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BPS/INTERSTITIAL CYSTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Sacral Neuromodulation in the Management of Bladder Pain Syndrome/Interstitial Cystitis

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Abstract

Purpose of Review In this review, the current literature available about sacral neuromodulation (SNM) in the management of bladder pain syndrome/interstitial cystitis (BPS/IC) will be addressed.

Recent Findings SNM has emerged in recent years as a minimally invasive option of management for refractory BPS/IC patients that otherwise should undergo reconstructive procedures. Although not approved by the FDA for this specific group of patients, the available data show a favourable response in both objective and subjective variables with a long-lasting effect. The implantation rate after the test phase is greater with the insertion of the quadripolar tined lead than with the monopolar percutaneous nerve evaluation. Most complications can be managed with reprogramming. The reintervention rate is still high, although it decreases when excluding surgeries for battery exchange.

Summary Sacral neuromodulation should be considered in the treatment algorithm of patients with BPS/IC, as suggested in international guidelines. It provides symptomatic relief in a significant proportion of patients, being a fully reversible procedure with a very favourable complications' profile. Reintervention or explantation risk factors have not been consistently established.

Keywords Bladder pain syndrome · Interstitial cystitis · Sacral neuromodulation

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic pelvic pain syndrome (> 6 months) perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as urgency or increased frequency, in the absence of urinary tract infection or other obvious pathology [1, 2]. Its primary aetiology remains unknown, and it probably has a multifactorial origin. Several mechanisms have been proposed that seem to be initially linked with a chemical, biological or autoimmune aggression:

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- Glycosaminoglycans layer defect [3–5];
- Mast cell-induced inflammation of the bladder wall [6, 7];
- Autoantibodies [8–13];
- Infectious mechanisms: as a proper urinary tract infection or as a disturbance of the normal bladder microbiota [14–17];
- Crossed organ sensitisation [18–21];
- Peripheral and central nerve system sensitisation [22, 23].

Due to the difficulties underlying this condition's diagnosis, which is done mainly by exclusion of confusable diseases, there is a huge variability in the definition of BPS/IC used in the literature, and consequently, it is difficult to establish the real incidence and prevalence of this syndrome. One of the first population studies, performed in Finland, set BPS/IC prevalence in 10.6 cases per 100,000 inhabitants with a higher rate in women (18.1 cases per 100,000 women). Men account only for 10% of the population diagnosed with BPS/IC [24]. However, several years after, another Finnish group reported higher figures, more than 200 cases per 100,000 inhabitants [25]. In the USA, epidemiological studies reported a variable prevalence. One of the first studies published [26] estimated BPS/IC global prevalence in 43,500–90,000 cases (doubling Oravisto's Finnish results). In Spain, the first epidemiological study was published recently by members of IFU Group (Group of Investigation of Health Outcomes in Functional and Urodynamic Urology) with the collaboration of 37 Functional Urology units from all over Spain. The results obtained showed that 5.4% of the patients visiting these units were diagnosed with BPS/IC, with 9 women for each man [27]. When the diagnosis includes a cystoscopic confirmation, prevalence falls. Nevertheless, it is well known that this syndrome is heavily underdiagnosed and, for this reason, population-based surveys might be closer to the real prevalence of this entity [28].

Management of BPS/IC is complex and requires a multidisciplinary approach involving urologists, gynaecologists, physiotherapists, nurses, psychotherapists, and chronic pain specialists. Stepwise approach from less invasive to more invasive therapies must be followed. Conservative and pharmacological treatments have been already treated in this issue, but it is well known that up to 10% of BPS/IC patients are refractory to these therapies. Before the development and introduction of non-invasive methods, the options available for those patients included major surgeries such as augmentation cystoplasty; supratrigonal and subtrigonal cystectomy; urinary diversion without cystectomy; and, finally, simple cystectomy with formation of an ileal conduit. But even after the complete removal of the bladder and the urethra, pain may persist [29], a point that should be thoroughly clarified to patients before considering surgical options. Furthermore, some groups have reported that patients with BPS/IC without Hunner's lesions, with a greater bladder capacity [30, 31] and localising the main painful point at the urethra [32] could have a worse response to reconstructive surgery. Although it is not yet approved by the FDA for this indication, sacral neuromodulation (SNM) has been used for refractory BPS/IC by multiple authors with an acceptable effectiveness, considering that in this group of patients, behavioural, oral, and intravesical treatments have previously failed.

Role of Sacral Nerve Neuromodulation in BPS/IC

Mechanisms of Action

Neuromodulation can be defined as a physiological process in which the influence of activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction [33]. SNM is supposed to balance excitatory and inhibitory impulses from and to the pelvic organs at sacral and suprasacral centres through the stimulation of afferent nerves in the pelvis. The electric pulses are supposed to modulate not only the spinal cord reflexes but also brain networks. The latter has been investigated with functional magnetic resonance. In a study with overactive bladder patients, brain activity decreased in the left anterior cingulate cortex, the bilateral insula, the left dorsolateral prefrontal cortex and the bilateral orbitofrontal cortex after sacral neuromodulation [34•]. It has been also studied that changing SNM stimulus intensity alters the patterns of brain activity changes [35•].

The effect of SNM on pain disorders is usually explained by the gate theory proposed by Melzack and Wall [36]. They suggested that pain perceived to have a visceral origin, which stimulates primary afferent fibres and travels to the brain via transmission cells, could be blocked by converging impulses arising from a somatic origin (by non-nociceptive fibres at the same dermatome) that activate inhibitory interneurons located in the dorsal horn of the spinal cord. Impulses from the dorsal horn are controlled by a descending system containing fibres from the brainstem, thalamus, and limbic lobes, and thereby, SNM controls the pain sensations at the spinal segmental gate and modulates pain sensation at higher brain centres [33].

Birder and de Groat demonstrated that certain spinal areas (specially the dorsal commissure and the lateral laminae near the sacral parasympathetic nucleus) showed increased c-fos expression after both noxious (irritative intravesical stimulus) and non-noxious (bladder distension with saline) inputs, converging on the same dermatome [37]. It was also shown that a nociceptive afferent input from the pudendal nerve coming from the urethra activated cells in similar regions of the cord as does a nociceptive input from the bladder. This finding supports Ruch's convergence theory of visceral referred pain [38]: nociceptive input from visceral and somatic structures converge onto the same central nociceptive pathways.

In 1991, Thon et al. hypothesised that SNM could reduce the perceived intensity of the pain by masking or changing it through the sensation of the electrical stimulation [39].

Clinical Findings

We can find in the literature small case series and retrospective and prospective studies showing the efficacy of SNM in patients with BPS/IC refractory to conservative treatments, including both oral and intravesical drugs. Some studies also include a heterogeneous patient population (pelvic pain syndromes and bladder pain syndromes with and without typical cystoscopic findings), making the comparison between results suboptimal. However, the evidence regarding the effectiveness of SNM in BPS/IC is increasing. Table 1 summarises the main findings of those studies focused on the use of SNM for the treatment of BPS/IC or associated chronic pelvic pain conditions.

SNM for the treatment of BPS/IC first appeared in the report by Shaker et al. in 1999 on patients implanted for urgency-frequency syndrome that also complained of pelvic pain, although no specific data and figures are given [40]. Zermann et al. published the first case report on the use of sacral neuromodulation in a patient with severe pain due to interstitial cystitis, with a significant improvement 6 months after implantation [41]. At the same year, Chai et al. reported their initial experience with the percutaneous nerve evaluation (PNE) in 6 patients, showing an improvement in both objective (voiding frequency, urinary heparin-binding epidermal growth factor–like growth factor concentration, urinary antiproliferative factor activity) and subjective (pelvic pain and urinary urgency scores, patient's impression of improvement) data [42]. One year later, Maher et al. reported their data on 15 women diagnosed with refractory IC who underwent PNE. The patients showed a significant increase of + 53 ml in the mean voided volume and also in patients' quality of life (improvement in the Short Urinary Distress Inventory and SF-36 Health Survey). They also had a decrease in − 9 episodes of day-time micturition, − 4 nocturia episodes, and − 6.5 points in the visual analogue pain scale [43]. However, in these first reports, no follow-up information is given.

Siegel et al. published in 2001 their experience with a prospective series of 10 patients with chronic pelvic pain who underwent InterStim® implantation after successful PNE, showing a decrease in pain scores from an average of 9.7 to 4.4. At the end of the follow-up (average of 19 months), 9 patients had a decrease in the severity of the worst pain compared with baseline. Seven patients answered to a pelvic pain questionnaire mailed by the authors, and although they all would undergo again the procedure, only 6 still were using the InterStim® with a median improvement of 85%. They also reported 27 adverse events; 3 patients asked for device explantation due to lack of efficacy, another one required implantable pulse generator (IPG) removal due to wound infection with successful re-implantation, and a fifth one needed IPG relocation due to pain at IPG site [44].

Comiter published a prospective study in 2003 evaluating 25 patients with BPS/CI refractory to conservative treatments. The evaluation of results was done through voiding diary, pain score on a scale of 0–10, and the Interstitial Cystitis Symptom Index-International Cystitis Problem Index (ICSI-ICPI) questionnaires. The response rate to the test phase was 68% (40% in patients tested with PNE and 87% in patients tested with quadripolar lead insertion). With a mean follow-up of 14 months, there are significant improvements in voiding diary parameters and ICSI-ICPI scores and an average decrease in pain of 4.2 points. Loss of effect of SNM therapy occurred in one patient [45].

In the same year, Peters et al. reported their experience in 37 tested patients, from whom 26 (21 women and 15 men) underwent permanent quadripolar lead and IPG implant. They also reported a better response to test phase in patients with the quadripolar lead than with the monopolar PNE lead [46]. The same observation has been made in the study by Powell and Kreder, although long-term efficacies in both groups are similar [47].

Whitmore et al. also published a multicentre study sponsored by the manufacturer in which 33 women with BPS/IC were tested for SNM. It was a clinically homogeneous population refractory to conservative treatment with oral drugs (hydroxyzine, amitriptyline, and pentosan polysulfate) and intravesical instillations (dimethyl sulfoxide). Improvements ≥ 50% in urgency and bladder pain scales, parameters of the voiding diary, and/or ICSI-ICPI questionnaires were found in 76% of the women tested, but the device was implanted in 51.6% of the patients. No relationship was found between previous failure to oral pentosan polysulfate or intravesical dimethyl sulfoxide and patient's response to SNM [48].

The Swiss Sacral Neuromodulation Working Group published in 2007 the results of a nationwide registry of SNM for refractory lower urinary tract dysfunction including 17 tested patients with chronic pelvic pain syndrome (11 women and 6 men). Bilateral implantation was done in two patients and unilateral in 5 patients. With a mean follow-up of 10 months, patients maintained a 65% of improvement at the last visit [49].

Regarding mid- and long-term results of SNM in BPS/IC patients, Marinkovic published in 2011 a retrospective series of 30 patients with a mean follow-up of at least 6 years. Their results showed significant improvements in voiding diary's variables (frequency, nocturia, voided volumes) and urinary symptom scales, and an average decrease in VAS from 6.5 to 2.4. The reintervention rate not related to battery changes in this series is high (27%), but in all cases, they were related to trauma of various kinds that caused electrode migration or skin erosion at the pulse generator site [50].

Table 1 Summary of the main findings of those studies focused on the use of SNM for the treatment of BPS/IC or associated chronic pelvic pain conditions

Study	Type	Women/men	Mean age (range, years)	Mean duration of BPS/IC (range, years)	Diagnosis BPS/IC	Evaluation	Variables				Improvement threshold for implantation (%)	Implantation rate (%)	Follow-up (months)	Reintervention rate (%)	Explantation rate (%)
							Bladder diary	VAS	SF-36	Other questionnaires					
Chai [42]	P	6/1	-	-	NIDDK	PNE	x	x				-	-	-	-
Maher [43]	P	15/0	62 ± 17.8 (26–87)	5.2 ± 2.7 (2–12)	NIDDK	PNE	x	x	x	x		73	-	-	-
Siegel [44]	P	9/1	48 (22–60-)*	3 (1.5–11)	n/s	PNE		x	x	x	40	10/10	19 (6–74)	50	30
Comiter [45]	P	9/1 15/0	46 (22–77)	-	NIDDK	PNE Quadripolar lead	x	x		x	50	40 87	14 (2–28)	0	0
Peters [46]	P	21 16	45 (17–68-)*	-	NIDDK	PNE Quadripolar lead	x			x	50	52 94	5.6	43 0	0
Whitmore [48]	P	33/0	44.0 ± 15.7	4.1 ± 4.7	NIDDK	PNE	x	x		x	50	51.5	-	-	-
Zabihi [63]	P	21/9	46.3	-	Clinical	Bilat caudal epidural SNM		x	x	x	50	77	15 (6–32)	39.1	22
Powell [47]	R	32/7	54.4	-	NIDDK	PNE Quadripolar lead					50	39.4 81.8	59.9	50[¥]	27.3
Marinkovic [50]	R	34/0	41 ± 14.8 (23–61)	7.81 ± 5.58 (1–20)	n/s	Tined lead	x	x		x	50	76.5	86 ± 9.8 (60–94)	27	
Gajewski [51]	R	70/8	42.4 ± 11.7	49.7 ± 40.8	ICI-ESSIC	PNE/tined lead	x			x	50	59	61.5 ± 27.7 (12–132)	50	28
Ghazwani [52]	R	21/0	44.3 ± 8.9 (33–54-)*	3 ± 0.8 (2–4)*	NIDDK	PNE	x	x		x	50	52.4	71.5 ± 9.3 (60–84)*	36.4	0
Hernández 2020	R	17/2	53 (35–77)	-	Clinical	Tined lead		x		x	50	63.15[§]	96.25 (12–204-)*	75[¥]	16.66

*Only implanted patients; [¥] including battery exchange; [§] 15 implanted, 12 followed

BPS/IC, bladder pain syndrome/interstitial cystitis; *NIDDK*, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases; *n/s*, not specified; *P*, prospective study; *PNE*, percutaneous nerve evaluation; *R*, retrospective; *SF-36*, SF-36 Health Survey; *SUDI*, Short Urinary Distress Inventory; *VAS*, visual analogue scale

Gajewski and Al-Zahrani published two studies in 2011 regarding the long-term follow-up of patients treated with SNM, but only one of them focused exclusively on patients with BPS/IC [51]. Seventy-eight patients underwent the test phase (70 PNE and 8 quadripolar leads) and 46 proceeded to the implantation of the InterStim® device (59%). Long-term success rate (average follow-up 62 months) was 72% and the average Global Response Assessment scale improvement in these patients was 80%. Reasons for device removal were poor outcome (9 patients), painful stimulation (3), and radiation of the stimulation to the leg (1 patient). Average durability of the battery was 93 months (± 25.1).

Ghazwani et al. also reported their results with SNM specifically in patients with BPS/IC. They evaluated the improvement in pain score and in the urinary distress inventory short form (UDI-6). They observed that the response for the voiding diary variables and bladder pain scale was not only evident in the 1-year follow-up, but it continued to improve thereafter with a mean follow-up of 71.5 months [52].

The most concerning problem with SNM besides reprogramming is the reoperation rate, which has been addressed in large series studying all indications. Shih et al. analysed possible predictors of reintervention in a series of 142 implanted patients, including age, sex, obesity, diabetes, chronic pain, type of urinary tract dysfunction, and use of non-TinedLead electrode versus TinedLead. A total of 55 (38.2%) patients required reoperation, and the overall explantation rate was 24.6% (35/142 patients) with an average time to device removal of 44 months (range 3–124 months). They observed an increased risk of reintervention in those patients with BPS/IC or a history of chronic pain (including fibromyalgia, chronic spinal pain, chronic pelvic pain and use of narcotic medication), although it did not reach statistical significance. However, the multivariate analysis did not show any association between any of the factors studied and the risk of reintervention [53]. In a study with 407 implanted patients and a median follow-up of 28.9 months (range 1.6–121.7) designed specifically to assess predictive factors of reintervention, Peters et al. found 134 patients (32.9%) requiring reoperation at (median) 22.9 months (25th and 75th percentiles, 8.6 and 45.1 months, respectively), including 78 patients (19%) who had their lead and/or IPG revised and 56 (14%) explantations at median 18.4 months (range 1–87.5) since implant. After excluding battery replacements, the overall reoperation rate was 24%. They found a higher proportion of reinterventions among patients with a diagnosis of BPS/IC. However, when it was analysed with other variables like independent factors (gender, body mass index, follow-up time, medical comorbidities, and presence of complications), a longer follow-up time and the presence of any complications with the procedure were the only statistically significant factors of reoperation [54].

Some groups have reported their overall experience with SNM including patients with BPS/IC. For example, Donon et al. published a series with 12 patients referring BPS/IC and 8 patients with bladder hyperactivity and pain, and they found that a 58.3% were improved, having 2 considering themselves as cured [55]. Peeters et al., in a retrospective study with 217 implanted patients for different indications (70 urgency incontinence, 34 urgency-frequency syndrome, 94 idiopathic urinary retention, 11 neurogenic bladder, 8 BPS/IC, 1 nocturnal enuresis) and with a mean follow-up of 20 months in the subgroup of BPS/IC, showed that all these patients reported a subjective improvement in pain of between 70 and 79% with no postoperative complications [56]. But not all groups have had a good experience with SNM in BPS/IC patients. For example, Elhilali et al. reported their long-term experience including two patients with BPS/IC and two patients with chronic pelvic pain, but only one of the patients with pelvic pain reported improvement [57].

Significant reductions in the use of narcotics have been reported in several studies, but it was the main focus in the study by Peters et al. in 2004. Eighteen of the 21 patients included used chronic narcotics before the InterStim®, and the other three took non-narcotic analgesics. With a mean follow-up of 15.4 months after implantation, the mean narcotic use decreased from 81.6 mg/day of morphine dose equivalents (MDE) before implantation to 52.0 mg/day (36%; $P = 0.015$), having four patients that ceased using all narcotics [58]. In the study by Powell and Kreder, medication use also decreased after implantation with 46.2% of patients dependent on amitriptyline stopping this medication completely, 54.5% on hydroxyzine stopping, 60% stopping pentosan polysulfate, 60.0% no longer requiring DMSO, and 20% no longer requiring narcotics postoperatively [47]. A reduced intake of different drugs has been reported in other studies [52].

Other formulas to objectively assess the effect of SNM have been explored. We have already seen that in year 2000, Chai et al. identified a seven-fold increase in urinary heparin-binding epidermal growth factor–like growth factor concentration and a decrease in the urinary antiproliferative factor activity besides a clinical response to SNM [45]. Fourteen years after, Peters et al. studied the changes on the urinary secretion of different chemokines. Before treatment, urine levels of CXCL-1, sIL-1ra, monocyte chemotactic protein-1 (MCP-1), and CCL2 positively correlated with clinical variables (pain score, urgency, Interstitial Cystitis Symptom Problem Index [ICSPI], daily voids). After 24 weeks of treatment, the chemokines' urinary level decreased [59].

Mahran et al. [60••] have performed a systematic review independently analysing patients with BPS/IC and those with chronic pelvic pain of different aetiologies (such as chronic anal pain or chronic postsurgical pelvic pain).They reported that, although patients with pelvic pain not specifically due to BPS/IC show slightly better response to SNM, patients with

pure BPS/IC also have statistically significant improvement in pain according to visual analogue scales (−4.13 in BPS/IC versus −5.72 in non-BPS/IC).

Wang et al. have also reviewed 17 studies including more than 500 patients with follow-ups of up to 86 months [61]. Main variables analysed were reduction of pain, reduction of the ICSI-ICPI questionnaire scores, and success rates of SNM therapy. Twelve studies evaluated pain using a visual analogue scale (VAS), with an average reduction of 3.99 points on a 0–10 scale, somewhat lower than that reported in our series (5.85). The ICSI-ICPI questionnaire scores were also significantly reduced, and success rates reported were between 60 and 98%. Complication rates ranged between 0 and 56%, with a mean explantation rate of 8%. Medium and long-term results (76% success) did not differ significantly from the short-term results (88% success), thus not confirming findings previously reported by other authors according to which the effect of SNM therapy in BPS/IC could be less durable than in other indications [62, 63].

Other implantation routes have been proven. Zabihi et al. reported the short-term follow-up (mean of 15 months) of 21 women and 9 men treated with bilateral lead implantation accessing the sacral epidural space through the sacral hiatus and placing the quadripolar tined leads in a retrograde fashion under fluoroscopy over the S2–S4 sacral nerve roots (caudal epidural SNM). Patients not only refractory to conservative management but also those who have not previously responded to S3 InterStim® implantation were included and evaluated with the O'Leary IC symptom and problem index (ICSI-ICPI), the short form of the Urogenital Distress Inventory (UDI-6), and the RAND 36-item health survey (SF-36). They reported an implantation rate of the 77%. There were four infections; three patients underwent revisions and one had the device removed. In total, five devices were explanted (four for failure and one for infection). One other patient underwent revision for device malfunction. The authors blame this high infection and reintervention rate to the learning curve [63].

Some authors have reported that other stimulation routes like posterior tibial nerve stimulation [64, 65], chronic pudendal nerve stimulation [66], or the laparoscopic implantation of neuroprosthesis to the sacral plexus [67] can be effective in the neuromodulating treatment of different chronic pelvic pain syndromes, but these are not the focus of this review.

Position of SNM in Clinical Practice Guidelines

Based on growing evidences, major international clinical practice guidelines currently consider SNM as a therapeutic alternative in patients with refractory BPS/IC before considering more invasive therapies [68]. The International Consultation on Incontinence of 2016, the guideline of the International Continence Society (ICS) and the International Consultation on Urological Diseases (ICUD) [69••], and the American Urological Association (AUA) propose to perform a test with SNM in selected patients with symptomatology refractory to oral, intravesical, and hydrodistension treatments, considering SNM within the fourth-line treatments, before considering treatment with oral cyclosporine or invasive surgeries such as augmentation cystoplasty or urinary diversions with or without cystectomy [70]. This decision should be left to the individual clinician and patient. The European Association of Urology (EAU), in its 2019 update of its Guidelines on Chronic Pelvic Pain, also recommends to offer SNM before performing more invasive interventions [71].

Our Experience with Sacral Neuromodulation for Bladder Pain Syndrome/Interstitial Cystitis

Study Population and Methods

We have retrospectively analysed our results with sacral neuromodulation in the management of patients with BPS/CI refractory to third-line treatments. After local research ethics committee approval, medical records of patients who underwent sacral root testing (stage 1 of sacral neuromodulation) and those implanted with the InterStim® I and II devices (Medtronic, Inc., Minneapolis, MN, USA) between December 1999 and January 2017, with at least 1-year follow-up, have been reviewed. Also, for the evaluation of the quality of life and overall satisfaction with SNM therapy, a telephone survey was carried out by a nurse not linked to the SNM procedure with three questions: health-related quality of life before and after the implant ("being 0 the worst health status you can imagine and 100 the best health status you can imagine"), satisfaction with the SNM procedure ("score your satisfaction with the whole sacral root neuromodulation procedure from 0 to 10), and if they would recommended SNM to a friend or relative.

Variables analysed were perception of pain on a Numerical Pain Rating Scale (NPRS) from 0 to 10 before and after treatment, subjective global response to neuromodulation using a Global Response Assessment tool of 0–100%, complications (device-related pain, infection, migration), reinterventions, device explants, and battery life. Categorical variables are described with frequencies and percentages; quantitative variables, on the other hand, are described with means, standard deviations, median, and percentiles, as appropriate.

Table 2 Numerical Pain Rating Scale (NPRS)

	Mean	Standard deviation	Mean standard deviation
NPRS before SNM	8.38	.870	.241
NPRS after SNM	2.54	1984	.550

Results

Nineteen patients with refractory BPS/IC were tested. Patients operated before year 2003 (three patients) underwent the open procedure with percutaneous nerve evaluation, and after year 2003, patients underwent implantation of the TinedLead® percutaneous electrode. Women comprised the 89.5% of patients, and average age at the test time was 53 years (range 35 to 77 years). Successful test phase was reported by 15 patients, and they underwent the InterStim® implant. However, three patients were lost from follow-up, so they were excluded from the analysis, considering that 63.15% of patients were successfully implanted and followed (12 of 19 patients). The average follow-up was 96.25 months (range 12–204 months). During this period, loss of therapeutic effect was seen in 4 patients (33% of implanted patients), between 6 and 90 months after the implant.

Approximately four out of 5 patients reported a subjective clinical improvement after the InterStim® implantation between 50 and 90% (83.4%), and the other 16.6% of patients expressed a complete resolution of symptoms (subjective clinical improvement of 90–100%). The reduction in the numerical pain scale score was statistically significant ($t12 = 9.45$; $p < 0{,}001$), with an average change of − 5.85 points after SNM therapy (Table 2).

Mean score on the health-related quality of life scale 0–100 improved significantly from 17.86 (± 16.04) before the intervention to 75.71 (± 24.9) after SNM therapy. Satisfaction with the procedure was high, with an average score of 7.71 (± 2.81) on a 0–10 scale, and 100% of implanted patients would recommend SNM to a friend or relative.

Focusing on SNM complications, 41.7% of the patients reported pain or discomfort related to the device, being resolved in most cases by reprogramming stimulation parameters except in 2 cases, which required InterStim® explant (both associated with loss of effect). We have not had any case of lead migration, but there was a lead rupture during the test phase that required major intervention for extraction. The reintervention rate was 75% (9 of 12 patients), including 7 battery replacements and both aforementioned explants, with an average battery duration of 67.17 months (± 26.38).

In our experience, 6 out of 10 patients with refractory BPS/IC can be successfully managed with SNM therapy, with a significant improvement in their quality of life.

Conclusions

Sacral nerve neuromodulation has proven its effectiveness in the treatment of patients with bladder pain syndrome/interstitial cystitis, as well as in other painful chronic pelvic syndromes. With a fairly favourable safety profile, but at the cost of a high rate of reinterventions, it is a therapeutic alternative to consider before aggressive and/or potentially mutilating surgeries in patients with BPS/IC who are refractory to conservative and pharmacological therapies.

Compliance with Ethical Standards

Conflict of Interest Bárbara Padilla-Fernández has received speaker honorarium from Medtronic.

David M. Castro-Díaz has received speaker honorarium from Medtronic.

All other authors declare that they have no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;53(1):60–7. https://doi.org/10.1016/j.eururo.2007.09.019.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167–78. https://doi.org/10.1002/nau.10052.
3. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol. 1991;145(4):732–5. https://doi.org/10.1016/s0022-5347(17)38437-9.
4. Hauser PJ, Dozmorov MG, Bane BL, Slobodov G, Culkin DJ, Hurst RE. Abnormal expression of differentiation related proteins and proteoglycan core proteins in the urothelium of patients with interstitial cystitis. J Urol. 2008;179(2):764–9. https://doi.org/10.1016/j.juro.2007.09.022.
5. Keay S, Kaczmarek P, Zhang CO, Koch K, Szekely Z, Barchi JJ Jr, et al. Normalization of proliferation and tight junction formation in bladder epithelial cells from patients with interstitial cystitis/painful bladder syndrome by d-proline and d-

pipecolic acid derivatives of antiproliferative factor. Chem Biol Drug Des. 2011;77(6):421–30. https://doi.org/10.1111/j.1747-0285.2011.01108.x.
6. Dundore PA, Schwartz AM, Semerjian H. Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. J Urol. 1996;155(3):885–7.
7. Peeker R, Enerback L, Fall M, Aldenborg F. Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. J Urol. 2000;163(3):1009–15.
8. Silk MR. Bladder antibodies in interstitial cystitis. J Urol. 1970;103(3):307–9. https://doi.org/10.1016/s0022-5347(17)61948-7.
9. Mattila J, Linder E. Immunoglobulin deposits in bladder epithelium and vessels in interstitial cystitis: possible relationship to circulating anti-intermediate filament autoantibodies. Clin Immunol Immunopathol. 1984;32(1):81–9. https://doi.org/10.1016/0090-1229(84)90045-x.
10. Anderson JB, Parivar F, Lee G, Wallington TB, MacIver AG, Bradbrook RA, et al. The enigma of interstitial cystitis–an autoimmune disease? Br J Urol. 1989;63(1):58–63. https://doi.org/10.1111/j.1464-410x.1989.tb05124.x.
11. Ochs RL. Autoantibodies and interstitial cystitis. Clin Lab Med. 1997;17(3):571–9.
12. Peeker R, Atanasiu L, Logadottir Y. Intercurrent autoimmune conditions in classic and non-ulcer interstitial cystitis. Scand J Urol Nephrol. 2003;37(1):60–3. https://doi.org/10.1080/00365590310008721.
13. Breser ML, Salazar FC, Rivero VE, Motrich RD. Immunological mechanisms underlying chronic pelvic pain and prostate inflammation in chronic pelvic pain syndrome. Front Immunol. 2017;8:898. https://doi.org/10.3389/fimmu.2017.00898.
14. Lynes WL, Sellers RG, Shortliffe LMD. The evidence for occult bacterial infections as a cause for interstitial cystitis. J Urol. 1989;141:268A.
15. Warren JW, Brown V, Jacobs S, Horne L, Langenberg P, Greenberg P. Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. Urology. 2008;71(6):1085–90. https://doi.org/10.1016/j.urology.2007.12.091.
16. Siddiqui H, Lagesen K, Nederbragt AJ, Jeansson SL, Jakobsen KS. Alterations of microbiota in urine from women with interstitial cystitis. BMC Microbiol. 2012;12:205. https://doi.org/10.1186/1471-2180-12-205.
17. Nickel JC, Stephens A, Landis JR, Mullins C, van Bokhoven A, Lucia MS, et al. Assessment of the lower urinary tract microbiota during symptom flare in women with urologic chronic pelvic pain syndrome: a MAPP network study. J Urol. 2016;195(2):356–62. https://doi.org/10.1016/j.juro.2015.09.075.
18. Qin C, Foreman RD. Viscerovisceral convergence of urinary bladder and colorectal inputs to lumbosacral spinal neurons in rats. Neuroreport. 2004;15(3):467–71. https://doi.org/10.1097/00001756-200403010-00017.
19. Malykhina AP, Qin C, Greenwood-van Meerveld B, Foreman RD, Lupu F, Akbarali HI. Hyperexcitability of convergent colon and bladder dorsal root ganglion neurons after colonic inflammation: mechanism for pelvic organ cross-talk. Neurogastroenterol Motil. 2006;18(10):936–48. https://doi.org/10.1111/j.1365-2982.2006.00807.x.
20. Yoshikawa S, Kawamorita N, Oguchi T, Funahashi Y, Tyagi P, Chancellor MB, et al. Pelvic organ cross-sensitization to enhance bladder and urethral pain behaviors in rats with experimental colitis. Neuroscience. 2015;284:422–9. https://doi.org/10.1016/j.neuroscience.2014.08.064.
21. Grundy L, Erickson A, Caldwell A, Garcia-Caraballo S, Rychkov G, Harrington A, et al. Tetrodotoxin-sensitive voltage-gated sodium channels regulate bladder afferent responses to distension. Pain. 2018;159(12):2573–84. https://doi.org/10.1097/j.pain.0000000000001368.
22. Nazif O, Teichman JM, Gebhart GF. Neural upregulation in interstitial cystitis. Urology. 2007;69(4 Suppl):24–33. https://doi.org/10.1016/j.urology.2006.08.1108.
23. Engeler DS, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ, et al. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol. 2013;64(3):431–9. https://doi.org/10.1016/j.eururo.2013.04.035.
24. Oravisto KJ. Epidemiology of interstitial cystitis. Annales chirurgiae et gynaecologiae Fenniae. 1975;64(2):75–7.
25. Leppilahti M, Sairanen J, Tammela TL, Aaltomaa S, Lehtoranta K, Auvinen A. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. J Urol. 2005;174(2):581–3. https://doi.org/10.1097/01.ju.0000165452.39125.98.
26. Held P, Hanno P, Wein A. Epidemiology of interstitial cystitis. In: Hanno P, Staskin D, Krane R, editors. Interstitial cystitis. New York: Springer-Verlag; 1990. p. 29–48.
27. Morales-Solchaga G, Zubiaur-Libano C, Peri-Cusi L, Adot-Zurbano JM, Arlandis-Guzman S, Franco-de Castro A, et al. Bladder pain syndrome: prevalence and routine clinical practice in women attending functional urology and urodynamics units in Spain. Actas Urol Esp. 2019;43(2):62–70. https://doi.org/10.1016/j.acuro.2018.06.004.
28. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM Jr, McKinlay JB. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol. 2007;177(4):1390–4. https://doi.org/10.1016/j.juro.2006.11.084.
29. Baskin L, Tanagho E. Pelvic pain without pelvic organs. J Urol. 1992;147(3):683–6.
30. Rössberger J, Fall M, Jonsson O, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology. 2007;70(4):638–42.
31. Peeker R, Aldenborg F, Fall M. The treatment of interstitial cystitis with supratrigonal cystectomy and ileocystoplasty: difference in outcome between classic and nonulcer disease. J Urol. 1998;159(5):1479–82. https://doi.org/10.1097/00005392-199805000-00018.
32. van Ophoven A, Oberpenning F, Hertle L. Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. J Urol. 2002;167(2 Pt 1):603–7. https://doi.org/10.1097/00005392-200202000-00033.
33. Tahseen S. Role of sacral neuromodulation in modern urogynaecology practice: a review of recent literature. Int Urogynecol J. 2018;29(8):1081–91. https://doi.org/10.1007/s00192-017-3546-6.
34.• Weissbart SJ, Bhavsar R, Rao H, Wein AJ, Detre JA, Arya LA, et al. Specific changes in brain activity during urgency in women with overactive bladder after successful sacral neuromodulation: a functional magnetic resonance imaging study. J Urol. 2018;200(2):382–8. https://doi.org/10.1016/j.juro.2018.03.129 **Functional MRI is changing the paradigm of the mechanism of action of neuromodulation.**
35.• Gill BC, Pizarro-Berdichevsky J, Bhattacharyya PK, Brink TS, Marks BK, Quirouet A, et al. Real-time changes in brain activity during sacral neuromodulation for overactive bladder. J Urol. 2017;198(6):1379–85. https://doi.org/10.1016/j.juro.2017.06.074 **Functional MRI is changing the paradigm of the mechanism of action of neuromodulation.**
36. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971–9. https://doi.org/10.1126/science.150.3699.971.

37. Birder LA, de Groat WC. Induction of c-fos expression in spinal neurons by nociceptive and nonnociceptive stimulation of LUT. Am J Phys. 1993;265(2 Pt 2):R326–33. https://doi.org/10.1152/ajpregu.1993.265.2.R326.
38. Ruch TC. Visceral sensation and referred pain. Fulton Howell's Textbook of Physiology. 15th ed. Philadelphia, PA: Saunders; 1946. p. 385–401.
39. Thon WF, Baskin LS, Jonas U, Tanagho EA, Schmidt RA. Neuromodulation of voiding dysfunction and pelvic pain. World J Urol. 1991;9(3):138–41. https://doi.org/10.1007/BF00202508.
40. Shaker H, Hassouna MM. Sacral root neuromodulation in the treatment of various voiding and storage problems. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(5):336–43. https://doi.org/10.1007/s001929970012.
41. Zermann DH, Weirich T, Wunderlich H, Reichelt O, Schubert J. Sacral nerve stimulation for pain relief in interstitial cystitis. Urol Int. 2000;65(2):120–1. https://doi.org/10.1159/000064852.
42. Chai TC, Zhang C, Warren JW, Keay S. Percutaneous sacral third nerve root neurostimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis. Urology. 2000;55(5):643–6. https://doi.org/10.1016/s0090-4295(00)00476-3.
43. Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol. 2001;165(3):884–6.
44. Siegel S, Paszkiewicz E, Kirkpatrick C, Hinkel B, Oleson K. Sacral nerve stimulation in patients with chronic intractable pelvic pain. J Urol. 2001;166(5):1742–5.
45. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. J Urol. 2003;169(4):1369–73. https://doi.org/10.1097/01.ju.0000053863.96967.5a.
46. Peters KM, Carey JM, Konstandt DB. Sacral neuromodulation for the treatment of refractory interstitial cystitis: outcomes based on technique. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14(4):223–8; discussion 8. https://doi.org/10.1007/s00192-003-1070-3.
47. Powell CR, Kreder KJ. Long-term outcomes of urgency-frequency syndrome due to painful bladder syndrome treated with sacral neuromodulation and analysis of failures. J Urol. 2010;183(1):173–6. https://doi.org/10.1016/j.juro.2009.08.142.
48. Whitmore KE, Payne CK, Diokno AC, Lukban JC. Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14(5):305–8; discussion 8-9. https://doi.org/10.1007/s00192-003-1080-1.
49. Kessler TM, Buchser E, Meyer S, Engeler DS, Al-Khodairy AW, Bersch U, et al. Sacral neuromodulation for refractory lower urinary tract dysfunction: results of a nationwide registry in Switzerland. Eur Urol. 2007;51(5):1357–63. https://doi.org/10.1016/j.eururo.2006.11.011.
50. Marinkovic SP, Gillen LM, Marinkovic CM. Minimum 6-year outcomes for interstitial cystitis treated with sacral neuromodulation. Int Urogynecol J. 2011;22(4):407–12. https://doi.org/10.1007/s00192-010-1235-9.
51. Gajewski JB, Al-Zahrani AA. The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int. 2011;107(8):1258–64. https://doi.org/10.1111/j.1464-410X.2010.09697.x.
52. Ghazwani YQ, Elkelini MS, Hassouna MM. Efficacy of sacral neuromodulation in treatment of bladder pain syndrome: long-term follow-up. Neurourol Urodyn. 2011;30(7):1271–5. https://doi.org/10.1002/nau.21037.
53. Shih C, Miller JL, Fialkow M, Vicars BG, Yang CC. Reoperation after sacral neuromodulation therapy: a single-institution experience. Female pelvic medicine & reconstructive surgery. 2013;19(3):175–8. https://doi.org/10.1097/SPV.0b013e31828ab3c9.
54. Peters KM, Killinger KA, Gilleran JP, Bartley J, Wolfert C, Boura JA. Predictors of reoperation after sacral neuromodulation: a single institution evaluation of over 400 patients. Neurourol Urodyn. 2017;36(2):354–9. https://doi.org/10.1002/nau.22929.
55. Donon L, Robert G, Ballanger P. Sacral neuromodulation: results of a monocentric study of 93 patients. Prog Urol. 2014;24(17):1120–31. https://doi.org/10.1016/j.purol.2014.09.037.
56. Peeters K, Sahai A, De Ridder D, Van Der Aa F. Long-term follow-up of sacral neuromodulation for lower urinary tract dysfunction. BJU Int. 2014;113(5):789–94. https://doi.org/10.1111/bju.12571.
57. Elhilali MM, Khaled SM, Kashiwabara T, Elzayat E, Corcos J. Sacral neuromodulation: long-term experience of one center. Urology. 2005;65(6):1114–7. https://doi.org/10.1016/j.urology.2004.12.016.
58. Peters KM, Konstandt D. Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. BJU Int. 2004;93(6):777–9. https://doi.org/10.1111/j.1464-410X.2003.04745.x.
59. Peters KM, Jayabalan N, Bui D, Killinger K, Chancellor M, Tyagi P. Effect of sacral neuromodulation on outcome measures and urine chemokines in interstitial cystitis/painful bladder syndrome patients. LUTS: Lower Urinary Tract Symptoms. 2015;7(2):77–83. https://doi.org/10.1111/luts.12054.
60.•• Mahran A, Baaklini G, Hassani D, Abolella HA, Safwat AS, Neudecker M, et al. Sacral neuromodulation treating chronic pelvic pain: a meta-analysis and systematic review of the literature. Int Urogynecol J. 2019;30(7):1023–35. https://doi.org/10.1007/s00192-019-03898-w **The most recent systematic review on the topic.**
61. Wang J, Chen Y, Chen J, Zhang G, Wu P. Sacral neuromodulation for refractory bladder pain syndrome/interstitial cystitis: a global systematic review and meta-analysis. Sci Rep. 2017;7(1):11031. https://doi.org/10.1038/s41598-017-11062-x.
62. Al-zahrani AA, Elzayat EA, Gajewski JB. Long-term outcome and surgical interventions after sacral neuromodulation implant for lower urinary tract symptoms: 14-year experience at 1 center. J Urol. 2011;185(3):981–6. https://doi.org/10.1016/j.juro.2010.10.054.
63. Zabihi N, Mourtzinos A, Maher MG, Raz S, Rodriguez LV. Short-term results of bilateral S2-S4 sacral neuromodulation for the treatment of refractory interstitial cystitis, painful bladder syndrome, and chronic pelvic pain. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(4):553–7. https://doi.org/10.1007/s00192-007-0466-x.
64. Istek A, Gungor Ugurlucan F, Yasa C, Gokyildiz S, Yalcin O. Randomized trial of long-term effects of percutaneous tibial nerve stimulation on chronic pelvic pain. Arch Gynecol Obstet. 2014;290(2):291–8. https://doi.org/10.1007/s00404-014-3190-z.
65. Ragab MM, Tawfik AM, Abo El-enen M, Elnady M, El-Gamal OM, El-Kordy M, et al. Evaluation of percutaneous tibial nerve stimulation for treatment of refractory painful bladder syndrome. Urology. 2015;86(4):707–11. https://doi.org/10.1016/j.urology.2015.06.041.
66. Peters KM, Killinger KA, Boguslawski BM, Boura JA. Chronic pudendal neuromodulation: expanding available treatment options for refractory urologic symptoms. Neurourol Urodyn. 2010;29(7):1267–71. https://doi.org/10.1002/nau.20823.
67. Possover M. The laparoscopic implantation of neuroprothesis to the sacral plexus for therapy of neurogenic bladder dysfunctions after failure of percutaneous sacral nerve stimulation. Neuromodulation. 2010;13(2):141–4. https://doi.org/10.1111/j.1525-1403.2009.00230.x.
68. Malde S, Palmisani S, Al-Kaisy A, Sahai A. Guideline of guidelines: bladder pain syndrome. BJU Int. 2018;122(5):729–43. https://doi.org/10.1111/bju.14399.

69.•• Hanno P, Cervigni M, Dinis P, Lin A, Nickel JC, Nordling J et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Wagg A, Wein A, editors. Incontinence. 6th ed.: International Consultation on Incontinence 2017. **The ICI document (ICS guideline) gives evidence-based recommendations on the topic.**

70. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, FitzGerald MP et al. Diagnosis and treatment interstitial cystitis/bladder pain syndrome (2014). American Urological Association Education and Research; 2014.

71. Engeler D, Baranowski AP, Berghmans B, Borovicka J, Cottrell AM, Elneil PS, et al. EAU guidelines on chronic pelvic pain in: EAU guidelines. The Netherlands: European Association of Urology; 2019. https://uroweb.org/guideline/chronic-pelvic-pain/