Int J Colorectal Dis (2012) 27:921–926
DOI 10.1007/s00384-011-1394-2

ORIGINAL ARTICLE

Sacral nerve modulation in the treatment of chronic pelvic pain

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Accepted: 16 December 2011 / Published online: 29 December 2011
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Abstract
Background Chronic pelvic pain is a common condition that significantly compromises the quality of life of affected patients. Unfortunately, despite treatment procedures, the results are often ineffective and symptoms persist for years. For these reasons, the search for less aggressive treatment options with fewer negative consequences leading to minimally invasive techniques was conducted.
Objective The aim of the present study was to evaluate the efficacy of sacral nerve modulation in the treatment of chronic pelvic pain. Moreover, we aimed to identify potential predictors of positive results of sacral neuromodulation through the comparison between failed and successful patients.
Patients From January 2004 to December 2009, all consecutive patients suffering from chronic pelvic pain and tested for sacral nerve modulation in three pelvic floor dedicated centers were evaluated. Severity of symptoms were analyzed by a visual analog scale (VAS)
Results Twenty-seven patients (2 males; mean age, 53 years) were tested for sacral nerve modulation in the screening period and were included in the present study. The mean duration of pain was 51 months (range, 10–132 months). The mean preoperative VAS was 7.8 (range, 5–10). Previous pelvic surgery was reported in 18 patients (66.5%). Sixteen patients (59%) fulfil the successful criteria and were definitively implanted. The mean follow-up was 37 months (range, 12–71 months). The mean preoperative VAS was 8.1 (range, 6–8) and decreased to 2.1±1.2 at 6-month follow-up ($p<0.0001$), to 2.1±1.1 at 12 months (16 patients), to 2.0±1.2 at 24 months (13 patients), to 2.3±1.4 at 36 months (9 patients), to 2.1±1.5 at 48 months (5 patients), and to 1.9±1.3 at 60 months (3 patients).
Conclusions Sacral neuromodulation proved to be effective in the treatment of some patients affected by chronic pelvic pain, and the effect persists over time. A positive screening phase and a positive response to gabapentin or pregabalin showed to be predictors of a successful response. Multiple localizations of pelvic pain and pain occurred after stapler surgery seem to be negative factors for the success of the treatment.

Keywords Chronic pelvic pain · Sacral nerve stimulation · Surgery · Stapler · Gabapentin · Neuromodulation

Authors contribution Jacopo Martellucci had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.M. was involved in the study concept and design, acquisition, analysis and interpretation of data, and statistical analysis and performed the procedure. N.G. was the main performer of the procedure and was responsible for supervising the patients in Pisa Department. C.A. was the main performer of the procedure and was responsible for supervising the patients in Montecchio Emilia Department.

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Introduction

Chronic pelvic pain (CPP) is a common condition that significantly compromises the quality of life (QoL) of affected

patients. This painful condition could be defined as a nonmalignant and noninfective pain referred in structures related to the pelvis, constant or recurring over a period of 6 months or more, and associated with negative behavioral and social consequences [1]. Patients often present with various associated diseases including bladder, sexual, gynecological, or bowel dysfunction.

The first reference to pelvic pain appeared in 1859 when Simpson [2] described the syndrome, which he called *coccygodynia*. Since then, a number of different terms have been used, leading to confusion as to the definition of this syndrome. The lack of consensus on the definition of CPP greatly hinders epidemiological and comparative studies, and it is very difficult to give a precise estimation of the real prevalence of this condition.

The treatment of these patients includes from pharmacological, psychological, and physical therapy to surgery. Unfortunately, despite treatment procedures, the results are often ineffective, and symptoms persist for years. Moreover, many patients become unsatisfied about the care they receive and refrain from seeking help, despite continuous symptoms [3].

Objectives of the treatment should be focused on restoring normal function, improving QoL, and preventing relapse of symptoms. For these reasons, search for less aggressive treatment options with fewer negative consequences leading to minimally invasive techniques was conducted.

Electrotherapy has been used in the treatment of pain since ancient times. In 46–47 AD, Scribonus Largus, Roman emperor Claudius court physician, in his *Compositiones,* reported the treatment of headaches with electric eels (40–100 V, 100 Hz).

Sacral nerve modulation (SNM) was first described by Tanagho and Schmidt [4] in 1982 and first applied in human patients in 1988 [5].

SNM is an effective treatment for some urological and proctological disorders. Even if the mechanisms for the efficacy of SNM are not completely understood, the ability of this stimulation to reduce the concomitant pain symptoms in patients treated for voiding dysfunction has been shown [6, 7].

The aim of the present study is to evaluate the efficacy of SNM in the treatment of patients with CPP.

Materials and methods

From January 2004 to December 2009, all consecutive patients suffering from CPP and tested for SNM in three pelvic floor dedicated centers (Montecchio Emilia, Pisa, Siena) were considered for the present study. All patient data were prospectively collected by a single physician (M.J.) in a common database and were analyzed by the same physician.

The inclusion criteria for the present study were as follows: age >18 years and nonorganic or noninfective pelvic pain without recognizable cause, in which symptoms lasted for at least 6 months. The exclusion criteria were as follows: presence of neurologic diseases (Parkinson's disease, multiple sclerosis, spinal cord injury, cauda equina syndrome, etc.), presence of psychiatric disorders that could affect patients' understanding and adherence to treatment, and pain in oncological patients or affected after demolitive surgery for cancer. Patients who underwent the SNM testing phase with peripheral nerve evaluation (PNE) with monopolar electrode were excluded from the study.

Informed consent for the treatment was obtained from all patients, and the procedure was approved by local ethics committee in all centers. A complete history was obtained in all cases. All patients were previously assessed for the exclusion of pathologic causes with appropriate examinations. A psychological evaluation was recommended to all patients.

Age, sex, duration and features of pain, associated pelvic or systemic diseases, pharmacological therapy (PT), previous surgery, and previous treatments for CPP were preoperatively recorded in all the patients. Symptoms were analyzed by a visual analog scale (VAS) varying from 0 to 10, in which 0 represents no pain and 10 represents the maximum tolerable pain.

VAS was recorded by one of the authors (M.J.) preoperatively (without PT taken for at least 4 h), at 14–21 days after temporary SNM testing, and on every follow-up control.

Follow-up was performed every 7–10 days after temporary testing; after 15 days and 1, 3, 6, and 12 months; and then every year in the definitively implanted patients. Every additional evaluation required by the patients was recorded in the database.

QoL was evaluated with Short Form-36 questionnaire [8] at baseline and at 6-month follow-up.

SNM test stimulation and implant were performed in the two-stage technique as proposed by Spinelli et al. [9] and as previously described [10, 11].

In the first step (screening phase), the patients fulfilling the selection criteria underwent temporary stimulation. After the identification of the sacral foramen bilaterally (S2, S3, S4), the lead that obtained the best motor responses, based on surgeon's visual impression, and the best sensitive response, based on the patient's impression, were left in the site, and the other was removed. The S3 foramen was chosen whenever possible. The screening phase lasted at least 4 weeks in all patients to exclude false responses and eliminate any placebo effects. In every patient, PT was correctly interrupted before the testing phase of the treatment, and every analgesic requirement during the treatment was recorded. In patients with unsuccessful stimulation, PT was restored before the removal of the electrode for the evaluation of the combined therapy. In patients with positive

but insufficient response, a bilateral electrode was also proposed.

In the second step, in patients who fulfil the successful criteria, the implantable pulse generator was placed under local anesthesia into a subcutaneous pocket prepared on the buttock and connected to the implanted electrode. The screening phase was considered successful when (at least one of the following):

- VAS score <3 or 5-point reduction compared to baseline (without PT)
- Reduction of pharmacotherapy: in which the association between SNM and PT allowed a reduction of PT with VAS score <3
- Referred satisfaction of the patients who required definitive implantation in front of a subjective improvement of pain or concurrent diseases symptoms

Statistical analyses were performed with SPSS 17.0. Continuous variables were expressed as mean±SD, and categorical variables as percentages. Comparison between baseline and follow-up data were performed using the Student's *t* test. χ^2 Test or Fisher's exact test were used for categorical variables, as appropriate. A p value of <0.05 was considered statistically significant.

Results

Twenty-seven patients (2 males; mean age, 53 years) were tested for SNM in the screening period and were included in the present study.

The mean duration of pain was 51 months (range, 10–132 months). The mean preoperative VAS was 7.8 (range, 5–10). The site of pain was anus (22 patients: 81.5%), vagina (9 patients: 33.5%), perineum (4 patients: 15%), and diffuse or difficult to localize (2 patients). Pain was also defined as deep in 16 patients (59%) and superficial in 11 (41%).

Thirteen of the female patients were multiparous (range, 2–5), all with vaginal birth; 8 patients had only one vaginal birth, 2 patients gave birth by cesarean section, and 3 patients were nulliparous.

Previous pelvic surgery was reported in 18 patients (66.5%). Five patients (27.5%) reported more than one pelvic operation. The interventions are reported in Table 1.

Twelve patients (44%) reported the onset of pain occurred after surgery. Previous use of nonsteroid anti-inflammatory drugs was recorded in all cases: opioids in 13 cases (48%), antidepressant in 7 (26%), and gabapentin/pregabalin in 9 patients (33.5%).

The patients underwent biofeedback in six cases and local anaesthetic injection in three with no results.

The starting stimulation parameters were common in all patients (frequency was 18–25 Hz, pulse width was 210 μs, and amplitude was just above the threshold of patient sensation). Electrode configuration was set, trying to overlay the stimulation sensation in pain site.

Table 1 Previous pelvic surgery reported

STARR	7
Hysterectomy	4
Hemorrhoidectomy (Milligan and Morgan)	4
Stapled hemorrhoidopexy	3
Fistulectomy	2
Anal sphincterotomy	1
Appendectomy with viscerolysis	1
Explorative laparoscopy for endometriosis	1

STARR Stapled TransAnal Rectal Resection

Sixteen patients (59%) (15 females; mean age, 51.7 years; range, 29–75 years) fulfil the successful criteria and were definitively implanted.

The mean follow-up was 37 months (range, 12–71 months). No perioperative or long-term complications were reported. No patients need to suspend the treatment or remove the stimulator during the follow-up period. In one patient, a bilateral stimulator was placed. The electrode was implanted in S3 in 15 patients, and in S4 in 1. Bilateral stimulations were performed in the right/left S3.

In all patients, the screening period configuration was confirmed (frequency was 18–25 Hz, pulse width was210 μs, and amplitude was just above the threshold of patient sensation).

The mean duration of pain in the successfully implanted patients was 59 months (range, 16–132 months).

Nine patients have a follow-up duration longer than 3 years, and 3 patients longer than 5 years without loss of efficacy. Preoperative and follow-up VAS was reported in Fig. 1.

The site of pain reported by the implanted patients was anus in 12 patients (75%), vagina in 3 (19%), and perineum in 2 (12.5%). Pain was defined as deep in 10 patients (62.5%) and superficial in 6 (37.5%).

None of the patients who correlated the onset of pain with previous surgery with stapler was definitively implanted (five patients). All patients who reported the onset of pain after hysterectomy were definitively implanted (four patients). No statistically significant differences in previous surgery were noted between patients with success or failure of SNM.

All patients who reported a positive control of pain with gabapentin or pregabalin (nine patients) had a successful response to SNM and were definitively implanted. No differences in pharmacotherapy were noted among implanted and not implanted patients, No differences were noted between successful and failed patients regarding age, duration of symptoms, mean preoperative VAS, site of pain, previous treatments for pain, or onset of pain related to previous surgery (Table 2).

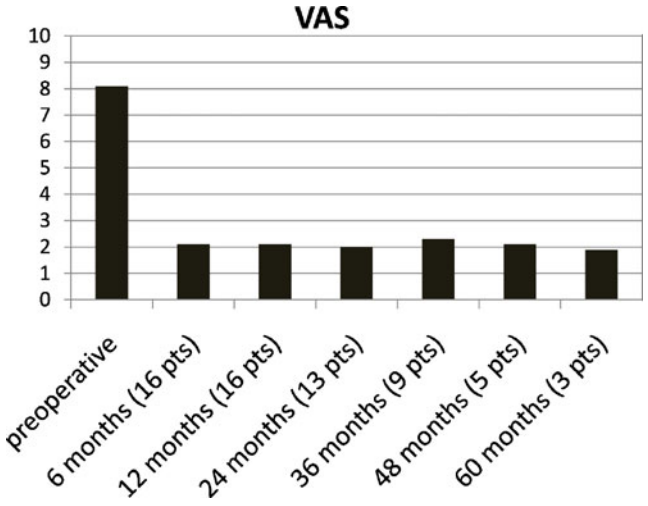

Fig. 1 Preoperative and follow-up VAS

Considering the definitively implanted patients, manometric and functional data were available at baseline in all patients and at 6-month follow-up evaluation in 15 patients. No significant differences were observed between baseline and last follow-up in resting pressure (58±31 mm Hg vs. 64.7± 27.2 mm Hg), voluntary contraction amplitude (104.1± 33.8 mm Hg vs. 96.4±48.2 mm Hg), voluntary contraction duration (6±3 s vs. 6.3±4 s), sensitivity threshold (48.2± 31 ml vs. 66.5±39 mm Hg), and maximum tolerated volume (133.2±99 ml vs. 146.5±79 mm Hg).

Discussion

Although some studies reported some favorable results with SNM [12–19], the treatment of CPP still remains a clinical challenge. Seventy percent of patients who underwent SNM had previously presented with pelvic pain unsuccessfully to 2 to 10 physicians [17].

The device currently marketed for transforaminal SNM (Interstim II; Medtronic, Minneapolis, MN) is not specifically indicated for treatment of pelvic pain. However, a number of publications reported the ability of such stimulation to relieve pain in patients treated for interstitial cystitis [7, 14, 19], raising great interest about some possible new indications for this procedure.

The data from the present study seem to confirm the effectiveness of SNM in improving symptoms of CPP in some patients. The percentage of success and the mean improvement of the VAS score were comparable to previously published study (Table 3).

Our data also seem to confirm the long-term efficacy of SNM, considering the persistence of inhibition of pain in patients with a follow-up duration longer than 3 years (nine patients). Other authors reported maintenance of results over time, even if the longest follow-up period reported was at 24 months [12, 13].

Previous pelvic surgery was reported in 18 (66.5%) of our patients and was connected with the onset of pain in 12 (44%) of them, confirming pelvic surgery as an important

Table 2 Comparison between implanted and failed patients

	Implanted, 16 patients (59%)	Failed, 11 patients (41%)	*p* Value
Age (years)	51.7	54.3	NS
Sex (f/m ratio)	15:1	10:1	NS
Duration of pain (months)	59	43	NS
Site			
- Anus	12 (75%)	10 (91%)	NS
- Vagina	3 (19%)	6 (54.5%)	NS
- Perineum	2 (12.5%)	2 (18%)	NS
- Diffuse	0	2 (18%)	NS
- Multiple sites	1 (6%)	6 (54.5%)	0.008
- Deep	10 (62.5%)	6 (54.5%)	NS
- Superficial	6 (37.5%)	5 (45.5%)	NS
VAS (preoperative)	8.1	7.5	
Previous surgery	11 (68.5%)	7 (63.5%)	NS
- Stapled	0	5 (45.5%)	0.005
- Hysterectomy	4 (25%)	0	NS
Pharmacotherapy			
- NSAID	16 (100%)	11 (100%)	NS
- Opioids	8 (50%)	5 (45.5%)	NS
- Antidepressant	4 (25%)	3 (27%)	NS
- Gabapentin/Pregabalin	9 (56%)	0	0.008

NSAID nonsteroidal anti-inflammatory drug, *f* female, *m* male, *NS* not significant

Table 3 Percentage of success and mean improvement of the VAS score in previously published study

Author	Tested patients/ successful patients	%	Kind of pain	Preoperative VAS	Postoperative VAS
Siegel et al. [17]	Not stated/10		Pelvic/urogenital	9.7	4.4
Everaert et al. [16]	26/11	42	Pelvic/urogenital	NS	NS
Falletto et al. [13]	27/12	44	Anorectal	8.2	2.2
Govaert et al. [12]	9/4	44	Anorectal	8.0	1.0
Martellucci et al. [18]	17/8	47	After pelvic surgery	8.2	1.9
Present series	27/16	59	Pelvic/urogenital/ anorectal	8.1	2.1

NS not significant

pathogenetic factor for the development of CPP. Falletto et al. [13] reported previous pelvic surgery in 9 of 12 patients, but in only 5 (41.5%), the onset of pain occurred after surgery.

In the study of Govaert et al. [12], seven previous pelvic surgical procedures were performed in nine patients, but no data were given about the number of intervention per patient or the relation between pain and surgery.

Moreover, also in the present study and as previously reported [18], SNM proved to be ineffective in the treatment of pain that occurred after stapler surgery.

Conversely, SNM showed excellent results for the treatment of posthysterectomy pain.

This may lead to suppose a different pathogenetic mechanism behind these two pain conditions. Pain after stapler procedures was often related to agraphes retention but also to persistent hemorrhoidal disease, sphincter spasm, rectal spasm or high anal resting pressures, suture dehiscence, anal fissure and anorectal sepsis [20]. Considering that pain after stapler surgery is mostly reported as postdefecatory and that the removal of staples from the puborectalis muscle has been described, it is possible that after deeper stapled resections, the rectum is fixed to the surrounding muscular structures, thus reducing its mobility during defecation and causing traction on the surrounding structures at straining.

In pain after hysterectomy, the damage could be related to a peripheral nerve trauma that may induce neuroplastic changes in central nervous system, leading to abnormal processing of sensory input from the site of injury [21].

SNM has been less useful in the patients reporting pain in more than one pelvic area, while pain referred in a single localization (anus, vagina, perineum, urethra, etc.) could be better controlled.

Even if suggested to all patients, only nine patients underwent a psychological evaluation. Although only seven patients were taking antidepressant, the role of psychological factors in many patients suffering from pain or other functional anorectal disorders is well known [22]. Moreover, a previous study reported that psychological factors significantly affect also the response to SNM [10]. Unfortunately, alternative procedures to relief pelvic pain are often useless, as reported also in our patients. Considering that the cause of pain is still not well understood and that a specific therapy has still to be identified, SNM should be seen as a minimally invasive attempt for these patients, and the psychological factors should not exclude them from the treatment.

In the present study, patients tested with PNE test were excluded because, as previously reported by Everaert et al. [16] and confirmed in our experience, a high false-positive PNE rate was noted.

An interesting thing was noted regarding pharmacotherapy. In fact, all patients who had a good control of pain with gabapentin or pregabalin showed a positive result with SNM.

The role of these drugs in the treatment of neuropathic pain is well documented [23–25], but the possibility of an incomplete efficacy and some dose-limiting side effects, especially when given as monotherapy, are also well known.

The results of our study suggest that gabapentin and pregabalin could share the same mechanism of action of SNM. Unfortunately, the precise mechanisms of action of SNM, as the precise nervous pathways of chronic pain stimuli, remain to be completely defined.

Hanai [26] demonstrated that the electrical stimulation of peripheral nerves results in an inhibitory input to the pain pathways at the spinal cord level, and the effects of SNM on sensory perception were previously described by Uludag and colleagues [27]. The main effect of stimulation appears to be a reflex and not a direct action on central nervous system through a somatic afferent inhibition of sensory processing in the spinal cord.

However, other mechanisms could be involved as an improved neural metabolism, a down-regulation of facilitating peptide expression, a more efficient neural reflex regulation [28].

Also non-*N*-methyl D-aspartate receptors seem to be involved in the effect of sacral neuromodulation, whereas *N*-methyl D-aspartate receptors appear to have no role [29].

Moreover, some other neurophysiologic mechanisms have been proposed, for example, simple blocking of pain transmission by a direct effect on the spinothalamic tracts, activation of descending inhibitory pathways, effects on central sympathetic systems, segmental inhibition via coarse

fiber activation and brain stem loops, inhibition by increasing GABA levels in the dorsal horn, and thalamocortical mechanisms masking the nociceptive input [30–32].

Further studies are needed to solve this problem, but the real effect will probably be discovered to originate from several sources.

Conclusions

SNM proved to be effective in the treatment of some patients affected by CPP, and the effect persists over time. A positive screening phase and a positive response to gabapentin or pregabalin showed to be predictors of a successful response. Multiple localizations of pelvic pain and pain occurred after stapler surgery seem to be negative factors for the success of the treatment.

However, the real mechanism of action still remains unclear, as well as patients who may benefit from the treatment.

Conflicts of interest The authors have no conflict of interest to be disclosed.

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