provided kit. A needle with markings every centimeter is used to direct the lead into the corresponding foramen canal. An acute test stimulation is performed to confirm appropriate placement of the lead in relation to the sacral nerve. For the targeted S3 nerve, movement should be observed in the perineum, buttocks, as well as in the toes. The patient should confirm stimulation by reporting pulling sensations in the rectum towards the scrotum or labia. The lack of response to stimulation should prompt the repositioning of the lead, either in terms of depth or angle. All the electrodes should be tested, and amplitude of stimulation should be determined. For maximum efficiency, the drawn current should be within a range of 1 to 2 mA. Higher values impact battery life, so a fine adjustment of the leads should be performed.

There are certain precautions that should be taken instances. No type of diathermy treatment should be used on patients who are using SNM, since the energy deployed can damage tissues at the implantation site, as well as cause damage to the device. The severity of the injury can be life-threatening.

Using electrocautery on device parts or near them can cause device failure or malfunction, tissue damage, or shock delivery to the patient. In the absence of an alternative, the neurostimulator should be turned off and the cautery method employed should be bipolar, or unipolar and set on the lowest power, on low-voltage mode and with the grounding pad set far from the stimulator.

All other electrical currents employed in treatments such as electroconvulsive therapy can cause heating in the electrode area and subsequent tissue damage. Precautions should be taken in all instances since their consequences have not been yet completely assessed.

3. THE INTERSTIM THERAPY

The InterStim device for SNM consists of a small implantable device, basically a pacemaker for the bladder used to reestablish appropriate neuromodulation of the bladder. Currently, one of the most frequently used devices is InterStim Model 3058, also called InterStim II, a smaller version that uses fewer screws and which allows the user to undergo MRI scans. The whole procedure is divided into two steps. A trial period, when patient familiarization and adjustments occur, followed by the permanent implantation if preliminary results from the trial session show benefit. The procedures should be done with perioperative antibiotic prophylaxis and no contact between the device and the patient's skin.

The trial assessment is a procedure much less invasive than the permanent implantation, that delivers similar stimulation and implicitly sensations as the final device. However, the device will not be implanted in the patient's body, limiting the intervention to a minimally invasive technique performed under local anesthesia with radiological control either by a urologist or a gynecologist. It consists in inserting a thin probe in the S3 foramen that will deliver the nerve stimulation, then taping it to the patient's skin and connecting it to the trial stimulator.

The stimulator has a similar function to InterStim but is externally placed, usually carried by the patient at the waistband. The following period, which usually ranges between 7 and 14 days, the patients should resume their typical everyday life and should record their symptoms.

Fig. 1 – InterStim II

A satisfying report compared to the initial assessment and good tolerability report makes them good candidates for the permanent device.

Fig. 2 – The control panel of the Interstim Neurostimulator

Fig. 3 – Test stimulation using long term lead.

The final assessment should prove at least 50 % improvement in at least one major symptom:

- number of days with incontinence episodes per week;
- number of urgency episodes per week.

The second step of the procedure is the final, permanent implantation of the InterStim device if the trial device had successful results. The probe is replaced with a permanent wire or lead that is connected to the stimulator. The wiring is placed under the skin, as well as the device, that is mounted in the upper part of the buttocks, for easy access in case of troubleshooting. The device should be inserted superficially, within a maximum tissue depth of 2.5 cm and placed parallel to the skin, so the telemetric connection with the programming devices is not disturbed. The InterStim II device measures only 51/44 mm and 22 g, has a built-in battery that does not require charging, and can be externally programmed initially by the doctor, then slightly adjusted by the patient, or the caretaker using a controller. Once activated, the intensity of the sacral nerve stimulation can be modulated to fit every user. Monitoring and revision should be done every 6-12 months, as well as symptom assessment.

Fig. 4 – Interstim Neurostimulator Kit.

Technical difficulties and functional challenges can occur, as with any other electrical device, but they are approximated at 2 %.

Revisions should be done to reprogram the device or to remove it if the problem is not fixable. However, side effects may appear, and they have been analyzed in multiple trials [11] – local pain (15 %), pelvic pain (9 %), lead migration (8 %), infection (6 %), sudden intense stimulation (6%), pain at the lead site (5 %) or bowel dysfunction (3 %).

Rare side effects, occurring in less than 0.5 % of the cases, include hematoma, numbness, alteration in sensations, leg stimulation, vaginal or anal abnormal sensations, stress urinary incontinence, or urinary hesitancy.

4. CLINICAL DATA

The long-term follow-up data that is readily available looks promising. One study [12] shows that from 64 patients with SNM therapy, pain developed in only 17 cases (27 %), but in 9 patients (14 %) pain went away after reprogramming the device; in 8 cases (13 %) a surgical intervention to remove the device was necessary. Other possible complications include hematoma in 3 patients and wound infection in 1 patient. There had been 23 reinterventions performed in 21 patients (33 %): INS removed in 7 patients, INS repositioned for pain in 7 patients, and lead revision in 5 patients: (lead migration (1), decreased efficacy (3), and pain (1). There has been a mean of 0.7 reprogramming interventions per patient per year.

The medium-term follow-up data of SNM by tined lead implantation [13] looks promising. When this intervention was performed on a lot of 49 patients, divided in 2 groups (39 had refractory OAB symptoms, 10 had urinary retention), a mean follow-up of 12.4 days was necessary for patients to reach at least 50 % improvement in voiding parameters so they could shift from the test period to the permanent device. The participants were given either a one-stage (10 patients) or a two-stage implant (39 patients, out of which only 80 % had a positive response). In total, 31 patients were followed up for a mean of 15.5 months, during which the modified voiding parameters were analyzed. 90 % of them had at least 50 % improvement. The results for the 21 patients with urgency were: the mean number of voids decreased from 11.7 to 7.3 per day, voided volume increased from 160.2 to 231.1 ml and leakage episodes decreased from 9.5 to 3.3 per day. By comparison, the 10 patients with urinary retention progressed from a mean of 5.44 to 1.2 catheterizations per day, with volumes from 297.6 to 111.6 ml respectively, while voids progressed from 3.7 to 4.2 per day, with volumes from 123.3 to 248.3 ml. The authors conclude that this procedure has positive results on the medium-term and that the two-stage testing with the tined lead seems more reliable than the classic percutaneous nerve evaluation

The female sexual function after SNM Therapy was the subject of another study [14] which aimed to assess changes in quality of life of women with OAB who underwent two-stage SNM therapy. The 16 eligible patients had the results analyzed multiple times during the follow-up. The mean improvement of the Female Sexual Function Index was 27.9 % for the mid-term follow-up (after a median of 22.5 months) and 29.3 % for the last follow-up (after a median of 36.3 months). However, improvement greater than 50% was found in only 4 women (25 %) at mid-term and only 3 women at the last follow-up. There was no correlation between improvement of the Sexual Function Index and quality of life, thus the quality of sexual function correlates with clinical improvement of urinary symptoms.

In men, a study with 54 male participants who have had SNM for lower urinary tract symptoms and suffered from erectile impairment based on the International Index of Erectile Function Score (IIEF-5), showed an improvement in erectile function [15]. After 3 months, 34 % of the patients showed a more than 25 % improvement of the IIEF-5 score. The results of the study also show that the men who benefit the most are the neurogenic retentionists.

Concerns regarding the burden of reprogramming the device were addressed by a study conducted on 47 consecutive patients who underwent SNM implantation and had a satisfactory follow-up [16]. The main indications were urinary symptoms such as frequency, urgency, and incontinence, out of which 47.4 % were attributed to interstitial cystitis. The total number of reprogramming visits was 239, which accounted for a mean of 2 sessions per patient per year. Since there was not found any correlation with predictable variables (gender, age, medical indication), and their number and frequency are reasonable, these sessions are considered a part of the routine follow-up.

5. NEW INDICATIONS FOR SNM THERAPY

Bilateral SNM proved to be (at least in experimental studies) more efficient than the classic unilateral approach [17]. In a study conducted on pigs with iatrogenic detrusor hyperactivity who underwent either unilateral or bilateral SNM, contraction and their amplitude were analyzed. The

results show a greater improvement in contraction number for bilateral compared to unilateral stimulation (from 4.73 to 1.08 and 2.73, respectively), as well as in terms of contraction amplitude (from 12.86 to 3.08 and 8.32, respectively). The authors agree that greater improvement is seen in bilateral stimulation due to higher chance of stimulating relevant nerve fibers.

Another emerging indication is for patients with underlying neurologic dysfunction [18].

Promising clinical data is available for patients with multiple sclerosis, Parkinson's disease, as well as other causes of neurogenic bladder.

When comparing bladder diaries of patients with multiple sclerosis, Parkinson's disease, and other neurologic conditions before and after the procedure, 93% of them described overall satisfaction.

There has been reported improvement in incontinence episodes (68 % reduction), number of voids (43% reduction), nocturia (70 % reduction) and number of necessary self-catheterization maneuvers (58 % reduction).

Despite of its many advantages, there have been discussions comparing SNM therapy to the minimally invasive injection of botulinum toxin A in the detrusor. Relevant variables are the cost and the effectiveness of the treatment, as well as compliance of the patient to each therapy type.

We tried to compare both therapies in terms of advantages and disadvantages:

BoTox-A – Advantages:

- applicable by general urologist;
- "maintenance free" between injections;
- no diathermy or MRI restrictions;
- ease of applications;
- short term safety;
- short term efficacy.

BoTox-A – Disadvantages:

- risk of urinary retention 4-15 %;
- not enough data from randomized trials;
- expensive;
- need for anesthesia;
- need for repeat injections;
- "you can get worse".

InterStim – Advantages:

- long term safety and efficacy;
- pre-testing possible;
- ability to treat concomitant conditions (constipation, pain);
- fast onset of action;
- reversibility;
- "you cannot get worse";
- adjustable level of stimulation.

InterStim – Disadvantages:

- small risk of hematoma at puncture site;
- local anesthesia;
- expensive;
- pp to 50 % non-responders.

6. **CONCLUSIONS**

Sacral neurostimulation is undoubtedly a promising treatment alternative for OAB patients, regardless of whether they are incontinent or not. The technology behind this device is advanced and proves effective, mainly in neurogenic bladder patients. Alternate treatments available also have their benefits and limits as well and no therapeutic option can impose itself over the others. Further development of the devices is underway, and the future is promising for this therapy.

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