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Applications of Neuromodulation of the Lower Urinary Tract in Female Urology

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ABSTRACT

Neuromodulation is becoming part of clinical armamentarium for treatment of a variety of lower urinary tract conditions in female urology. Its increased usage stems from need of patients who have exhausted all other therapeutic options for their complex and poorly understood lower urinary tract disorders. Currently neuromodulation may consist of the use of sacral nerve stimulation (SNS) and injectable therapies. Herein, we will discuss the background and development of SNS, its current indications, methods of patient selection and will review the results of the recent published literature on SNS. In addition, we will discuss some of the newer developments in SNS such as Bion device and the future direction in integration of SNS in female urology.

Key words*: bladder; urination disorders; female; neuromodulation; sacral plexus; electric stimulation*
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INTRODUCTION

The first attempt at electrical stimulation of the lower urinary tract (LUT) may date back to 1878, when the Danish surgeon Saxtorph treated patients with urinary retention by intravesical stimulation (1), in which he inserted a special catheter with a metal electrode transurethrally.

After experimentations with various methods of simulating the bladder through the transurethral approach, direct detrusor stimulation (2), pelvic nerve stimulation (3) pelvic floor stimulation (4), spinal cord stimulation (5), with pioneering work of Tanagho and later Schmidt (6-9), it was demonstrated that the stimulation of sacral root S3 generally induces detrusor and sphincter action (10). Following 2 decades of experimentation with various approaches to sacral root stimulation, finally in October of 1997, sacral neuromodulation for treatment of refractory urge incontinence was approved by the Food and Drug Administration in the United States. Since then and at the time of this writing, more than 20,000 of Interstim (Medtronic Inc., Minnesota, Minneapolis, USA) have been implanted for 3 approved indications of the sacral nerve stimulation (SNS) of the lower urinary tract.

Herein, we will review the various aspects of the electrical stimulation of the bladder and its application in management of the LUT dysfunctions.

MECHANISMS OF ACTION

Neuromodulation of lower urinary tract function can be explained by relatively simple spinal circuits mediating somato-visceral interactions within the sacral spinal cord. It is proposed that SNS activates or “resets” the somatic afferent inputs that play a

pivotal role in the modulation of sensory processing and micturition reflex pathways in the spinal cord (11). Urinary retention and dysfunctional voiding can be resolved by inhibition of the guarding reflexes. Detrusor hyperreflexia and the overactive bladder syndrome can be suppressed by one or more pathways, i.e. direct inhibition of bladder preganglionic neurons, as well as inhibition of interneuronal transmission in the afferent limb of the micturition reflex.

PATIENT SELECTION

The selection of patient for SNS begins with a careful history, physical examination, routine tests such as urinalysis and urine culture, and most importantly use of bladder diaries to objectively record voiding variables.

The important elements of history focuses on the primary voiding variables such as the frequency and severity of urge incontinent episodes and the number of pads used per 24-hour period. For patients with refractory urgency frequency, the number of voids, the voided volumes and the degree of urgency are assessed, and in patients who experience inefficient voiding or urinary retention, the amount voided versus catheterized volumes per 24 hours and the patient's sense of completeness of evacuation are gathered. A voiding diary is invaluable in order to objectively document the patient's voiding habits and complaints. Urodynamic examination is commonly used to identify the patients with detrusor overactivity (DO) with or without urinary leakage or urinary retention. Some reports suggest the utility of the urodynamic studies (UDS) in identification of proper candidates to SNS (12).

ANATOMICAL LANDMARK AND SURGICAL TECHNIQUES OF SACRAL NEUROMODULATION

Sacral S3 foramen is the desired anatomical landmark for placement of lead of the sacral neuromodulation. The techniques for S3 localization have included manual or fluoroscopic methods. The manual approach includes the palpation of the sciatic notch, observation for least curved portion of the sacrum, and measurement of approximately 11 cm from the caudal tip of coccyx (Figure-1). The manual method is more difficult for obese patients or those without palpable landmarks. Chai & Mamo introduced the use of "cross-hair" fluoroscopic technique for S3 localization in 2001 (13). The intent of the fluoroscopy was not meant to see the S3 foramen, but rather help the surgeon to identify a specific region to start percutaneous access of S3 foramen (Figure-2). More importantly, the use of lateral imaging helped determine the depth required for implanting S3 lead (Figure-3). Use of fluoroscopy was familiar to surgeons such as urologists as they use of fluoroscopy in stone surgery and therefore, the application of fluoroscopy to sacral neuromodulation surgery was quickly accepted. The widespread use of fluoroscopic localization of S3 later allowed the introduction of tined S3 lead (14) and transformed the placement of a lead from an open procedure (15) to a completely percutaneous one. The widely adopted percutaneous use of tin lead approach abandoned the need for fixation of the lead by methods such as bone anchors.

Janknegt et al. (16) first described the staged implantation approach in which an implanted S3 lead, rather than the temporary lead, was used for initial testing. The staged technique bypassed the problems

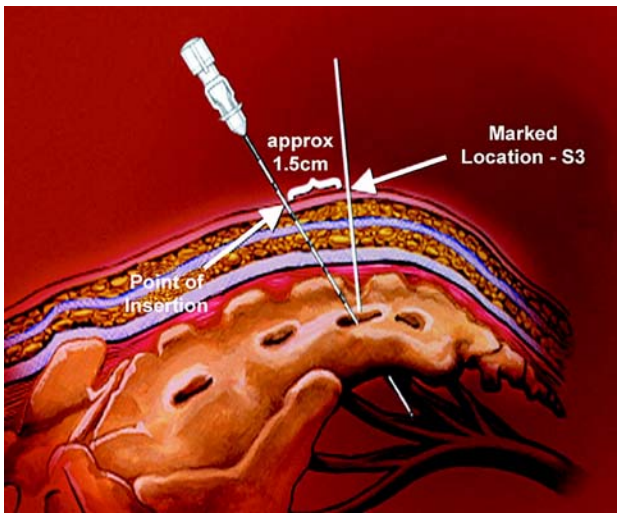

Figure 1 – *Localization of S3 foramen by anatomical landmark.*

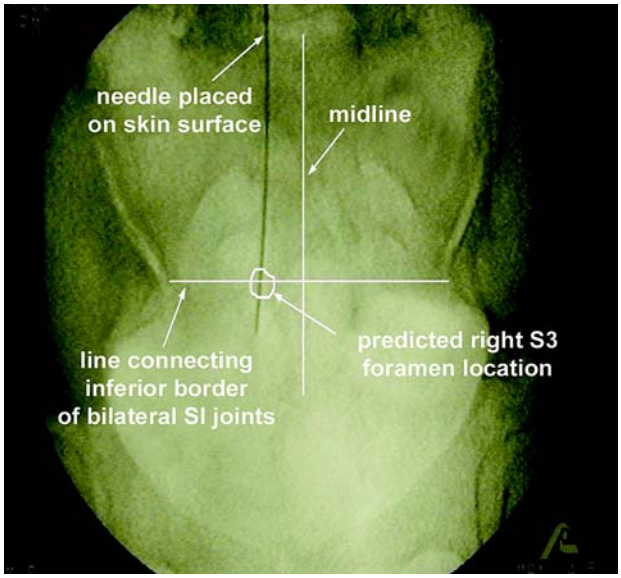

Figure 2 – *Localization of S3 Foramen by cross hair technique (from Chai TC, Mamo GJ: Modified techniques of S3 foramen localization and lead implantation in S3 neuromodulation. Urology. 2001; 58: 786-90, with permission).*

with percutaneous needle examination (PNE) which included a high risk of lead migration and the fact that the original response of the patient obtained by the temporary wire may have not been reproduced by the permanent lead. Several reports later confirmed a higher response rates and lesser rate of lead migration obtained by the staged approach.

After placement of the lead, the following sensory and motor responses related to stimulation of the specific sacral root may be observed:

S2 - Clamp movement or twisting and pinching of the anal sphincter (pulling down the coccyx).
- Plantar flexion of the entire foot, lateral rotation.

S3 - Bellows movement of the pelvic floor.
- Plantar flexion of the great toe(s).
- Parasthesia in the rectum, perineum, scrotum or vagina.

S4 - Bellows motion of the pelvic floor.
- No lower extremity activity.
- Sensing pulling in the rectum only.

The desired response and localization for electrical stimulation of LUT should include S3 responses.

Implantation of SNS consists of 2 steps. Stage I, or the trial stage, which involves the placement of a stimulation lead next to the dorsal root of S3 for a test period between 1-4 weeks (Figure-4). If the patient's symptoms under the existing list of indications for SNS improve more than 50% then the

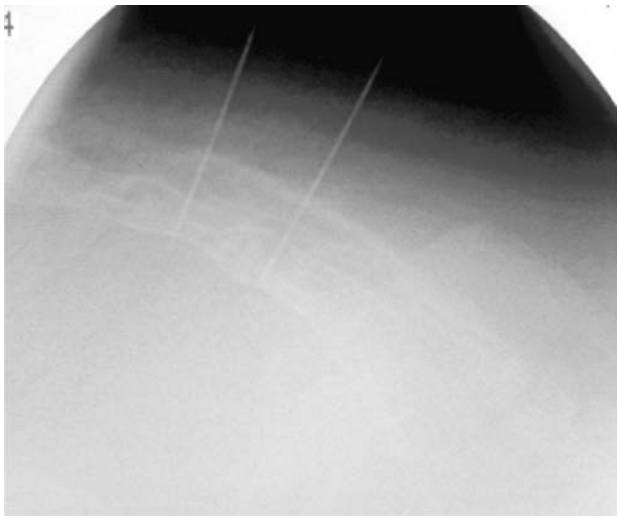

Figure 3 – *Site of percutaneous placement of needle stimulations and stage I lead.*

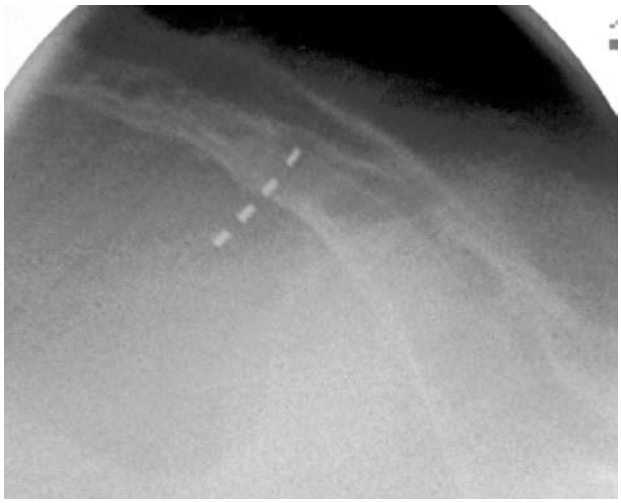

Figure 4 – *Tined lead is in proper position-2-3 contact plates of the quadripole lead are resting on the S-3 dorsal root nerve.*

patient is a candidate to undergo the stage II or permanent step in which the permanent implantable pulse generator (IPG) unit is implanted in the soft tissue of the buttock of the patient (Figures-5 to 7).

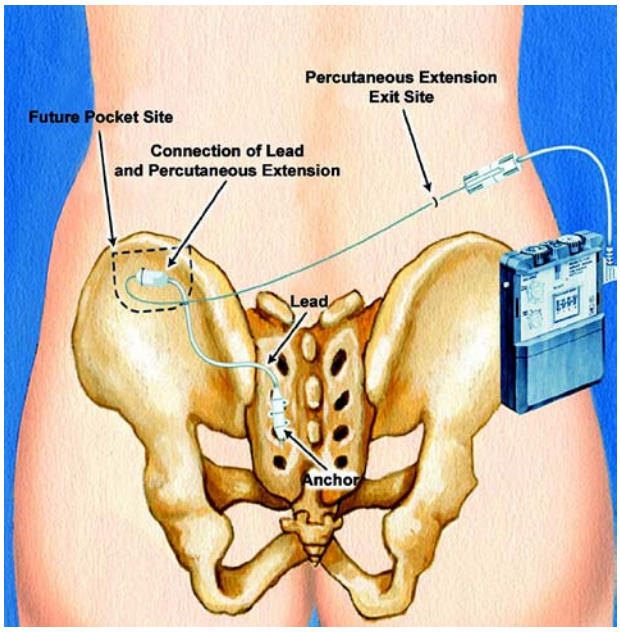

Figure 5 – *Stage I sacral neuromodulation - External stimulator connected to chronic lead for test period.*

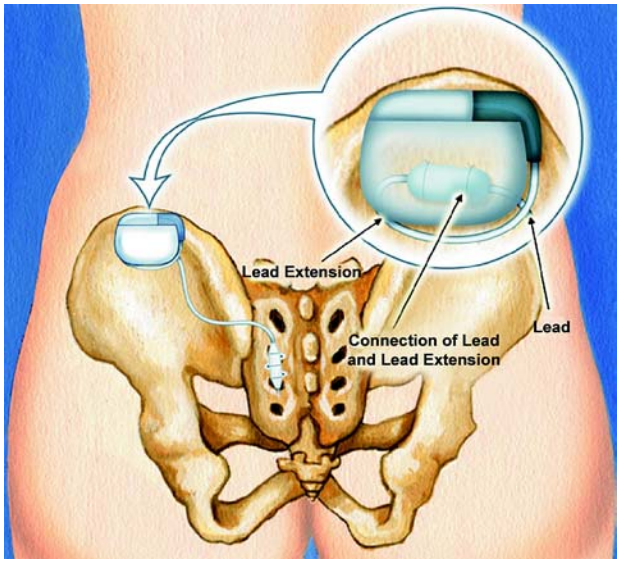

Figure 6 – *Stage II sacral neuromodulation- Implantable pulse generator (IPG) unit is placed in the subcutaneous pocket.*

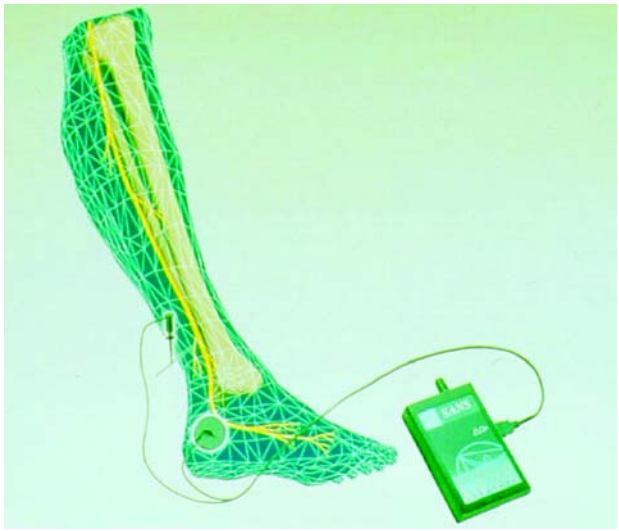

Figure 7 – *SANS device for percutaneous neurostimulation.*

There is no consensus as to whether 1 or 2 implanted S3 leads should be performed as in first stage. Bilateral implantation allows for testing for both the left and right S3 nerve roots. A time of the second stage, the side that is less efficacious can be removed or remain implanted for possible “backup” in case the other side fails. Currently, there is no evidence that bilateral simultaneous stimulation has any added benefits to unilateral stimulation. Furthermore, there is not the ability to stimulate both wires with one IPG in the USA because the IPG is not a dual channel stimulator. One would need to implant 2 IPGs for bilateral simultaneous stimulation. Nevertheless, bilateral implantation allows for a more complete evaluation and possibly offers the patient a higher chance of responding to sacral neurostimulation.

CLINICAL RESULTS

The reported outcomes of the SNS therefore includes the response of patients to the stage I (test stage) and to stage II (permanent implantation).

No discussion on the assessment of a treatment options could be complete without a discussion on the issue of level of evidence. The evidence required in the medical literature is limited to data reported in clinical trials, specifically

excluding expert opinion. This is similar to that required to determine the final judgment of a jury in a legal proceeding, which must be based upon the material evidence presented during the trial. The judgment (opinion) of the jury is not evidence. Evidence is factual information presented.

International Consultation on Incontinence has adopted the Oxford level of evidence as the following categories:

Level 1 - usually involves meta-analysis of trials, randomized clinical trials or a good quality randomized controlled trial (RCT) or "all or none" studies in which no treatment is not an option, for example, vesicovaginal fistula.

Level 2 - includes "low" quality RCT or meta-analysis of good quality prospective "cohort studies". These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

Level 3 - evidence includes: A) Good quality retrospective "case-control studies" where a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition, B) Good quality "case series" where a group of patients all, with the same condition, disease and therapeutic intervention, are described, without a comparison control group.

Level 4 - evidence includes expert opinion where the opinion is based not on evidence but on "first principles" (e.g., physiological or anatomical) bench research. The Delphi process can be used to give "expert opinion" or greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of "options"; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

Reports of Clinical Trials on Urge Incontinence, Urgency / Frequency and Non-Obstructive Urinary Retention

At this point in time, the SNS has been approved by the FDA for 3 indications: urge incontinence (UI), urgency frequency (U/F), and non-obstructive urinary retention (UR). However, SNS has also been reported to be used for other "off label" indications, such as neurogenic bladders in multiple sclerosis, interstitial cystitis, and chronic pelvic pain. Also, there are reports regarding the possible benefits of bilateral SNS. The majority of the reports on the non-formally indicated usages of SNS appear in the form of abstracts or case series.

The initial report on the efficacy of SNS on treatment of refractory urinary urgent incontinence was reported in 1999 (17) (level 2). This study reported the treatment of 76 patients with refractory urgent urinary incontinence from 16 contributing worldwide centers. The patients were randomized to immediate implantation and a control group with delayed implantation for a six-month period. At six months, the number of daily incontinence episodes, severity of episodes, and absorbent pads or diapers replaced daily due to incontinence was significantly reduced in the stimulation group compared to the delayed group. Of the 34 stimulation group patients, 16 (47%) were completely dry, and an additional 10 (29%) demonstrated a greater than 50% reduction in incontinence episodes. The interesting finding was that during the therapy evaluation, the group returned to the baseline level of incontinence when the stimulation was inactivated. Complications were site pain of the stimulator implantation in 16%, implants infection in 19%, and leak migration in 7%.

The use of SNS in urgency frequency was reported in 2000 by Hassouna et al. (18). Similar to the previous design, 51 patients from 12 centers were randomized into an immediate stimulation group and a control group (25 and 26 patients respectively) (level 2). Patients were followed for 1, 3 and 6 months, and afterwards at 6-month intervals up to 2 years. At the 6-month evaluation, the stimulation group showed improvement in the number of voiding dailies (16.9 ± 9.7 to 9.3 ± 5.1) volume per void (118 ± 74 to 226 ± 124 mL) and degree of urgency (the rank 2.2 ± 0.6 to 1.6 ± 0.9). In addition, significant improvement in quality of life was demonstrated, as measured by SF-36.

The report of use of SNS in urinary retention was published in 2001 by Jonas et al. (19), and in this

study, 177 patients with urinary retention refractory to conservative therapy were enrolled from 13 worldwide centers between 1993 and 1998 (level 2). Thirty-seven patients were assigned to treatment and 31 to the control group. The follow-up was done at 1, 3, 6, 12 and 18 months. The treatment group showed 69% elimination of catheterization at 6 months and an additional 14% with greater than 50% reduction in catheter volume per catheterization. Temporary inactivation of SNS therapy resulted in significant increase in residual volume, but the effectiveness of central nervous stimulation was sustained for 18 months after implantation.

In 2000, a follow-up report of some of the above series was published (20) (level 3). This report showed follow-up results after 3 years in all the approved indications. Fifty-nine percent of 41 patients had urinary urgent incontinence. Patients showed greater than 50% with 46% of patients being completely dry. After 2 years, 56% of the urgency frequency patients showed greater than 50% reduction in voids per day, and after 1-1/2 years, 70% of 42 retention patients showed greater than 50% reduction of catheter volume per catheterization.

The results of the use of SNS in the U.S. patient registry were published in 2002 (21) (level 3). The report included the use of SNS in 81 patients with all 3 indications: 27 for urgent continence, 10 with urgency frequency and 10 with urinary retention. In this report, 27 from 43 patients with urgent continence, 10 out of 19 with urgency frequency and 10 out of 19 with urinary retention showed improvement of more than 50%.

The results of an Italian registry were published in 2001 (22) (level 3). This report included the reports of 196 patients - 46 males and 150 females - for idiopathic urinary retention. Fifty percent of patients stopped catheterization and another 13% catheterized once a day at 1 year after implantation. At the 12-month follow-up, 50% of patients with hyperreflexia had less than 1 incontinence episode daily and the problem was completely solved in 66 patients. Of the patients with urgent continence, 39% were completely dry and 23% had less than 1 incontinence episode daily.

Results of use of SNS in Norway were published in 2002 (23) (level 3). The author reported the first 3 years of experience with 53 patients: 45 women and 8 men. This study showed similar results to previous reported series.

Table-1shown the published reports of use of SNS in various conditions of lower urinary tract dysfunction.

Other Indications

Use of SNS for other off-labeled applications has been reported for treatment of interstitial cystitis, chronic pelvic pain, pediatric voiding dysfunction, and neurogenic lower urinary dysfunction seen in multiple sclerosis. None of the reported case series (level 4) has led to new approved indications for SNS at the time of this writing.

COMPLICATIONS

A number of reports have published the complications of the SNS (17-19). The earlier reports describe the complications with PNE, which is no longer used in majority of the centers in the United States. Seigel et al. (20) summarized the complications in patients with refractory urge incontinence, urgency-frequency and urinary retention that were included in the original trials of SNS. The complications were divided into both percutaneous test stimulation related and post implant related problems. Of the 914 test stimulation procedures done on the 581 patients, 181 adverse events occurred in 166 of these procedures (18.2% of the 914 procedures). The vast majority of complications were related to lead migration (108 events, 11.8% of procedures). Technical problems and pain represented 2.6% and 2.1% of the adverse events. For the 219 patient who underwent implantation of the Interstim® system (lead and generator), pain at the neurostimulator site was the most commonly observed adverse effect at 12 month (15.3%). Surgical revisions of the implanted neurostimulator or lead system were performed in 33.3% of cases (73 of 219 patients) to resolve an adverse event. These included relocation of the neurostimulator because of pain at

Table 1 – *Published reports of use of SNS in various conditions of lower urinary tract dysfunction: urge incontinence (UI), urgency frequency (U/F), and non-obstructive urinary retention (UR).*

Study	**Total**	**Patients with UI**			**Patients with U/F**		**Patients with UR**		**Follow up**
		cured	> 50%	Improved	> 50%	Improved	> 50%	Improved	
US National Patient Register (21)	81		27/43		10/19		10/19		
Amundsen & Webster (28)	12		12/12	2/12					
Hedlund et al. (23)	14		13/14	8/14					
Bosch & Groen (30)	45		27/45	18/45					
Shaker & Hassouma (31)	18		12/18	8/18					
Siegel et al. (20)	112		21/41	19/41	16/29	5/29	29/42	24/42	
Schmidt et al. (17)	34	16/34	10/34	26/34			16/34		18m
Grunewald et al. (25)	39		13/18				18/21		18m
Jonas et al. (19)	29						20/29		12m
Hassouna et al. (18)	25				14/25				
Aboseif et al. (32)	32						18/20	2/20	24m

the subcutaneous pocket site and revision of the lead for suspected migration. Explant of the system was performed in 10.5% for lack of efficacy.

Everaert et al. (24) reported the complications related to SNS itself. Among the 53 patients who had undergone implantation of the quadripolar electrode (Medtronic Interstim, Model 3886 or 3080) and subcutaneous pulse generator in the abdominal site (Medtronic Interstim: Itrel 2, IPG) between 1994 and 1998, device related pain was the most frequent problem, occurred in 18 of the 53 patients (34%) and occurred equally in all implantation sites (sacral, flank or abdominal). Pain responded to physiotherapy in 8 patients and no explantation was done for pain reasons. Current related complications occurred in 11%. Fifteen revisions were performed in 12 patients. Revisions for prosthesis related pain (n = 3) and for late failures (n = 6) were not successful.

Grunewald et al. (25) reported their results after 4 years of use of SNS (Grunewald 1999). Complications requiring surgical revisions occurred in 11 of the 37 implanted patients (29.7%). They included infections in 3 cases (8.1%), lead migration in 2 cases (5.4%), pain at the site of the implanted pulse generator in 3 cases (8.1%) and a lead fracture, an electrode insulation defect and skin erosion at the

site of the impulse generator in 1 case (2.7%) respectively.

Hijaz & Vasavada (26) reported the complications of our group at the Cleveland Clinic Foundation. On hundred eighty stage I procedures were performed for indications of refractory overactive bladder, idiopathic and neurogenic urinary retention and interstitial cystitis. Among this cohort 130 (72.2%) proceeded to stage II implantation of the implantable pulse generator. In this group, 59 stage I leads were explanted (27.8%). The majority of lead explants were performed for unsatisfactory or poor clinical response (46/50; 92%). The rest of the explants were done for infection (4/50; 8%). Stage one revisions totaled 22 of the 180 stage one (12.2%). Revisions were done for marginal response (13/22), frayed subcutaneous extension wire (6/22), lead infection (3/22) and improper localization of stimulus (1/22). Eleven (50%) of the revisions proceeded for stage two generator implant. When the revision was done for a marginal response (13/22), the response was ultimately clinically satisfactory in 5/13 (38.5%) and they proceeded to generator implant. For stage II complications, explants was performed in 16/130 (12.3%) of the CCF group. Explants were done for infection and failure to maintain response in 56.3% and 43.7% respectively. Revisions were done for infection, mechanical (generator related), and response causes. The revision rate with stage II was 20% (26/130).

In summary, stage I complications can lead to either explants or revision of the tined lead. The reasons for either cause could be related to response of patient, mechanical failure or infection. Explants for response reasons should not truly be considered a complication as much as it is an integral part of the procedure. Stag II complications are also seen for decay of response, mechanical or infection reasons. Table-2 summarized the common complications of SNS reported in several series.

Hijaz & Vasavada (26) have also presented algorithms for trouble shooting of the SNS problems. When infection at the generator site is diagnosed, the best management would be explanation of the whole system. Despite attempts to salvage some of these patients, follow up revealed that the infection persisted in all and eventual explant was inevitable. Trouble shooting algorithm include search for causes of a) pocket (IPG site) discomfort; b) recurrent symptoms; c) stimulation occurring in the wrong area of pelvic; d) no stimulation; and e) intermittent stimulation.

THE BION DEVICE

In search for a smaller, lesser invasive and more selective electrical stimulation of the bladder, use of the Bion devise (Advanced Bionics Corporation, Valencia CA, USA) in 2 forms (radiofrequency activated bion or RF-bion; and rechargeable bion or bion-r) have been reported. The Bion device is a self-contained, battery-powered, telemetrically programmable, current-controlled mini-

Table 2 – *Summary of common complications of sacral nerve stimulation (SNS).*

	Siegel et al. (20)	**Everaert et al. (24)**	**Grunewald et al. (25)**	**Hijaz & Vasada (26)**
Number of patients	581		37	167
PNE- overall	18.02%	53	N/A	N/A
Stage I- overall	N/A	N/A		12.2%
Stage II- overall			29.7%	20%
Pain at neurostimulator site	15.3%	34%	8.1%	
Suspected lead migration	8.4%		5.4%	10.7%
Infection	6.1%		8.1%	20%
Revision of permanent SNS	33.3%	23%	29.7%	

PNE = percutaneous needle examination.

neurostimulator with an integrated electrode. It has a size of 27 x 3.3 mm and weighs only 0.7 g. It can be implanted adjacent to the pudendal nerve at Alcock's Canal (Figure-8), Bosch, 2005 (27). The results of the Bion pilot studies indicate that a considerable reduction in the degree of detrusor overactivity incontinence can be obtained in severely refractory cases, including women who had failed sacral nerve neuromodulation. The described technique is well tolerated by the patients. It is minimally invasive and relatively simple. Clinical trials of the Bion-r device involving larger numbers of patients are currently under way in the US and Europe.

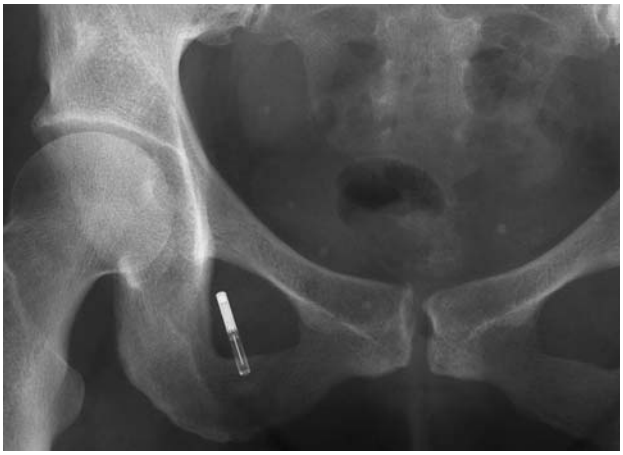

Figure 8 – *Bion device (from Bosch JL: The bion device: a minimally invasive implantable ministimulator for pudendal nerve neuromodulation in patients with detrusor overactivity incontinence. Urol Clin North Am. 2005; 32: 109-12, with permission).*

FUTURE DIRECTIONS

The initial success of via SNS in treatment of some of the most bothersome conditions of the bladder has entered the electrical stimulation of the LUT into the therapeutic armamentarium of physicians dealing with those conditions. Subsequently, entry of this therapy has introduced new lines of research to enable us to answer many open and unresolved questions related to various issues of SNS in clinical practice. Daneshgari and Abrams compiled a list of the pertinent research questions that in the opinion of several experts in the area of SNS need to be addressed. Among those research questions were:

1. Clinical predictors of responders- it is highly desirable to predict, with a reasonable level of accuracy, the potential response of the patients to SNS, thus avoiding the test trial.
2. A comparison between effects of continuous versus intermittent stimulation with aim of improving the percent of patients benefiting from SNS.
3. Whether a unilateral versus bilateral stimulation in either categories of the current indications would lead to an improved and more durable response.
4. Comparing the effects of direct pudendal nerve stimulation versus SNS in patients with refractory OAB
5. Functional brain imaging of responders and failures after implant of SNS, to study possible differences in CNS effects of SNS in these 2 groups
6. Animal models to better delineate mechanisms of action for neuromodulation (i.e. neurotransmitters).
7. Longitudinal study to better understand the interaction between GU, GI and gynecologic complaints.

As in other areas in medicine, we are looking for those sparks of success that will lead to creative fires of expanding knowledge. But no shortcuts are acceptable. Further use of neuromodulation of the lower urinary tract will have to be examined though the time-tested tools such as properly designed clinical trials as we protect and explore the increasing territory of electrical stimulation of the lower urinary tract.

CONFLICT OF INTEREST

None declared.

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