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ORIGINAL ARTICLE

Sacral neuromodulation treating chronic pelvic pain: a meta-analysis and systematic review of the literature

Amr Mahran[1,2,3] · Gina Baaklini[2] · Daisy Hassani[4] · Hassan A. Abolella[3] · Ahmed S. Safwat[3] · Mandy Neudecker[5] · Adonis K. Hijaz[1,2] · Sangeeta T. Mahajan[1] · Steven W. Siegel[6] · Sherif A. El-Nashar[1,4]

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Abstract

Introduction and hypothesis Sacral neuromodulation (SNM) is gaining popularity as a treatment option for chronic pelvic pain (CPP). Our hypothesis is that SNM is effective in improving CPP.

Methods A systematic search was conducted through September 2018. Peer-reviewed studies using pre- and postpain intensity scores were selected. The primary outcome was pain improvement on a 10-point visual analog scale (VAS) (adjusted or de novo) in patients with CPP. Secondary outcomes included comparing SNM approaches and etiologies and evaluating lower urinary tract symptoms (LUTS).

Results Fourteen of 2175 studies, evaluating 210 patients, were eligible for further analysis. The overall VAS pain score improvement was significant [weighted mean difference (WMD) −4.34, 95% confidence interval (CI) = −5.22, to−3.64, $p < 0.0001$)]. Regarding SNM approach, both standard and caudal approaches had significant reduction in pain scores: WMD −4.32, CI 95% = −5.32, to −3.31 ($p < 0.001$) for the standard approach, compared with WMD −4.63, 95% CI = −6.57 to −2.69 ($P < 0.001$), for the caudal approach ($p = 0.75$). While significant improvement in pain was observed both in patients with and without interstitial cystitis/bladder pain syndrome (IC/BPS), the observed improvement was lower in patients with (WMD −4.13, CI 95% −5.36 to −2.90 versus without (WMD −5.72, CI 95% = −6.18, to−5.27) IC/BPS ($p = 0.02$). SNM was effective in treating voiding symptoms (frequency, urgency, nocturia) associated with IC/BPS (all $p < 0.01$).

Conclusions SNM is an effective therapy for CPP in both IC/BSP and non-IC/BSP patients, with better results in non-IC/BSP patients. Outcomes of the antegrade caudal approach were comparable with the standard retrograde approach.

Keywords Sacral neuromodulation · Chronic pelvic pain · Visual analog scale

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✉ Sherif A. El-Nashar
sherif.el-nashar@uhhospitals.org

[1] Division of Female Pelvic Medicine and Reconstructive Surgery, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Mailstop MAC 5034, Cleveland, OH 44106, USA

[2] Urology Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA

[3] MetroUrology, Minneapolis, MN, USA

[4] Department of Obstetrics and Gynecology, Assiut University, Assiut, Egypt

[5] Department of Urology, Assiut University, Assiut, Egypt

[6] Core Library, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Abbreviations

SNM	Sacral neuromodulation
CPP	Chronic pelvic pain
VAS	Visual analog scale
IC	Interstitial cystitis
BPS	Bladder pain syndrome
WMD	Weighted mean difference
PNE	Percutaneous nerve evaluation

Introduction

Pelvic pain is a complex condition experienced by both men and women and has a great impact on patient quality of life (QoL) and productivity. Chronic pelvic pain (CPP) is defined as pain with a minimum duration of 6 months after the exclusion of surgical etiologies [1]. It has a multifactorial nature that

may have numerous etiologies. These include psychological, urological, gynecological, musculoskeletal, infectious, and hormonally driven causes [2, 3]. Pelvic pain can be idiopathic in up to two thirds of cases [1]. A cross-sectional analysis of the MediPlus UK Primary Care Database concluded that CPP has an annual prevalence of 38.3/1000 [4]. In women, associated conditions include abnormal uterine bleeding (AUB), premenstrual symptoms, and pelvic inflammatory disease [5]. Risk factors include smoking, anxiety, major depression, and history of sexual assault. Physical exercise and fish intake are associated with a decreased risk [6, 7].

Sacral neuromodulation (SNM) is an emerging treatment option for refractory CPP. It is a minimally invasive option, which increases its potential utility. It involves the electrical stimulation of afferent nerve roots (usually S3) to restore the balance between inhibitory and excitatory reflexes [8, 9]. Its hypothesized therapeutic effect in treating pain is mostly related to reviving brainstem autoregulation and help reset the function of the pelvic floor and the associated neuromuscular unit [7, 10]. It is approved by the US Food and Drug Administration (FDA) for treating urge urinary incontinence (UUI), nonobstructive urinary retention, and urinary urgency/frequency [8]. Any associated urinary symptoms can be FDA-approved indications for SNM. However, its use to treat pelvic pain is still off-label. In this systematic review, we reviewed the literature on the efficacy of SNM in treating CPP.

Materials and methods

This is a systematic review study that comprised a systematic search and summary of the literature related to the use of SNM in improving the symptoms of CPP. We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [11]. The study was registered by the international prospective register of systematic reviews (PROSPERO) under CRD42017074708. The study used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (www.gradeworkinggroup.org) to generate and evaluate the evidence [12].

Literature search

A search was conducted using online databases: MEDLINE, Embase, Cochrane (with online Ovid interface), Web of Science, and Scopus (abstract and indexing database) for articles that studied the efficacy of SNM in treating CPP. An expert reference librarian (MN) performed the search strategies. Only articles written in the English language were included. One article, written in Korean, was included because results tables were provided in English [13]. A relevant article was excluded, as it was based on a survey due to the high probability of recall bias [14]. One case report was excluded from the analysis [15]. Search terms included MeSH and Embase terms, in addition to keywords, including SNM, sacral nerve stimulation, pelvic pain, IC, sacral neurostimulation, and sacrum. The search included studies from 1980 through September 2018. The detailed search provided by the librarian was reviewed by two researchers (AM and GB) independently to identify eligible articles. The detailed search strategy is appended (Appendix).

Eligibility criteria and study selection

The primary population of interest included patients who had SNM implantation for any cause of CPP with the availability of pain scores pre- and post-SNM. Variables include type of CPP, number of patients who had percutaneous nerve evaluation (if available), first- and second-stage SNM, pain scores before and after SNM, and average duration of follow-up. Reported urinary symptoms (if available) before and after SNM (e.g., frequency, urgency, nocturia) were included.

Quality evaluation of the included studies

We evaluated the included studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies and the Oxford Centre for Evidence-based Medicine Levels of Evidence (Table 1) [29, 30]. Further evaluation using the quality assessment tool from the National Heart, Lung and Blood Institute was conducted (Supplementary Table 1) [31].

Data abstraction

Data abstraction was performed using a standardized form; study characteristics were author, year, type, and number of percutaneous nerve evaluations (PNE). If available, the number of first- and second-stage SNMs, pain scores, urinary frequency, urgency, nocturia before and after SNM, and average duration of follow-up were included.

Data analysis

Primary outcome was improvement on a 10-point visual analog scale (VAS) in patients with CPP and to compare the efficacy of SNM in different subgroups. Secondary outcomes included comparison of SNM effectiveness in patient subgroups based on SNM approach and etiology of CPP. Another secondary outcome was the evaluation of associated lower urinary tract symptoms (LUTS), if any. Differences in pain scores pre- and post-SNM in each study were analyzed using mean and standard deviation (SD). The effect size was expressed as a weighted mean difference (WMD), with 95% confidence interval (CI) and two-sided p values. A random-effect model was used to pool outcomes across studies due to anticipated heterogeneity. When a study did not provide pain-

Table 1 Study characteristics, reported outcomes, and quality assessment

Study	Study type, country	Indications	No.	Gender (F: M)	No. PNE/stage I SNM	No. progressed to second stage	VAS (or mean)	Implant location
Chai [16]	Prospective, USA	IC	6	5: 1	6 (PNE)	0	6	S3
Maher [17]	Prospective, Australia	IC	15	15:0	15 (PNE)	13 (86.7%)	15	S3
Siegel [18]	Prospective, USA	IC	10	9: 1	10 (PNE)	10 (100%)	10	S3, S4
Aboseif [19]	Prospective, USA	CPP, voiding dysfunction	160 Total	54: 10[a]	160 (PNE)	64 (41 had CPP) (64/160 ➔ 40%)	41	S3
Comiter [20]	Prospective, USA	IC	25	24: 1	25 (PNE: 10, SNS I: 15)	17 (68%)	17	S3
Whitmore [21]	Prospective, USA	IC	30[b]	30: 0	30 (PNE)	17 (56.7%)	22	S3
Lavano [22]	Prospective, Italy	Pelvic/urogenital pain	7	NR	7 (PNE)	5 (71.4%)	5	S3, S4
Chung [13]	Retrospective, , Korea	10 IC, 2 idiopathic CPP, 5 overactive bladder	30	8: 9*	30	17 (56.7%)	12	S3
Falletto [23]	Prospective, Italy	Chronic idiopathic anal pain	27	10: 2*	27 (PNE)	12 (44%)	12	S3
Ghazwani [24]	Retrospective, Canada	Bladder pain syndrome (BPS)	21	21: 0	21 (PNE)	11 (52%)	11	S3
Marinkovic [25]	Retrospective, USA	IC	34	34: 0	34 (SNS I)	30 (88.2%	30	S3
Martellucci [26]	Retrospective, Italy	Pelvic pain after pelvic surgery	17	14: 3	17 (PNE)	8 (47%)	8	S3, S4
Sokal [27]	Prospective, Poland	CPP: perineal, anal, perirectal, pudendal, or coccygeal region pain and failed back surgery syndrome	9	9: 0	9	9 (100%)	9	S2–S4 caudal pathway
Guardo [28]	Prospective, USA	5 coccydynia, 3 IC, 1 vulvodynia, 1 actinic proctitis, 1 CPP and 1 postsurgical neuropathic pain	12	10: 2	12 (PNE)	8 (66.7%)	12	S3 caudal pathway
Total			403		403	221	210	

Study	Stimulation laterality (SNM II)	Adverse events	SNM II stimulation failure	Follow-up (month)	LoE/R	Newcastle-Ottawa Quality Assessment Scale		
						Selection (4 stars)	Comparability (2 stars)	Outcome (3 stars)
Chai [16]	NR	None	NA	NR	4/C	**	*	**
Maher [17]	Unilateral	NR	None	NR	2b/B	**	**	**
Siegel [18]	Unilateral	2 removal, 4 pain location change, 2 urinary tract infection, 4 pain at implantation site, 3 recurrence of symptoms, 6 local wound complication,s 1 electrical shock sensation, 1 worse pain, 2 revision of the IPG/lead, 1 infection required removal	3 (30%)	19 (6–74)	2b/B	**	**	**
Aboseif [19]	Unilateral	6 spontaneously resolved seroma, 2 superficial wound infections,	None	24	2b/B	***	*	**

Table 1 (continued)

		2 sacral wire migrations (revisions), 2 device malfunctions (revisions)						
Comiter [20]	Unilateral	1 persistence symptoms (no improvement)	1 (6%)	14 (2–28)	2b/B	***	*	**
Whitmore [21]	Unilateral	Unpleasant tapping at skin site (resolved by turning off the external pulse generator)	NR	5.2	2b/B	***	**	**
Lavano [22]	3 Unilateral 2 Bilateral	1 lead fracture (revision), 1 lead partial displacement (reprogramming), 1 pain at implantation site (revision)	0 (0%)	8 (6–14)	4/C	**	*	**
Chung [13]	Unilateral	1 Infection and foreign-body sensation (removal), 1 lead migration (revision), 1 anal pain, 2 lower-limb numbness (2 removals)	3 (25%)	21.6 (6–43)	2b/B	***	*	**
Falletto [23]	Unilateral	1 infection (responded to antibiotics), 1 device failure after 2 years, 1 implantation-site pain	1 (9%) at 2 years	15 (3–80)	2b/B	***	**	**
Ghazwani [24]	Unilateral (left in 9, right in 2)	2 IPGs changing (ended battery life), 3 pain at implantation site, (2 revisions and 1 reprogramming)	0 (0%)	71.5 ± 9.3	2b/B	**	**	**
Marinkovic [25]	Unilateral	5 lead migrations due to trauma (replacements), 3 IPG erosions (replacements)	0 (0%)	86 ± 9.8	2b/B	***	*	**
Martellucci [26]	Unilateral	3 battery changes, 4 reprogramming (1 due to pain at implantation site)	0 (0%)	6–36	2b/B	**	*	**
Sokal [27]	Unilateral	3 infections (one at 1 month, two at 6 months), 2 required removal) 2 lead migrations (1 had associated infection; required removal at 8 month)	3 (30%)	1–12	4/C	**	*	**
Guardo [28]	Unilateral	2 pain at implantation site, 1 with slight displacement (revisions)	0 (0%)	24	2b/B	**	*	**
Total								

Stimulation failure was defined as no improvement or no satisfactory response after implanting SNM device and/or device removal

NR not reported, *NA* not applicable, *LoE* level of evidence, *R* recommendation (Oxford Center), *SNM* sacral neuromodulation, *IC* interstitial cystitis, *PNE* percutaneous nerve evaluations *BPS* bladder pain syndrome, *CPP* chronic pelvic pain, *IPGs* implantable pulse generators

[a] Gender was available for patients who progressed to second stage SNM

[b] After excluding three patients who were not included in the statistical analysis per Whitmore et. al

score means and/or SD, they were calculated using the Microsoft Excel average and STDEV formulas [16, 18, 20, 21, 25, 28]. All pain scores were standardized for a 10-point scale. Siegel et al. utilized a 5-point scale for pain-intensity scores, which were multiplied by 2 [18]; Whitmore et al. reported 3-point scale scores, which were multiplied by 3.33 [23]. In case a failed stimulation post-SNM was reported without assigning the post-SNM VAS score, then the post-SNM score was assumed to equal the pre-SNM score [16]. In one study that included mean pain score ± standard error (SE), SD was calculated using the equation $SE = SD/\sqrt{n}$ [22]. One study provided mean pain scores without SD; in this case, we used the average SD of the other studies included in this review [26]. GRADE pro tool was used to assess and evaluate study outcomes [12]. Review Manager 5.3 software was used to generate Forest and funnel plots and assess the risk of bias (Supplementary figure) (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results

We initially identified 2175 studies in the original search. Overall, 14 studies met inclusion criteria and were included in the analyses (Fig. 1). Ten studies were prospective, while four were retrospective chart reviews. Seven studies were conducted in the USA [16–18, 20, 23, 24, 26], three in Italy [25, 27, 31], one in Canada [28], one in Australia [22], one in

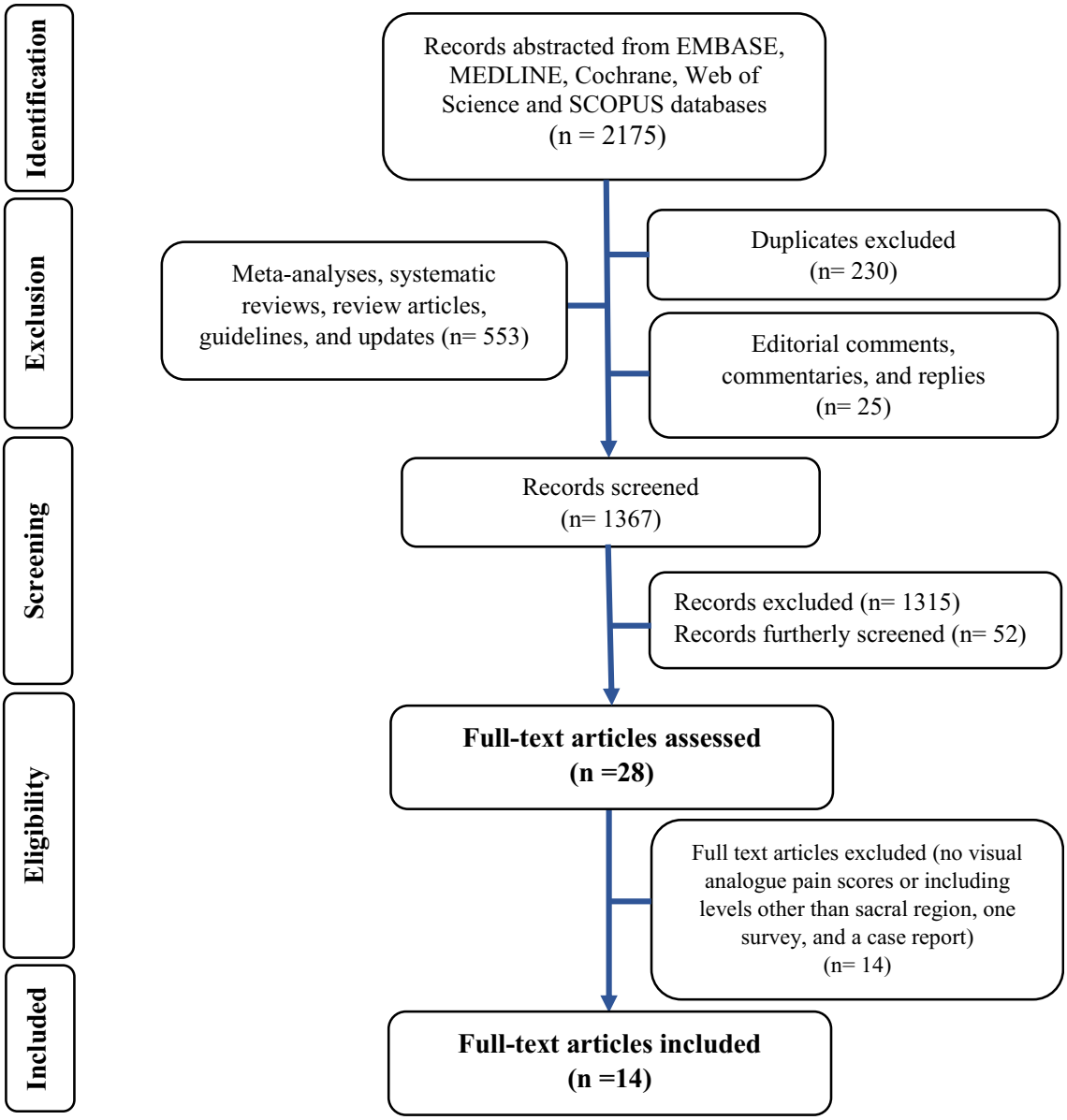

Fig. 1 Study flow chart

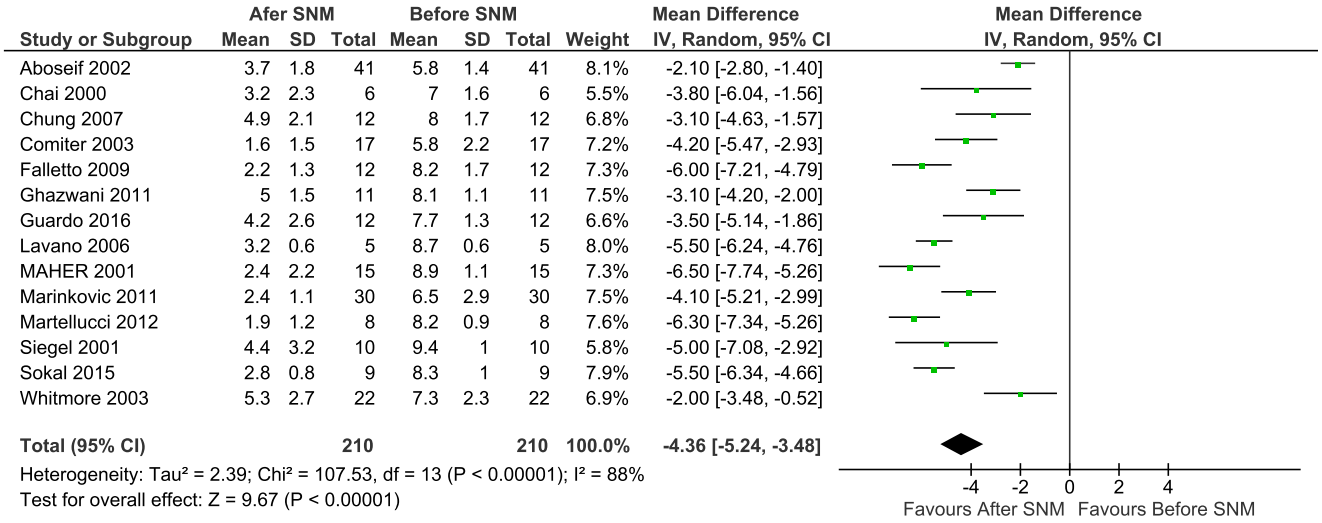

Fig. 2 Forest plot of pain improvement after sacral neuromodulation (SNM)

Poland [21], and one in Korea [13]. Evaluation of study quality was done using the Newcastle-Ottawa Scale (Table 1). Overall, quality was average for observational studies: 11 scored 2b as the level of evidence with grade B recommendation, while three studies scored 4 as the level of evidence with grade C recommendation (Table 1, Supplementary Table 1).

The summary of study findings is included in Table 1. In all, 403 patients had undergone percutaneous nerve evaluation and/or SNM stage 1: 29 (7%) were men; 221 (54.8%) progressed to the permanent implantation stage. The cause of pain was reported to be IC/BPS in 170 cases (42.2%). Pain etiologies and follow-up durations are provided in Table 1. VAS pain scores were available pre- and post-SNM in 210 patients. Overall improvement in pain scores was significant: WMD = −4.36, 95% CI = −5.24 to −3.48 ($p < 0.001$) (Fig. 2).

Interstitial cystitis vs. other etiologies

There were 105 CPP patients in seven studies with pure IC/BPS etiology compared with 34 patients who had pelvic pain due to other etiologies. Studies that included both IC and other causes of CPP were excluded from this subgroup analysis. There was significantly more improvement in pain scores in the non-IC/BPS group, WMD = −5.72, CI 95% = −6.18 to −5.27, than in the IC/BPS group, WMD = −4.13, CI 95% = −5.36 to −2.90 ($p = 0.02$) (Fig. 3).

Patients with IC usually have associated overactive bladder symptoms. Seven studies showed significant improvement in urinary frequency: WMD = −8.72, 95% CI = −10.85 to −6.59 ($p < 0.001$). Five studies revealed significant overall improvement in urgency: WMD = −1.2, 95% CI = −1.9, to −0.49

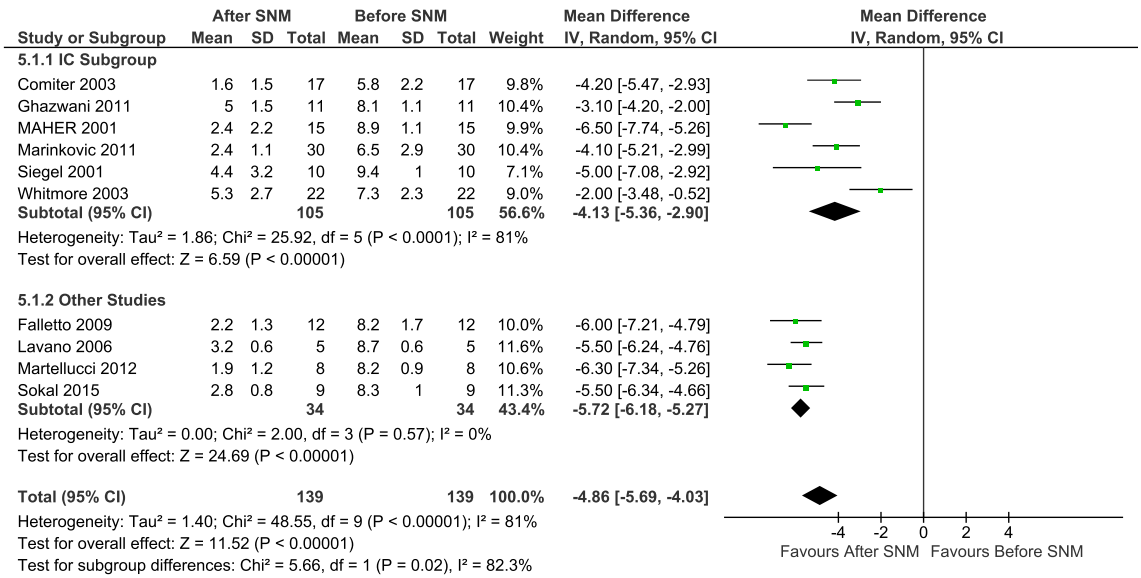

Fig. 3 Forest plot for pain improvement (interstitial cystitis vs other etiologies)

Table 2 Improvement in urinary symptoms in the interstitial cystitis (IC) group

Studies	Urinary symptom	WMD (95% CI)	Heterogeneity	Test for overall effect
(7) [13, 17, 20, 22–24, 28]	Frequency	−8.27 (−10.85 to −6.59)	$Tau^2 = 3.53$; $Chi^2 = 10.93$, df = 6 ($p = 0.09$); $I^2 = 45\%$	Z = 8.01 ($p < 0.00001$)
(5) [13, 22–24, 28]	Urgency	−1.20 (−1.90 to −0.49)	$Tau^2 = 0.54$; $Chi^2 = 31.55$, df = 4 ($p < 0.00001$); $I^2 = 87\%$	Z = 3.31 ($p = 0.0009$)
(5) [13, 17, 22, 24, 28]	Nocturia	−2.31 (−3.81 to −0.81)	$Tau^2 = 2.36$; $Chi^2 = 24.92$, df = 4 ($p < 0.0001$); $I^2 = 84\%$	Z = 3.02 ($p = 0.003$)
(5) [17, 20, 22, 23, 28]	Voided Volume	109.61 (57.79–161.43)	$Tau^2 = 3010.87$; $Chi^2 = 30.28$, df = 6 ($p < 0.00001$); $I^2 = 87\%$	Z = 4.15 ($p < 0.0001$)

($p < 0.001$), nocturia ; WMD = −2.31, 95% CI = −3.81 to −0.81 ($p = 0.003$), and voided volume: WMD = 109.61, 95% CI = 57.79–161.43, ($p < 0.001$) (Table 2).

Standard (retrograde) vs. caudal (antegrade) approach

Two studies for a total of 21 patients used different approaches of SNM implantation. Electrode implantation was done through the sacral hiatus and then inserted into the vertebral canal to cross the S4, S3, and S2 sacral roots (caudal approach). We compared pain improvement between this and the standard retrograde approach. Mean improvement was slightly better using the caudal pathway, WMD = −4.63, 95% CI = −6.57 to −2.69) when compared with the standard approach, WMD = −4.32, CI 95% = −5.32 to −3.31); however, there was no statistically significant difference ($p = 0.78$) (Fig. 4).

Adverse events in sacral neuromodulation

Adverse events were reported in 67/221 (30.3%) patients (Table 1). Wound infections were reported in nine (4%), lead migration/malfunction in 17 (8%: one was partial and resolved by reprogramming; five were due to trauma), pain at implantation site in 12 (5.4%), implantable pulse generator (IPG) erosions without infection in three (1.1%), and a spontaneously resolved seroma in six (2.7%). Five patients (2%) reported a change in pain location. Other rare events included two urinary tract infections, one electrical shock sensation, one foreign-body sensation, and two of lower-limb numbness.

Eleven of 221(5%) patients were reported to have either device failure or removal (removals were 5 for implant-associated infections, 3 for device failure, and 2 for associated limb numbness). Twenty-three patients (10%) underwent implant revision/replacements. Five patients were reported to have their device batteries/IPGs changed due to ended battery life.

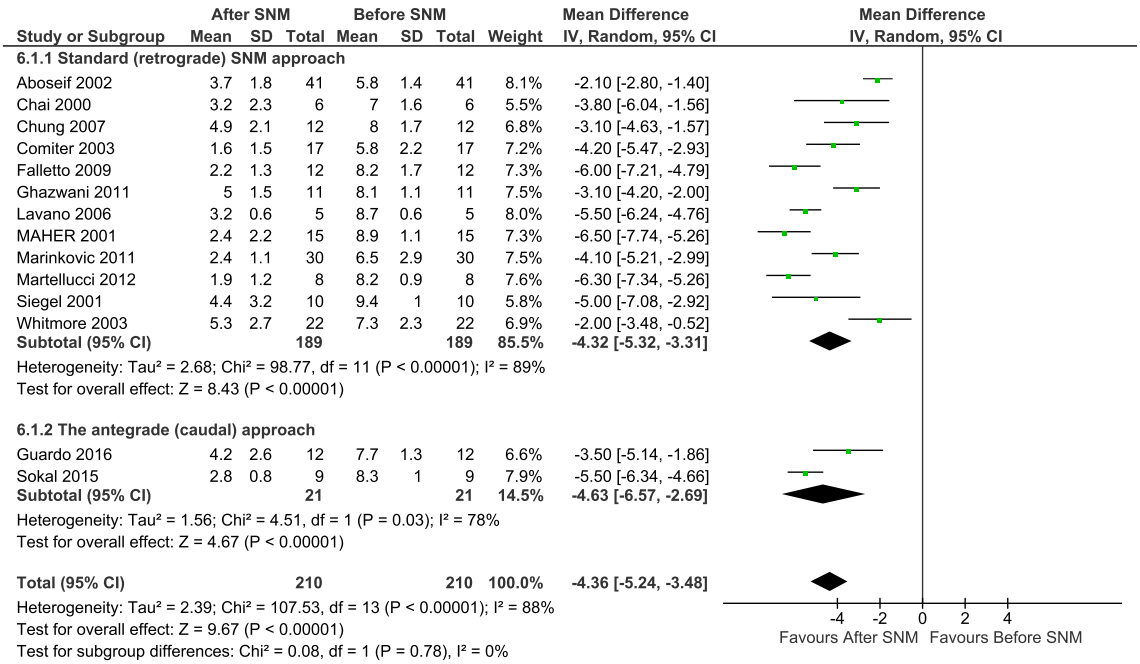

Fig. 4 Forest Plot for pain improvement (standard vs caudal approach)

Discussion

The main finding of this systematic review is that SNM is an acceptable treatment option for CPP in selected patients. While the implantation rate is lower than it is for other indications, based on our analysis, the improvement in VAS pain score obtained by using SNM ranges between 35 and 52%. Pain improvement was better in patients with CPP due to etiologies other than IC/BPS. The caudal (antegrade) SNM approach performed almost the same as the standard (retrograde) approach in treating patients with CPP.

Previous systematic reviews analyzed the efficacy of SNM in treating CPP associated with IC/BPS [32–34]. These studied showed a consistent reduction in pain symptoms associated with IC/BPS. Marcelissen and colleagues reported that there is insufficient evidence for the role of SNM in treating IC/BPS; however, their systemic review, which lacked quantitative analysis of pain scores, showed promising results with SNM [34, 35]. To our knowledge, none of the previous systematic reviews analyzed the efficacy of SNM in CPP due to other etiologies or compared SNM techniques. In our meta-analysis, we focused on all studies that included CPP, regardless of its etiology. We only included studies that reported pain scores before and after SNM in order to obtain a quantitative effect of SNM, followed by obtaining a WMD from all included studies. In addition, we compared the effect of SNM in two subgroups based on etiology (IC/BPS vs. all other etiologies) and SNM implantation approach (antegrade vs. retrograde).

CPP affects ~9.2 million women in the United States and is challenging to treat [1]. Because of the complicated, yet common, pelvic neuroanatomy through the sacral nerve roots, the definitive etiology of pain usually cannot be identified [36]. However, this common neuroanatomy can serve as a critical factor for the success of SNM as a treatment option for CPP symptoms in many cases [1, 18].

Electrical stimulation has been used on different pelvic organs (e.g., bladder and vagina), although it had a high therapeutic failure rate [37–39]. On the other hand, percutaneous tibial nerve stimulation has shown promising results. This method requires multiple patient visits to the clinic, since no device is implanted and it therefore relies greatly upon the compliance of each patient. The sacral nerve roots (S2–4) supply the autonomic and somatic innervation of the pelvis, including the pelvic floor, lower urinary tract, and rectum. SNM acts on these roots and can successfully modulate the different pelvic organs. A benefit of SNM is that it has a continuous effect through an implantable device, which can be externally adjusted. This makes SNM extremely convenient for intractable cases [26, 40, 41]. Although SNM is not devoid of adverse events, e.g., implantation-site pain, lead migrations, and/or device failures, SNM has shown successful outcomes in treating different pelvic dysfunctions, such as voiding issues, fecal problems, and CPP syndromes [18, 42, 43].

IC has complex multifactorial etiologies. Theoretically, it can be due to infections, inflammation, defects in the glycosaminoglycan layer of the urothelium, and neurogenic insult with subsequent sympathetic vasomotor-induced ischemia, among others [20]. IC encompasses pelvic pain in addition to voiding dysfunction symptoms. At least 10% of patients will not improve on conservative management [44]. Affected patients have a QoL that is worse when compared with patients on hemodialysis [45]. How SNM works in treating IC, or pelvic pain in general, is still not completely understood. It is suspected that SNM acts by blocking the bladder afferent pathway and therefore inhibits the incoming abnormal sensory transmission to the spinal and brain relays [46]. SNM is also found to reduce substance P at the rectal mucosa of successfully treated patients with fecal incontinence. This action theoretically can be applied to other targeted tissues [47]. In addition, SNM exerts a direct action on the bladder by normalizing urinary levels of antiproliferative factor (APF) and heparin-binding epidermal growth factor (HB-EGF) in patients with IC [24]. A pooled analysis of this study showed that SNM results are appealing in treating this complex disorder, including all of its components. It showed improvement in pain scores, urinary urgency, frequency, nocturia, and bladder capacity. However, the SNM response in IC/BPS patients was lower than in those with other etiologies. This can be explained by the complexity of the pathogenesis of IC and the additional effects of associated voiding dysfunctions.

Two prior studies [16, 21] considered the antegrade (caudal) approach in treating patients with CPP. This approach can be achieved by puncturing the sacral hiatus and cephalic advancement of the electrode [48]. On the other hand, the standard (retrograde) approach is performed by lumbar epidural puncture, and the electrodes are caudally advanced [49, 50]. These studies argued that adequate advancement of the electrode(s) in the sacral promontory in the retrograde pathway is difficult to achieve and has a higher rate of failure [51–53]. Others claim that the risk of lead migration is higher in the antegrade approach due to difficult anchoring [25, 54]. In our review, pooled analysis of both approaches showed slight superiority of the caudal (antegrade) pathway without significant difference in relieving CPP. Further prospective studies to compare both techniques are warranted.

SNM works by delivering electrical pulses to sacral nerves. Many factors contribute to the efficacy of the electric pulses generated, including amplitude, frequency, grounding, and resistance. There are additional factors affecting resistance, such as temperature, lead length, and conductivity of surrounding tissues. Reprogramming can be performed by changing amplitude, frequency, and width of pulse mode or polarity [55]. Along with patients' comprehensive and diagnostic

evaluation and individualizing treatment decisions, SNM treatment starts with placing a stimulation needle into the correct foramen [56]. We believe that the optimum placement of SNM is achievable by parallel and close placement of the lead to the S3 nerve, confirmed by low amplitude required for stimulation (e.g., < 1 or < 2 mA) and also by the small differences between the threshold of stimulation in each electrode (e.g., 0.7, 0.8, 0.7, 0.8 for leads 0, 1, 2, and 3) [57, 58].

The benefit of bilateral versus unilateral SNM is controversial. In an animal study, the effectiveness of bilateral was better than unilateral SNM for treating induced detrusor overactivity [59]. However, Scheepens and colleagues found that bilateral SNM did not offer superior effects in treating patients with chronic voiding dysfunction [60]. Two more studies have shown the efficacy of bilateral SNM in improving symptoms of IC. However, neither had a control group [18, 61, 62].

In conclusion, SNM is a promising treatment option for refractory CPP. This is mainly supported by level 2b studies with grade B recommendation according to the Oxford Center of Evidence [30]. Using the GRADE tool, our study certainty ranged from very low to moderate (Supplementary Table 2). Study analysis showed SNM exerts better effects in treating patients with etiologies other than IC/BPS. However, overall evaluation showed that SNM has beneficial effects on all components of IC/BPS. In addition, the study indicated that there is no significant difference regarding pain improvement after using the caudal (antegrade) pathway versus the familiar (retrograde) approach. Randomized prospective studies are warranted to compare SNM versus other modalities for CPP treatment. Further studies to compare antegrade versus retrograde SNM approaches are encouraged.

Compliance with ethical standards

Financial disclaimer None.

Conflicts of interest None.

Appendix

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 14 September 2018.

Search Strategy:

No.	Searches	Results
1	exp Electric Stimulation Therapy/	72,449
2	(electric adj2 stimulation*).ti,ab.	5183
3	(nerve adj2 stimulation*).ti,ab.	21,658
4	Neuromodulation*.mp.	6090
5	neurostimulat*.mp.	2998
6	or/1–5	98,181
7	URINARY INCONTINENCE/or FECAL INCONTINENCE/or URINARY INCONTINENCE, URGE/ or URINARY INCONTINENCE, STRESS/	37,753
8	incontinence.ti,ab.	42,912
9	incontinent.ti,ab.	3853
10	exp Urinary Bladder Diseases/	95,824
11	bladder.ti,ab.	142,717
12	cystitis.ti,ab.	10,417
13	Urination Disorders/	10,985
14	(urin* adj2 disorder*).ti,ab.	1609
15	Pelvic Pain/	4796
16	“pelvic pain”.ti,ab.	8048
17	or/7–16	230,545
18	exp SACRUM/	8306
19	sacrum.ti,ab.	4813
20	sacral.ti,ab.	15,321

21	or/18–20	22,162
22	6 and 17 and 21	1512
23	limit 22 to animals	150
24	22 not 23	1362
25	limit 24 to (case reports or comment or editorial or letter)	148
26	24 not 25	1214
27	limit 26 to (english language and last 30 years)	1061
28	from 27 keep 1–1061	1061

PubMed Medline

((((((((((Electric Stimulation Therapy[MeSH Terms]) OR electric stimulation*[Title/Abstract]) OR nerve stimulation*[Title/Abstract]) OR Neuromodulation*) OR neurostimulat*[Title/Abstract])) AND ((((((((((((URINARY INCONTINENCE[MeSH Terms]) OR FECAL INCONTINENCE[MeSH Terms]) OR urinary incontinence, urge[MeSH Terms]) OR urinary incontinence, stress[MeSH Terms])) OR incontinence[Title/Abstract]) OR incontinent[Title/Abstract]) OR Urinary Bladder Diseases[MeSH Terms]) OR bladder[Title/Abstract]) OR cystitis[Title/Abstract]) OR Urination Disorders[MeSH Terms]) OR Urination Disorder*[Title/Abstract]) OR "Pelvic Pain"[Mesh:noexp]) OR pelvic pain[Title/Abstract])) AND (((SACRUM[MeSH Terms]) OR sacrum[Title/Abstract]) OR sacral[Title/Abstract])))) NOT (((((((((Electric Stimulation Therapy[MeSH Terms]) OR electric stimulation*[Title/Abstract]) OR nerve stimulation*[Title/Abstract]) OR Neuromodulation*) OR neurostimulat*[Title/Abstract])) AND ((((((((((((URINARY INCONTINENCE[MeSH Terms]) OR FECAL INCONTINENCE[MeSH Terms]) OR urinary incontinence, urge[MeSH Terms]) OR urinary incontinence, stress[MeSH Terms])) OR incontinence[Title/Abstract]) OR incontinent[Title/Abstract]) OR Urinary Bladder Diseases[MeSH Terms]) OR bladder[Title/Abstract]) OR cystitis[Title/Abstract]) OR Urination Disorders[MeSH Terms]) OR Urination Disorder*[Title/Abstract]) OR "Pelvic Pain"[Mesh:noexp]) OR pelvic pain[Title/Abstract])) AND (((SACRUM[MeSH Terms]) OR sacrum[Title/Abstract]) OR sacral[Title/Abstract])) AND ((Case Reports[ptyp] OR Comment[sb] OR Editorial[ptyp] OR Letter[ptyp])))))) NOT ((((((((((Electric Stimulation Therapy[MeSH Terms]) OR electric stimulation*[Title/Abstract]) OR nerve stimulation*[Title/Abstract]) OR Neuromodulation*) OR neurostimulat*[Title/Abstract])) AND ((((((((((((URINARY INCONTINENCE[MeSH Terms]) OR FECAL INCONTINENCE[MeSH Terms]) OR urinary incontinence, urge[MeSH Terms]) OR urinary incontinence, stress[MeSH Terms])) OR incontinence[Title/Abstract]) OR incontinent[Title/Abstract]) OR Urinary Bladder Diseases[MeSH Terms]) OR bladder[Title/Abstract]) OR cystitis[Title/Abstract]) OR Urination Disorders[MeSH Terms]) OR Urination Disorder*[Title/Abstract]) OR "Pelvic Pain"[Mesh:noexp]) OR pelvic pain[Title/Abstract])) AND (((SACRUM[MeSH Terms]) OR sacrum[Title/Abstract]) OR sacral[Title/Abstract])) AND ((Case Reports[ptyp] OR Comment[sb] OR Editorial[ptyp] OR Letter[ptyp])))) AND Animals[Mesh:noexp]) English language- 1988-2018.

Embase Session Results (18 Sep 2018)

No.	Query	Results
30	27 NOT 28 AND [english]/lim AND [1988–2018]/py	1212
29	27 NOT 28	1413
28	25 NOT 26 AND [animals]/lim	177
27	25 NOT 26	1590
26	25 AND 'case report'/de	123
25	23 NOT 24	1713
24	23 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it)	1261
23	7 AND 11 AND 22	2974
22	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21	411,367
21	pelvis NEAR/2 pain	13,619
20	pelvic NEAR/2 pain	17,397
19	'pelvic pain'/exp. OR 'pelvic pain'	20,112
18	'urination disorder':ti,ab	46
17	'micturition disorder'/exp. OR 'micturition disorder'	143,105
16	cystitis:ti,ab	15,122
15	bladder:ti,ab	200,602
14	'bladder disease'/exp. OR 'bladder disease'	168,493
13	incontinence:ti,ab	67,242
12	'incontinence'/exp. OR 'incontinence'	107,391
11	8 OR 9 OR 10	29,033
10	sacral:ti,ab	21,699
9	sacrum:ti,ab	6670
8	'sacrum'/exp. OR 'sacrum'	12,712
7	1 OR 2 OR 3 OR 4 OR 5 OR 6	280,338
6	neurostimulat*:ti,ab	4112
5	neuromodulation	44,386
4	'neuromodulation'/exp. OR 'neuromodulation'	44,386
3	nerve NEAR/2 stimulation	70,552
2	electric NEAR/2 stimulation	7840
1	'electrotherapy'/exp. OR 'electrotherapy'	

Web of Science

TS = ("electric stimulation therapy" OR electric NEAR/2 stimulation OR nerve NEAR/2 stimulation OR neuromodulation* OR neurostimulat*) AND TS = (incontinence OR incontinent OR bladder or cystitis OR "urination disorder*" OR urin* NEAR/2 disorder* OR pelvic pain) AND TS = (sacrum OR sacral))*AND* **LANGUAGE:** (English) *AND* DOCUMENT TYPES: (Article).

Indexes = SCI-EXPANDED Timespan = 1988–2018.

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