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Sacral Neuromodulation in Non-Obstructive Urinary Retention and Painful Bladder Syndrome: an Update

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Abstract Sacral neuromodulation (SNM) is an established treatment option for several urologic conditions, and its use continues to grow. Indications and applications for SNM are expanding as our understanding of its mechanism of action improves, and our experience develops. Current urologic applications include overactive bladder (OAB), non-obstructive urinary retention, and pelvic pain disorders. SNM has become an established therapeutic modality for non-obstructive urinary retention, while SNM for pelvic pain disorders has found a place in accepted treatment guidelines. This review provides an update on SNM and focuses on developments in SNM relating to the less-studied applications of non-obstructive urinary retention and painful bladder syndrome.

Keywords Neuromodulation · Sacral nerve stimulation · Urinary retention · Cystitis · Interstitial · Pelvic pain · Voiding dysfunction

Introduction

Sacral neuromodulation (SNM) has developed considerably since Schmidt et al. originally described it in 1979 [1]. Since then, there have been significant ameliorations in technique to the point where it is now considered a minimally invasive procedure that can be carried out under local anesthesia [2]. SNM is believed to exert its effect through stimulation of the afferent pathways controlling detrusor function [3]. SNM acts on the S3 nerve root, containing sensory nerve fibers originating in the pelvic floor, which relays parasympathetic motor efferent nerve fibers to exert effect on the external urethral sphincter as well as the pelvic floor musculature [3]. It is through these mechanisms that SNM is thought to restore bladder function in those with non-obstructive urinary retention and improve pain in those with painful bladder syndrome.

The SNM procedure with InterStim (Medtronic, Minneapolis, MN) is typically performed in two stages. The first stage involves the insertion of a trial lead, while the second stage proceeds when a positive response occurs and consists of implantation of an implantable pulse generator (IPG) [4]. Once a patient is deemed suitable for SNM, two tools are available to evaluate its potential treatment effect. One method is peripheral nerve evaluation (PNE), which utilizes a standard electrical wire electrode, whereas first stage tined-lead placement (FSTLP) employs an anchor-studded electrode designed to minimize lead migration [5, 6]. PNE has the advantage of being performed in an outpatient setting with minimal resource use, though it has been shown in a comparison study that FSTLP is a more sensitive screening method to identify patients for SNM. As Leong et al. showed, evaluation with PNE provided a 47 % positive response rate, while that of FSTLP was 69 % ($p<0.001$) [6]. Though often performed under general anesthesia, there have been descriptions of the procedure being carried out under local anesthetic with good results [7].

We aim to present an update on the use of SNM in the setting of non-obstructive urinary retention and painful bladder syndrome.

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Non-obstructive Urinary Retention

Non-obstructive urinary retention represents a complex urologic condition that can pose challenges in its effective management. These patients are often reliant on intermittent or permanent catheterization to drain the bladder. Non-obstructive urinary retention can have a range of etiologies. It may result from detrusor underactivity due to a myogenic or neurogenic cause or may represent idiopathic non-obstructive retention [8]. An important consideration in young women is Fowler's syndrome, which is a disorder involving abnormal pelvic floor musculature and a failure to appropriately relax the external urinary sphincter [9]. Without treatment, urinary retention can lead to several urologic complications, including upper tract deterioration, overflow incontinence, urinary tract infection, bladder stones, and vesicoureteric reflux [10]. Thus, the advent of sacral neuromodulation for this condition is a distinct advancement in our treatment armamentarium.

SNM has emerged as a recognized treatment modality for idiopathic, non-obstructive chronic urinary retention, with favorable results [11]. SNM was approved for the treatment of non-obstructive urinary retention in 1999 and thus far has proven to be one of the few effective treatments [3]. It has been shown to restore volitional voiding in patients with an overactive pelvic floor musculature and urethral sphincter [12]. Though its mechanism of action in treating non-obstructive urinary retention remains incompletely understood, it is theorized to act upon the afferent innervation of the bladder [13]. Magnetic resonance imaging studies have shown that its therapeutic effect in restoring normal detrusor and sphincter function is realized upon the functional interactions between the midbrain and limbic cingulate cortex [13]. A meta-analysis by Gross et al. in 2010 concluded, from the available literature, that SNM is an effective therapy for non-obstructive urinary retention [14]. Though limited to one randomized control trial from 14 articles examining this treatment modality, the mean difference in post-void residual decreased 236 ml and voided volume increased by 299 ml ($p<0.00001$) [14].

Peeters et al. recently reported on their long-term outcomes of SNM for non-obstructive urinary retention [15•]. Of 217 patients with voiding dysfunction who had a successful PNE, a total of 93 patients with idiopathic retention (32 patients with Fowler's syndrome, 61 non-Fowler's syndrome) underwent SNM implantation. With an overall mean follow-up of 46.88 months, success rate was 73 % using a definition of success as >50 % reduction in intermittent self-catheterization rate. Cure rate (100 % success), defined as no intermittent self-catheterization and no voiding dysfunction, was reported as 62.5 and 53 % for Fowler's syndrome and idiopathic urinary retention, respectively [15•]. Complications were uncommon, though overall re-intervention rate was 41 % [15•]. This study represents one of the largest published data sets examining SNM in non-obstructive urinary retention.

Al-Zahrani et al. reported their 14-year SNM experience at a single center [16•]. A total of 41 patients with idiopathic urinary retention underwent PNE, of which 16 proceeded to a permanent SNM implant. With an overall median follow-up time of 50.7 months (all greater than 12 months), the long-term success of SNM was 87.5 % for idiopathic urinary retention. Success in this study was defined as greater than 50 % improvement in Global Response Assessment (GRA) [16•]. Though the overall number of patients with idiopathic urinary retention was relatively small, the long-term data supports the assertion that SNM is an effective option in those with a successful PNE.

A recent study by Saber-Khalaf et al. examined the use of SNM in male patients with chronic urinary retention [17•]. In their series, 21 males underwent stage 1 SNM, with complete voiding restored 14 patients (66.7 %). Thirteen of these successful stage 1 trials proceeded to stage 2, with durable effect at a mean follow-up time of 34 months (range 7–68 months). They also demonstrated a positive correlation between treatment success of SNM in younger males in this series ($p=0.025$) [17•]. This finding should help clinicians better select and inform patients who may be appropriate candidates for SNM. Though this paper is somewhat limited by a small sample size, it provides an interesting and encouraging perspective on SNM on the traditionally less-reported male patient population.

Proper work-up of the patient is essential, and urodynamic (UDS) assessment is crucial to help delineate who may be ideal candidates for SNM. If poor contractility exists on UDS during the voiding phase, then the probability of SNM success decreases. In those patients with poor contractility or a neurogenic etiology, the response of SNM may be less optimal, and patients should be counseled accordingly.

SNM can prove to be an especially attractive modality in non-obstructive retention given the lack of acceptable alternative treatment options. It is important for those patients with non-obstructive urinary retention to learn intermittent self-catheterization first. The benefits are twofold, as it helps assess response during the trial phase by documenting post-void residuals and voided volumes, as well as providing a "fall-back" treatment plan should SNM fail. To date, SNM for non-obstructive urinary retention has proven to be a safe and effective option. It should be considered in the appropriately selected patient to treat this difficult condition.

Painful Bladder Syndrome

Bladder pain syndrome (BPS) associated with interstitial cystitis (IC), also referred to as IC-BPS, is a chronic, often debilitating, condition that can prove challenging in its

management. The American Urological Association (AUA) has adopted the IC-BPS definition set forth by the Society of Urodynamics and Female Urology (SUFU): "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes" [18, 19].

The exact pathophysiology behind IC-BPS remains incompletely understood, though many theories have been put forward. In fact, it may be a multitude of factors combining to give the overarching symptomatology that typifies IC-BPS. It has been proposed that central nervous system deregulation and the associated responses may play an important role [20]. Urothelial cell dysfunction appears significant in the disease pathway, leading to central and peripheral neural upregulation, with the eventual perception of pelvic pain. IC-BPS may be also associated with an inflammatory response, leading to neurogenic inflammation (e.g., in pelvic floor overactivity), and final central and peripheral neural upregulation, and resultant mast-cell activation [21]. In the presence of this inflammatory response, it is thought that physiologic bladder filling may induce an afferent barrage via bladder unmyelinated C fibers, which carry nociceptive signals. This would then lead to the urinary frequency, urgency, and pain often experienced by IC-BPS patients [22]. These theories describing the putative neurogenic component in the etiology of IC-BPS lay the foundation for proposing potential targets and mechanism of action of SNM in alleviating symptoms.

As alluded earlier, our understanding of the mechanism of action of SNM for IC-BPS remains to be fully elucidated. There are two general hypotheses for its mechanism of action. The first is that SNM may restore an equilibrium among excitatory and inhibitory nerve impulses to and from the pelvic organs at a sacral and supra-sacral level [23]. The second theory is rooted in the belief that sacral neuromodulation balances afferent and efferent neural pathways that lead to improved bladder function [21, 24]. With these proposed improvements in bladder neural functioning, it is believed that the symptoms experienced should be ameliorated.

AUA guidelines for the treatment of IC-BPS include the option SNM as a fourth-line treatment option. This is provided that other therapies have proven ineffective for adequate symptom control, or if the clinician and patient agree that SNM is the optimal approach for a given patient [19].

Given that the US Food and Drug Administration has approved SNM for frequency, urgency, and urge incontinence, non-obstructive urinary retention, and fecal incontinence, it has been suggested by some that painful bladder syndrome as an approved indication should naturally follow [22]. While there remains a paucity of data from randomized controlled trials examining the use of SNM for IC-BPS, there have been several non-randomized prospective and retrospective studies documenting the efficacy in treating IC-BPS with SNM. Inherent challenges in designing and comparing studies on IC-BPS include the heterogeneous patient group, small patient numbers, relatively short follow-up duration, and the variability in outcomes recorded.

Comiter prospectively studied 25 patients with refractory IC, of which 17 proceeded to permanent SNM implant [25]. This study demonstrated significant patient improvements in mean daytime frequency and nocturia, with follow-up to 14 months. They also reported increased mean voided volume (111 to 264 ml), average self-reported pain (scale 1–10) decrease of 5.8 to 1.6 points, and decreased Interstitial Cystitis Symptom and Problem Index (ICSI and ICPI) scores from 16.5 to 6.8 and 14.5 to 5.4, respectively (all $p<0.01$) [25].

Zabihi et al. evaluated 30 consecutive patients with severe refractory chronic pelvic pain (CPP)/IC who underwent stage 1 SNM [20]. Twenty-three (77 %) had a successful trial and underwent permanent implantation with a mean follow-up of 15 months (range 6–32 months). They found that pain score improved by 40 % ($p=0.04$) and average patient reported improvement was 42 %. ICSI and ICPI scores improved by 35 and 38 %, respectively ($p=0.005$, 0.007). It should be noted that Short Form Health Survey-36 scores did not improve significantly and that five devices were explanted, four of which for failure, and the other infection [20].

Powell and Kreder reviewed 39 patients who underwent stage 1 SNM for refractory IC-BPS, of which 22 had permanent generator implanted for >50 % relief from presenting complaint [26]. It was found that 77 % (17 of 22) patients reported long-term cure or more than 50 % improvement in symptoms and 64.7 % reported no dysuria or pain on long-term follow-up with an average of 59.9 months duration. Of note, 11 of 22 patients (50 %) required device explantation or revision, 4 for battery depletion, and 3 for loss of effect [26].

Two recent studies reported on their long-term data for SNM in IC-BPS patients. Gajewski and Al-Zahrani retrospectively reviewed 14 years of SNM for patients with intractable bladder pain syndrome [27•]. A total of 78 patients with refractory symptoms of BPS were evaluated with PNE for SNM suitability. A positive response was seen in 44 patients (56.4 %), with equivocal results in 12 (15.3 %) who subsequently underwent staged lead insertion. Success was achieved in 72 % of patients undergoing SNM using a GRA improvement of at least 50 %. Median follow-up was 61.5 months, and revision rate was 50 % [27•].

Marinkovic et al. described their experience with SNM for IC, reviewing 34 patients with recalcitrant IC who underwent staged SNM testing [28•]. Thirty of 34 patients proceeded to stage 2 SNM implantation, with a median follow-up of 86 months (minimum of 72 months). A successful trial was defined as >50 % improvement in number of voids without return of urgency/frequency. This study did not incorporate pain scores into the determination to proceed to stage 2, though a significant decrease in post-op visual analog pain

scale (VAPS) was noted. Mean post-op VAPS was 6.5±2.9 compared with 2.4±1.1 pre-op ($p<0.01$) in treated patients. Mean pre-op/post-op pelvic pain and urgency/frequency scores were 21.61±8.6 compared to 9.22±6.6 ($p<0.01$) [28•]. Though a surprisingly high rate of stage 1 success was noted, the favorable results, long duration of follow-up, and high patient satisfaction at 80 % were encouraging.

There exists some controversy in regards to whether unilateral or bilateral lead placement is favored in those patients undergoing SNM for IC-BPS. There is a paucity of data examining unilateral versus bilateral lead placement in IC/PBS patients, though it has been studied in the refractory overactive bladder (OAB) population. Pham et al. reviewed 124 patients who underwent either unilateral or bilateral lead placement for refractory OAB. They found that those who underwent bilateral placement showed an improvement in success of stage 1 trials, with 58 and 76 % success rates seen in the unilateral and bilateral group, respectively [29]. Further, Marcelissen et al. reported on 12 patients who failed unilateral lead placement, who subsequently demonstrated treatment success when a contralateral lead was added [30]. It should be noted that these studies were not specific to the subset of patients undergoing SNM for IC-BPS, and it is not known whether the results can be extrapolated. Conversely, it has been reported by Scheepens et al. that bilateral lead placement is no more effective than unilateral lead placement for SNM for refractory OAB [31]. The sample size in this study was relatively small and underpowered to give a definitive answer on bilateral versus unilateral lead placement. Therefore, their conclusion was that bilateral SNM could be considered [31]. There is certainly some evidence for bilateral lead placement, and an argument for its routine use can be made, though we have had excellent results with unilateral lead placement in SNM for non-IC/PBS indications. It was suggested by Zabihi et al. that because PBS and pelvic pain is not a unilateral process, it would be reasonable to conclude that bilateral SNM may be superior to unilateral lead placement in PBS. As mentioned, they demonstrated a 77 % success rate with bilateral lead placement in patients with PBS/IC/CPP [20]. Though it is associated with increased costs, bilateral lead placement allows for a greater range of programming after lead placement, which we feel may translate into an improved chance of treatment success.

The above studies have proven valuable in documenting the efficacy of SNM in patients with refractory IC-BPS, which is encouraging given the recalcitrant nature of the condition. It is important that patients have realistic expectations and that they understand that cure is not always possible. There also exists a high explantation and revision rate, and patients should be counseled on this accordingly. SNM is a useful tool for patients with refractory IC-BPS and should most certainly be considered in the appropriately selected patient when other treatment options have failed.

Conclusion

SNM has an established place in the management of several lower urinary tract functional disorders, including non-obstructive urinary retention and bladder pain syndrome. It has become a useful tool in the urologists' treatment armamentarium, though appropriate patient selection is essential. Efforts to further our understanding of SNM and its potential applications are warranted. Continued research studying the use of SNM to treat urologic conditions is necessary, both to foster treatment innovation, as well as establish efficacy for existing indications.

Compliance with Ethics Guidelines

Conflict of Interest Nathan Hoag and Johan Gani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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