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ORIGINAL RESEARCH ARTICLE

Sacral neuromodulation in endometriosis – A promising treatment option for chronic pelvic pain

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Abstract

Introduction: Chronic pelvic pain (CPP) affects over one fifth of women worldwide, and endometriosis is one of the most common causes. In the present study, we examined whether sacral neuromodulation (SNM) is effective in the treatment of refractory chronic pelvic pain in women with endometriosis.

Material and methods: This multicenter prospective pilot study was started in 2017 and includes patients with chronic pelvic pain with no other obvious pathology than endometriosis. Other treatment options have been tried or they are unsuitable. Patients underwent SNM implantation. The main outcome was postoperative pain reduction and secondary outcome was quality of life. The following questionnaires were used to assess the outcomes: Brief pain inventory (BPI), clinical global impression - improvement (CGI-I), 15D-measure of health-related quality of life, and Biberoglu and Behrman (B&B) score.

Results: A total of 35 patients underwent the SNM procedure and, at the time of analysis, 15 patients had returned one-year questionnaires. The patients had a history of endometriosis for a median of 5.5 (interquartile range 2–9) years, with no correlation between the severity of symptoms and the duration of the disease ($p = 0.158$). A total of 31 patients (89%) were implanted with the internal pulse generator. There were statistically significant changes in BPI pain-related items. Worst experienced daily pain decreased among those who returned 12-month questionnaires from median 9 to 5 ($p = 0.006$), average daily pain from 6 to 3.5 ($p = 0.004$), and least daily pain from 3 to 1 ($p = 0.004$). Based on the CGI questionnaire ($n = 14$), at 12 months nine patients (60%) experienced great improvement in their symptoms, three patients (20%) much improvement and two patients (13%) minimal improvement. None of the patients experienced worsening of their symptoms. There was a statistically significant change in overall 15D score at 1 month ($p < 0.001$), 6 months ($p = 0.001$) and 12 months ($p = 0.018$), when the results were compared to baseline values. Median

B&B score also improved significantly and decreased from a baseline value of 8 (4–12) to 4.5 (0–6), $p = 0.002$.

Conclusions: Based on the preliminary findings of our study, SNM might be a promising treatment of CPP in endometriosis patients.

KEYWORDS
chronic pain, endometriosis, pelvic pain, sacral neuromodulation

1 | INTRODUCTION

Chronic pelvic pain (CPP) in women is defined as cyclical or non-cyclical pain that has lasted for at least 6 months and encompasses an unspecified combination of dysmenorrhea, dyspareunia and non-menstrual chronic pelvic–abdominal muscle pain.[1] CPP affects up to 24% of women worldwide.[1] CPP is often resistant to surgical and medical treatment and appears to respond better to a multimodal, holistic approach rather than to laparoscopy alone.[2,3]

Endometriosis is defined as the presence of functional endometrial glands and stroma outside the uterine cavity. Approximately 10%–15% of women of reproductive age suffer from pelvic endometriosis and up to 45% of patients with CPP have endometriosis.[4] Analgesics, hormonal therapies and surgery are the mainstay of the therapy, but pain often returns and is not necessarily associated with the relapse of lesions.[5] Currently, there are no means to predict which patients will experience long-term relief after conventional therapies.[5] Research data encourages a multidisciplinary approach in the treatment of endometriosis and underlines that major advances in improving understanding and alleviating pain in endometriosis will likely occur if the focus includes both lesions and pain mechanisms.[5]

Sacral neuromodulation (SNM) is an established therapy in managing a variety of functional pelvic disorders, the main indications being fecal incontinence, urge urinary incontinence and nonobstructive urinary retention. A relatively new application of SNM in pelvic area is chronic pain. SNM has been shown to be effective in urological patients with chronic pelvic pain (CPP)[6,7] and might play a role in endometriosis patients with CPP.[8,9]

To the best of our knowledge, this is the first study to investigate whether SNM is helpful in endometriosis patients with refractory CPP.

Key message

Endometriosis related chronic pelvic pain may be difficult to treat by conventional medical and surgical therapies. Sacral neuromodulation is an emerging and promising therapy with good results reported in this first prospective study.

2 | MATERIAL AND METHODS

This is a multicenter prospective pilot study (Turku, Helsinki and Oulu University Hospitals and Seinäjoki Central Hospital) that was started in 2017 and is still recruiting patients. Patients are eligible for the study if they meet the following two criteria: (1) Patients have chronic pelvic pain with no other obvious pathology than endometriosis; (2) Other treatment options have been tried or it is not possible to use them.

All the patients in the study so far had endometriosis confirmed by surgery and were divided into three groups:

1. They have undergone radical pelvic surgery (all endometriosis lesions have been resected with hysterectomy and/or bilateral adnexectomy) with no signs of recurrence clinically, in ultrasound or magnetic resonance imaging (MRI).
2. They have undergone fertility sparing pelvic surgery (all endometriosis lesions have been resected) with no signs of recurrence clinically, in ultrasound or MRI.
3. They have undergone radical or fertility sparing pelvic surgery, there is recurring or residual endometrial tissue, but reoperation is not desirable.

Suitable patients are referred to a participating study center by a gynecologist who has been treating them. Eligible patients were later admitted to a colorectal surgeon, who implanted SNM. This therapy requires two operations called stage 1 and stage 2. In stage 1, S3 nerve root (sometimes S4) is stimulated with low electrical current via an electrode placed through the sacral foramen. This electrode is connected to an external stimulator. Stage 1 of SNM is done unilaterally or bilaterally based on patient and doctor's preference. The same policy is used concerning local or general anesthesia. This set-up is used for 4 weeks. In stage 2, an internal pulse generator is implanted. The decision to proceed to stage 2, as well as evaluation of long-term results, are based on improvement of symptoms and patient's opinion. The medication remains unchanged during stage 1. The symptoms are evaluated at the baseline (before stage 1), at the end of stage 1, one to 2 months after stage 2, every 6 months after that for 2 years, and at 3 years after stage 2.

The main outcome measure was postoperative pain reduction and the secondary outcome measure was quality of life. Evaluation was based on the following questionnaires:

- Brief pain inventory (BPI). This is a generic pain questionnaire for chronic pain conditions available in two formats: short form and long form. We have used the short form, which comprises of two main scores: a pain severity score and a pain interference score. The pain severity score is calculated from the four items about pain intensity: worst pain in last 24 h, least pain in last 24 h, pain on average, and pain right now. Each item is rated from 0, no pain, to 10, worst pain you can imagine. The pain interference score is calculated from seven items on pain interference: general activity, mood, walking ability, normal work (including housework), relations with other people, sleep and enjoyment of life. The seven sub-items are rated from 0, does not interfere, to 10, completely interferes.[10]
- Clinical global impression – improvement (CGI-I). This questionnaire evaluates the change from the initiation of treatment on a seven-point scale: 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment); 5 = minimally worse; 6 = much worse; 7 = very much worse since the initiation of treatment.[11]
- 15D-measure of health-related quality of life. The 15D is a generic, 15-dimensional, standardized, self-administered instrument that can be used both as a profile and a single index score measure. The questionnaire is composed of the following dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, the respondent chooses one of the five levels best describing her state of health at present. The valuation system is based on an application of the multiattribute utility theory. The single index score (15D score), representing the overall HRQoL on a 0–1 scale (1 = full health, 0 = being dead) and the dimension level values, reflecting the goodness of the levels relative to no problems on the dimension (=1) and to being dead (=0), is calculated from the health state descriptive system by using a set of population-based preference or utility weights. A change of ≥0.015 in the 15D score is considered clinically important.[12]
- Biberoglu and Behrman 1981 (B&B score). This is a physician-completed questionnaire based on patient's interview referring to the previous 4 weeks. The B&B evaluates three cardinal symptoms reported by endometriosis patients: dysmenorrhea, dyspareunia, and pelvic discomfort/pain. Each symptom is rated from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) based on the patient's self-assessment of pain and the gynecological palpation by the attending physician. A summary score on these three items (0 = none, 1–3 = mild, 4–6 = moderate, and 7–9 = severe) is calculated. Physicians also rate 2 items on the same 0 to 3 scale that evaluate physical signs of endometriosis: pelvic tenderness and induration, yielding a summary score from 0 (none) to 5–6 (severe). A total symptom severity score is calculated by summing the pain/discomfort and physical signs scales.[13]
- McCoy female sexuality questionnaire, Pelvic floor distress inventory (PFDI-20) and endometriosis health profile questionnaire (EHP-30) are used in this prospective trial but they were not included in this study.

2.1 | Statistical analyses

All statistical analyses were carried out using either R software version 3.5.2 (R Foundation for Statistical Computing) or IBM SPSS Statistics version 25 statistical software for Windows (IBM corp.). Categorical variables were compared using the Chi-square and Fisher's exact tests. Nonparametric variables were compared using the Mann–Whitney U test. Pearson test was used to estimate correlation between two noncategorical variables. For noncategorial variables either median with min-max or interquartile range (IQR) was reported. A level of two-tailed $p < 0.05$ was considered statistically significant.

2.2 | Ethics statement

This study was approved by Tampere University Hospital Ethics committee ETL: R16122 13.12.2016. Written informed consent was obtained from all the participants. ClinicalTrials.gov Identifier: NCT03139734.

3 | RESULTS

The patient flow chart is shown in Figure 1. A total of 35 female patients underwent stage 1 and 31 stage 2 (89%). Four patients did not receive the internal pulse generator, two because of complications (one had pain and one had local infection) and two because of lack of efficacy. There were three complications (8.6%) after stage 1 (infection in one patient and pain in two patients). There were six complications (19%) after stage 2 (5 patients with infection and 1 patient with pain) and SNM had to be removed due to infection from three patients, but two were tested again later and an internal

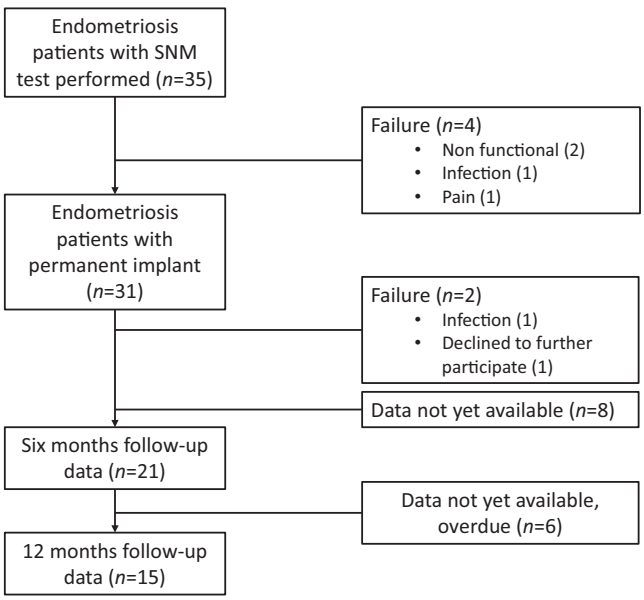

FIGURE 1 Patient flow chart.

pulse generator was placed. One patient left our study for unknown reasons, and the implanted SNM was not removed. At the time of analysis, 21 patients had returned six-month questionnaires, and 15 patients had returned one-year questionnaires. Patient characteristics are shown in Tables 1–4.

Patients have had a history of endometriosis for a median of 5.5 (interquartile range 2–9) years. There was no correlation between the severity of pain symptoms (average daily pain) and the duration of the disease ($p=0.158$). There were statistically significant changes in BPI pain-related items, as illustrated in Table 5 and Figure 2. Worst experienced daily pain decreased among those who returned 12-month questionnaires from median 9 to 5 ($p=0.006$), average daily pain from 6 to 3.5 ($p=0.004$), and least daily pain from 3 to 1 ($p=0.004$). At the time of analysis, eight patients (53%) still reported that they were suffering from occasional severe pain (BPI ≥ 5), and five patients (33%) reported suffering from at worst mild pain (BPI 1–3). There was no statistically significant decrease in the use of NSAID/paracetamol, weak or strong opioids, while use of pregabalin or gabapentin medication decreased from 86% to 43% ($p=0.018$). Significant improvements in BPI interference items were observed in enjoyment of life (median 8 to 2.5, $p=0.031$) and mood (7 to 2.5, $p=0.027$).

Based on the CGI questionnaire, at 12 months nine patients (60%) experienced great improvement of their symptoms, three patients (20%) much improvement and two patients (13%) minimal improvement. One patient did not complete the questionnaire. None of the patients experienced worsening of their symptoms. Symptoms improved very much in 40% of women in group 1 and in 83% of women in group 2, but on the other hand, symptoms improved both very much and much in 100% of women in group 1 and in 83% of women in group 2.

Changes in 15D questionnaire are illustrated in Figure 3. There was a statistically significant change in overall 15D score at 1 month ($p<0.001$), 6 months ($p=0.001$) and 12 months ($p=0.018$), when results were compared to baseline values. Median B&B score also improved significantly during the study period, and decreased from baseline value of 8[4–12] to 4.5 (0–6), $p=0.002$ (Figure 4).

There was no correlation between the severity of baseline pain symptoms according to BPI score and symptoms improvement according to CGI score ($p=0.652$). Neither was there a correlation

TABLE 1 Baseline characteristics.

Variable	
Age, years, median (min-max)	36 (19–59) years
BMI, median (min-max)	27 (18–43)
Graviditas, median (min-max)	1 (0–15)
Partus, median (min-max)	1 (0–4)
Co-existing diseases	32 (91.4%)
Anal fissure	3 (8.5%)
Hemorrhoides	2 (5.7%)
Cardiac comorbidity	2 (5.7%)
Celiac disease	2 (5.7%)
Interstitial cystitis	2 (5.7%)
Vulvodynia	1 (2.9%)
Lumbar prolapsed disc	1 (2.9%)
Overactive bladder	1 (2.9%)
Diabetes	1 (2.9%)
Inflammatory bowel disease	0 (0.0%)
Fibromyalgia	5 (14.3%)
Irritable bowel disease	9 (25.7%)
Migraine	16 (45.7%)
Depression	16 (45.7%)

TABLE 2 Endometriosis operations.

Endometriosis operations, median (min-max)	2 (1–5)
Hysterectomy	23 (65.7%)
Superficial peritoneal endometriosis resection	26 (74.3%)
Salpingectomy	19 (54.3%)
Ovariectomy	16 (45.7%)
Sacrouterine ligament resection	16 (45.7%)
Endometrioma enucleation	14 (40%)
Rectum anterior resection	10 (28.6%)
Appendectomy	8 (22.9%)
Bowel resection with temporary stoma[a]	2 (5.7%)
Sigmoid colon resection	2 (5.7%)
Ureter resection	1 (2.9%)

[a]One patient underwent anterior resection (rectovaginal fistula) and one patient sigmoid resection.

TABLE 3 Inclusion criteria and endometriosis types.

Inclusion criteria, radical surgery (no recurrence)	11 (31.4%)
Inclusion criteria, fertility sparing surgery (no recurrence)	16 (45.7%)
Inclusion criteria, either type with recurrence	6 (17.1%)
Superficial endometriosis	27 (77.1%)
Deep endometriosis	16 (45.7%)
Endometrioma	12 (34.3%)

TABLE 4 Other surgeries and medical therapies.

Previous abdominal operation, other indication	17 (48.6%)
Menopausal hormone therapy	9 (25.7%)
Progestin only pill	15 (42.9%)
Combined hormonal contraception	6 (17.1%)
Levonorgestrel-releasing intrauterine device	4 (11.4%)
GnRH analogs	4 (11.4%)
Aromatase inhibitor	3 (8.6%)
Combination therapy	3 (8.6%)

Abbreviation: GnRH, gonadotropin-releasing hormone.

TABLE 5 Outcomes at the time of analysis.

Variable	Baseline		At 12 months	*p*-value
	All patients	Patients with complete data at 12 months		
Pain medication				
Paracetamol/NSAIDs	35 (100%)	14 (100%)	13 (93%)	0.309
Weak opioids	21 (60%)	6 (43%)	5 (36%)	0.699
Strong opioids	16 (47%)	6 (43%)	5 (36%)	0.699
Pregabalin	24 (69%)	12 (86%)	6 (43%)	**0.018**
CGI-I score				
Very much improved	–	–	9 (60%)	–
Much improved	–	–	3 (20%)	–
Minimally improved	–	–	2 (13%)	–
No change from baseline	–	–	–	–
Minimally worse	–	–	–	–
Much worse	–	–	–	–
Very much worse	–	–	–	–
Information missing	–	–	1 (6.7%)	–
BPI items, median (min-max)				
Worst pain in last 24 h	8 (6–10)	9 (6–10)	5 (0–10)	**0.006**
Least pain in last 24 h	3 (0–6)	3 (0–6)	1 (0–3)	**0.004**
Pain on average	5.5 (3.5–7)	6 (3.5–7)	3.5 (0–7)	**0.004**
Pain right now	6 (0–9)	5 (0–9)	3 (0–7)	**0.044**
General activity	7 (2–10)	8 (2–10)	3.5 (0–10)	0.077
Mood	7 (1–10)	7 (1–10)	2.5 (0–10)	**0.027**
Walking ability	5 (0–10)	5 (0–10)	2.5 (0–10)	0.210
Normal work	7.5 (1–10)	8 (1–10)	3.5 (0–10)	0.104
Relationships with other people	6 (0–10)	7 (0–10)	1 (0–10)	0.114
Sleep	7 (0–10)	8 (0–9)	3 (0–10)	0.137
Enjoyment of life	8 (2–10)	8 (2–10)	2.5 (0–10)	**0.031**

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; CGI-I, clinical global impression – improvement score; BPI, brief pain inventory.

between time from endometriosis diagnosis and symptoms improvement ($p=0.542$). The correlation between the inclusion criteria and CGI score is illustrated in Figure 5.

4 | DISCUSSION

This is the first prospective study investigating the use of SNM in endometriosis patients with CPP and shows promising results.

Why do we need to look beyond conventional endometriosis therapies? Conventional therapies can be broadly classified into surgical removal of lesions and medical therapies (NSAIDs, other analgesics, hormonal therapies and neuromodulators/neuropathic medicines).[5,14] Most women with suspected or known endometriosis who seek pain relief are using over-the-counter medications such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs). However, the evidence that they are effective is of very low quality and based on one older study including only 24 women with endometriosis.[15] Hormonal suppressive therapy is routinely prescribed because of the evidence that steroids play a key role in the pathophysiology of endometriosis. The hormonal treatments may have side effects and act like contraceptives.[16] Tricyclic antidepressants (eg amitriptyline and nortriptyline), selective serotonin uptake inhibitors (eg duloxetine), and anticonvulsants (eg gabapentin and pregabalin) have all shown good results in the treatment of endometriosis.[16] However, in a recent RCT for the management of chronic pelvic pain (in the absence of endometriosis), gabapentin was not proven to be clearly superior to placebo[17] and other neuromodulators are sometimes associated with severe, dose-limiting side effects.[16]

The approach to surgical treatment of endometriosis in women with CPP is based on the oncologic principle of removing all lesions.[18,19] There is a strong evidence that surgery is

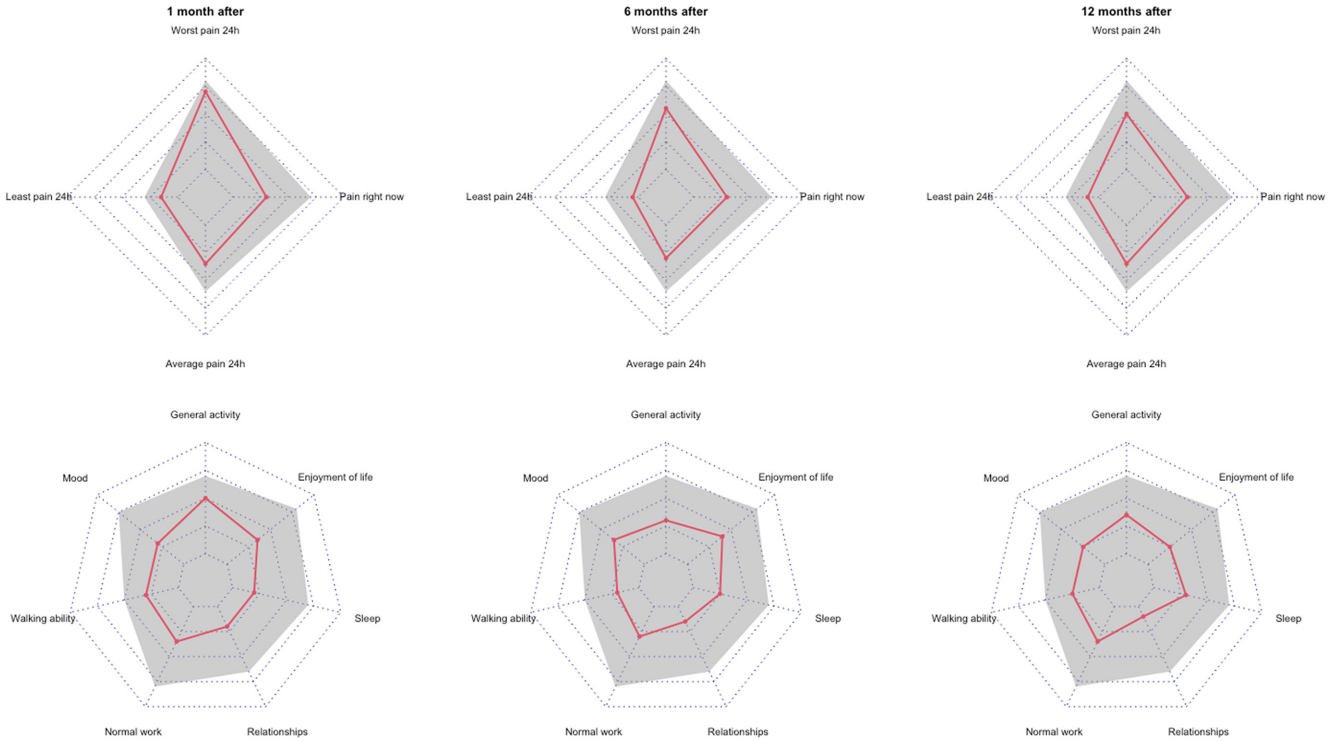

FIGURE 2 Average BPI scores of the study population at 1-month, 6-month and 1-year follow-up. The gray area illustrates average scores at the beginning of the study.

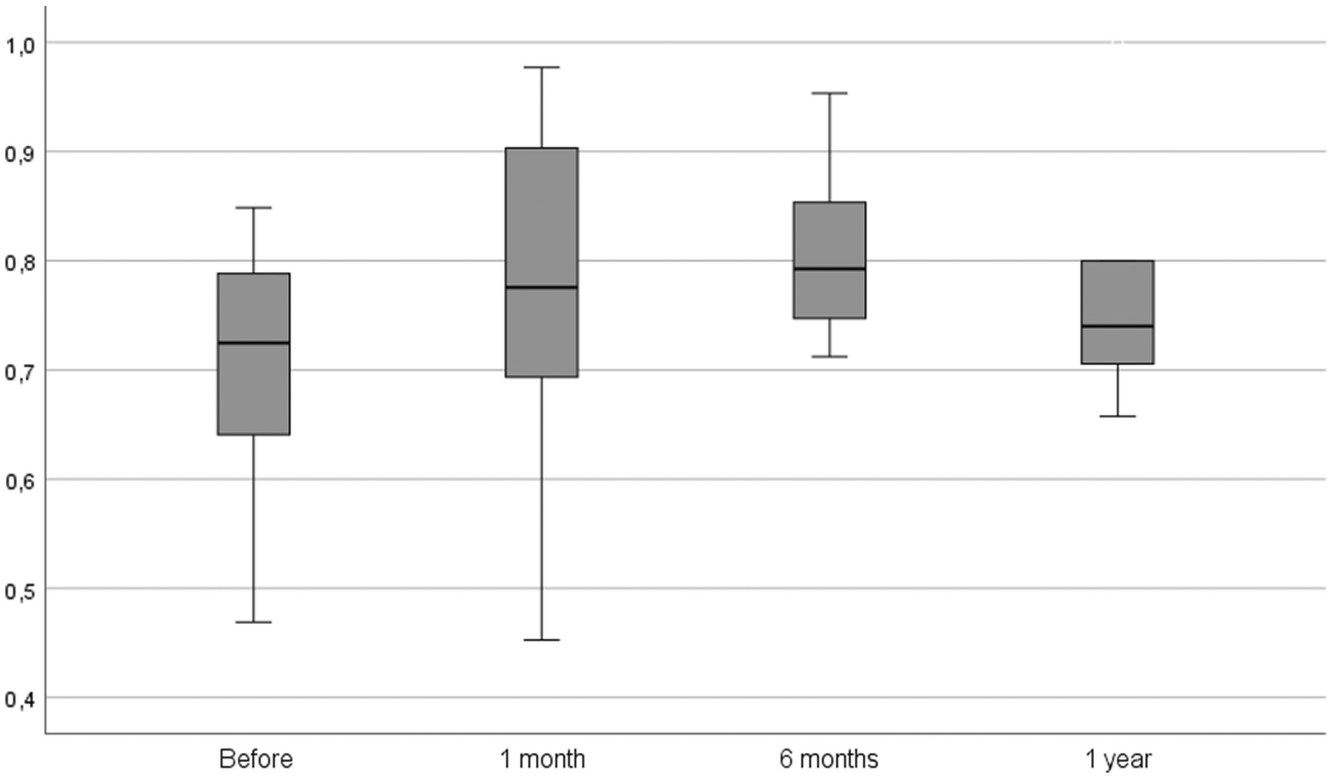

FIGURE 3 Changes in 15D questionnaire.

effective in the treatment of endometriosis related pelvic pain.[20] However, pain recurrence and reoperation rates are high, with reoperation rates for symptoms of 50%–60% by 5–7 years.[21,22] In the 19–29 year age group, over 70% have another surgery.[5] Seemingly complete surgical removal fails to alleviate pain for at least a year in up to 50% of carefully selected patients.[19]

Current analgesic, anti-inflammatory, surgical and hormonal treatments are beneficial for many endometriosis patients, but in some cases they remain unsatisfactory likely because treatments attempt to treat or eliminate the lesions.[5] Because pain of any type resides in nervous system activity, research also suggests that a major contributing factor for endometriosis-associated-pain is not the ectopic growths themselves, but rather the activity from nerves that have emerged from nearby tissues to innervate the growths, which affects the activity of neurons in the spinal cord and brain.[5] This is where neuromodulation may help. Neuromodulation mechanisms are not completely understood, but four basic mechanisms of action have been proposed and demonstrated in vitro: afferent modulation, synaptic facilitation, direct stimulation and increased neuroplasticity.[23]

The FDA approved SNM as a treatment option for patients with urge incontinence in 1997 and for urgency/frequency and nonobstructive urinary retention in 1999. Currently SNM does not have FDA approval for the treatment of chronic pelvic pain. There are studies suggesting that SNM could be used as a valuable alternative treatment option in patients with chronic pelvic pain.[6,8,9,24–26] However, the majority of the published studies used a retrospective approach, evaluated small groups of patients and provided data on a limited follow-up duration.

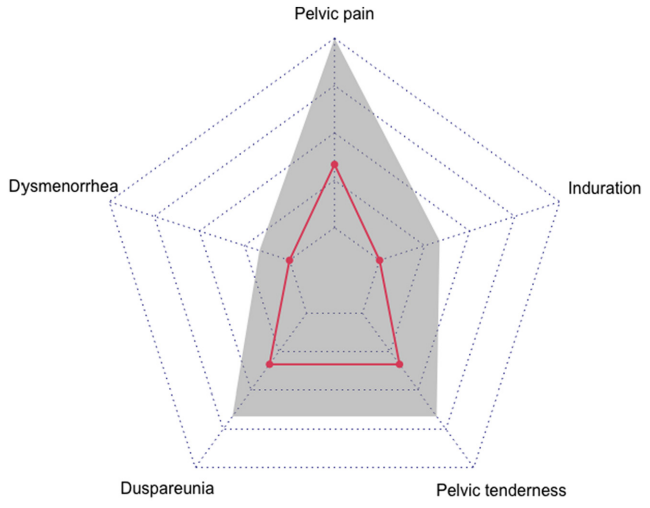

FIGURE 4 Bigeroglu and Behrman score (range 0–3 per item) in the beginning (gray area) and 6 months after sacral neuromodulation (SNM) therapy.

In our study, we included patients who had already undergone the conventional endometriosis therapies and they were insufficient. This is a group of patients that is very difficult to treat. SNM implantation rate of 89% is higher than the one of 59% reported by one previous prospective multicenter study with 27 patients suffering from medication resistant pelvic pain[25] and is similar to the implantation rate of 88% in endometriosis patients with chronic pelvic pain in our previous retrospective study.[9] Complication rates of 8.6% after stage 1 and 19% after stage 2 are quite low and are comparable to 30% reported in this meta-analysis.[6] Statistically significant symptom improvement was noticed in all BPI pain items, in two BPI interference items (mood and enjoyment of life), in the CGI questionnaire at 12 months, in overall 15D score as well as in the B&B score at 6 months. Symptom improvement was noticed regardless of the duration of endometriosis and in all three recruited groups, both in patients with or without endometriosis recurrence.

The best CGI results in our study at 12 months based on very much improved symptoms are seen after fertility sparing surgery with no recurrences (group 2) and this might encourage the use of SNM before radical surgery in CPP related to endometriosis. This result is difficult to explain when we take into consideration the fact that the mechanisms of pain in endometriosis and also the neuromodulation mechanisms are not completely understood, but SNM results might correlate with the amount of tissue damage during the surgery and the extent of inflammatory response. On the other hand, contradictory results were published in a

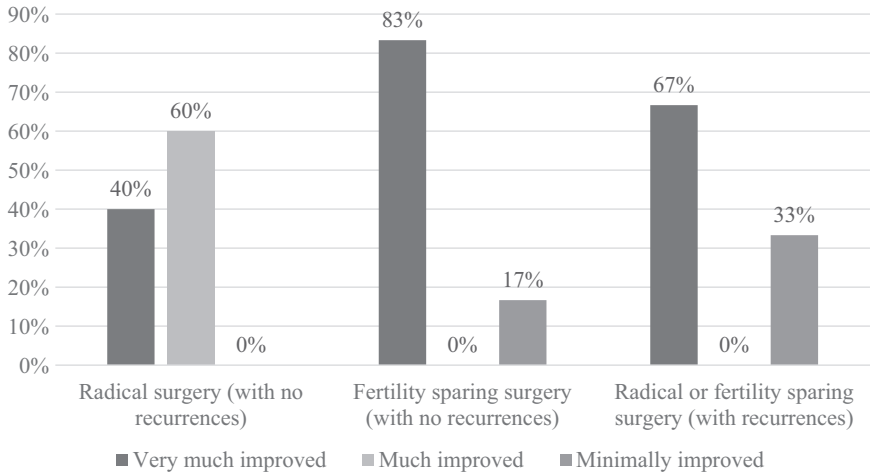

FIGURE 5 Inclusion criteria and clinical global impression – improvement score (CGI-I) at 12 months.

prospective multicenter study with 27 patients suffering from multietiological medication resistant pelvic pain, where all the patients with pelvic pain following hysterectomy received permanent implantation.[25] Nonetheless, all the women from group 1 (radical surgery with no recurrence) experienced very much or much improvement of symptoms. The results suggest that SNM could be a good option in women with severe pelvic pain and no recurrence of endometriosis lesions after both radical and fertility sparing pelvic surgery.

SNM should be regarded as an option to treat chronic pelvic pain in endometriosis patients when current medical and surgical therapies are unsuccessful. SNM is a minimally-invasive procedure that is usually performed in a day surgery setup and has only minor complications that are quite easy to deal with. SNM might be considered even before radical endometriosis surgery and, if successful, it helps avoid the risks that are linked to complex surgical therapies.

This study had some limitations, one being the relatively small number of patients. Recruiting patients is slow as this is a novel SNM indication, and we are prepared to publish more results at a later date.

5 | CONCLUSIONS

The treatment of chronic pelvic pain related to endometriosis is difficult and the mainstream remain medical therapy and surgery. Based on the preliminary findings of our study, it appears that SNM is a promising treatment option of CPP in endometriosis patients that do not respond to conventional therapies.

AUTHOR CONTRIBUTIONS

All authors contributed to this manuscript as follows: Study conception and design (all authors). Data collection (AZ, EO, PS, PV, HH, JM-K, TR, PH, SS, ML, TP). Formal data analysis (AZ, MU). Original manuscript (AZ). Critical review of the manuscript (all authors). Supervision (TP, ML, MU).

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CONFLICT OF INTEREST STATEMENT

All authors declare they have no conflicts of interest.

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