Sacral Neuromodulation

36

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Introduction

Sacral neuromodulation has effectively revolutionized the management of some intractable cases of fecal incontinence (FI) and those that are unresponsive to other more complex procedures.

Urologists first began to study the possibilities of an electrical stimulation to control bladder dysfunction. Initial attempts to provoke artificial micturition involved direct stimulation of the spinal cord [1, 2]. It was suggested as a technique for electrical stimulation of the bladder by Boyd in 1954, with the use of electrical stimulation of the detrusor muscle in the 1970s [3] and the use of intra-anal stimulation electrodes in 1972 by Hopkinson.

None of these methods produced satisfactory bladder voiding. Research was then focused on electrical stimulation of the sacral nerve roots in order to treat serious bladder voiding dysfunctions [4–6, 7]. Tanagho and Schmidt [8] from the University of California, San Francisco, first applied the principles of sacral nerve stimulation (SNM) to patients affected by voiding dysfunction or incontinence due to bladder instability. In 1981, they performed the first sacral nerve stimulation implant.

Currently, stimulation of the sacral nerve roots is used successfully to control voiding difficulties such as urge incontinence, urinary retention, frequency-urgency syndromes, and bowel dysfunction.

Matzel first reported its use in the treatment of FI in Lancet in 1995 [9]. It became an accepted first-line treatment for patients who have not benefited from medical and behavioral therapies [10, 11]. SNM has been approved for FI by the Food and Drug Administration (FDA) in 2011 and was supported by the UK Clinical Practice Guidelines in 2004, where it showed equal benefit in mild, moderate, and severe FI.

Encouraging results have also emerged from its use in other conditions. It was observed that, in some patients with FI, there was also a subjective effect on defecation. Evidence for a possible role in constipation initially came from urological patients. In a series of 48 patients with coexisting constipation, intestinal frequency increased in 78%. Two studies then reported the effects of temporary stimulation. One showed improvement in two of eight patients [12], and the second showed subjective improvement [13]. This led to the world's first implant of a sacral nerve stimulator for intractable idiopathic constipation.

Although the exact mechanism by which SNM works still remains unknown, it is likely multifactorial. The stimulated target is a mixed nerve-carrying efferent/somatomotor and afferent/sensory nerves as well as autonomic nerves [14]. It seems to be an effect on several nerves within the sacral plexus: the somatic pudendal nerves and the efferent nerves directed to the pelvic floor muscles appear to be involved with

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increased function of the external anal sphincter. However, studies on delay between stimulation and effect show a latency ten times greater than expected, suggesting a more complex, multisynaptic pathway [15].

There seems to be an effect on sensory afferent nerves with an acute sensation, but there is little effect on intrinsic enteric neurons, and the anorectal reflex is not affected [13]. This, however, is a crude indicator of the function of the enteric nervous system, in a nervous system that has the proven ability to adapt and regenerate. The balance between the autonomic nervous system, parasympathetic and sympathetic nerves, is the determining factor in the motility of the colon and the function of the internal sphincter. The modulation of these nerves can be an important part of the physiological mechanism. The new evidences highlight a facilitation effect on afferent pathways.

Technique of Sacral Neuromodulation

Classically, SNM consists of two stages: percutaneous nerve evaluation (PNE) in the diagnostic stage and permanent implant in the therapeutic stage.

Percutaneous nerve evaluation (PNE) of the sacral roots (S2, S3, and S4) is divided into two phases: an acute phase to test the functional relevance and integrity of each sacral spinal nerve to striated anal sphincter function [9] and a chronic phase to assess the therapeutic potential of sacral spinal nerve stimulation in individual patients.

Percutaneous nerve evaluation: With the patient in prone position, the three sacral foramina S2, S3, and S4 are located using bony landmarks (Fig. 36.1). The sacral foramen S2 is typically found just under the projection of the posterior superior iliac spines and about one finger lateral to the median line. When the sciatic notches, which correspond to level S3, are identified, S4 is about 2 cm under foramen S3. Foramina S3 and S4 are also positioned about one finger across from the median line.

The acute phase test is performed under local anesthesia using a 20-gauge spinal insulated needle (Medtronic™ #041828-004) and an external neurostimulator (Medtronic™ Model 3625 Screener). The needle is inserted perpendicular to the sacrum, with an inclination to the skin of 60–80 degrees (Fig. 36.2). After the needle is positioned in the chosen foramen, it is connected to the external neurostimulator. The stimulation parameters used in the acute phase are pulse width (PW) of 210 μsec, frequency of 5–25 Hz, and an amplitude which resulted in an increased contraction of the pelvic floor and a deepening and flattening of the buttock muscle. This usually occurred between 1 and 3 volts. Stimulation of specific sacral nerves typically results in specific movements of the perineum, anal sphincter, and ipsilateral lower extremity. This ensures correct lead placement. Stimulation of S2 causes some movement of the perineum and the external sphincter along with a lateral rotation of the leg and contraction of the toes and foot. Stimulation of S3 causes a contraction of the pelvic floor and the external sphincter, the "bellows" contraction, and a plantar flexion of the big toe. Stimulation of S4 causes a contraction of the anus with a clamp-like perineal movement with no leg or foot movement. Vesicle, vaginal (or scrotal), and rectal paresthesia may be perceived by the patient during sacral nerve stimulation. A radiological check of the electrode position is mandatory.

Temporary SNM: Once an adequate muscular response is obtained, a temporary stimulator lead (Model 3065 U Medtronic™, Minneapolis, MN, USA, or Model 3057-1, Minneapolis, MN, USA) is inserted through the needle, following which the needle is removed. The lead is connected to an external stimulator (Screener Model 3625, Minneapolis MN, USA) to allow evaluation of the functional responses to the test, both subjectively with regard to continence and objectively using rectoanal physiology. Ten to fourteen days of stimulation is the minimum period needed for the test.

To evaluate the functional results of PNE, patients completed a clinical diary of fecal incontinence and bowel movements episodes in the 2 weeks preceding, during PNE, and in the 2 weeks following the PNE.

Surgical technique for permanent implant: Only selected patients who achieve an improve-

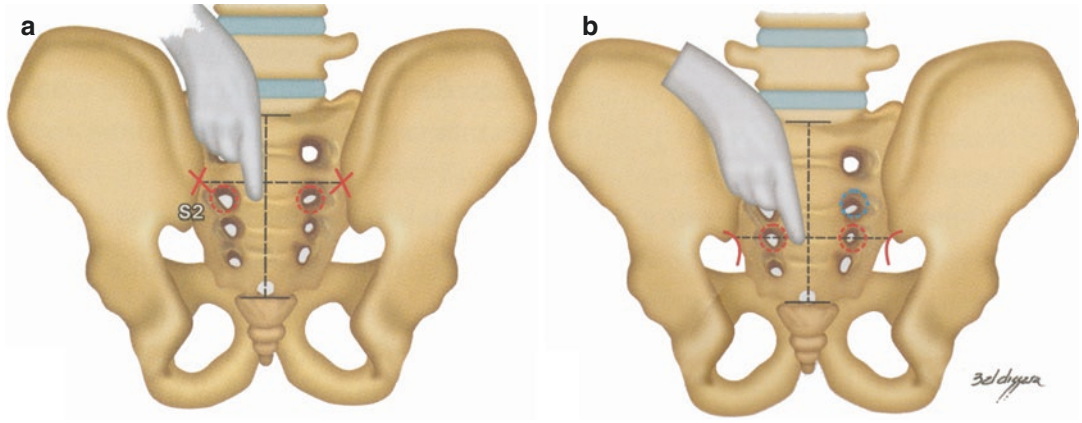

Fig. 36.1 The dorsal sacral foramina are positioned approximately 2 cm laterally to the sacral crest. S2 is about 1 cm medially and 1 cm below the posterior superior iliac spine, and S3 is positioned on a level with the upper border of the sciatic notch

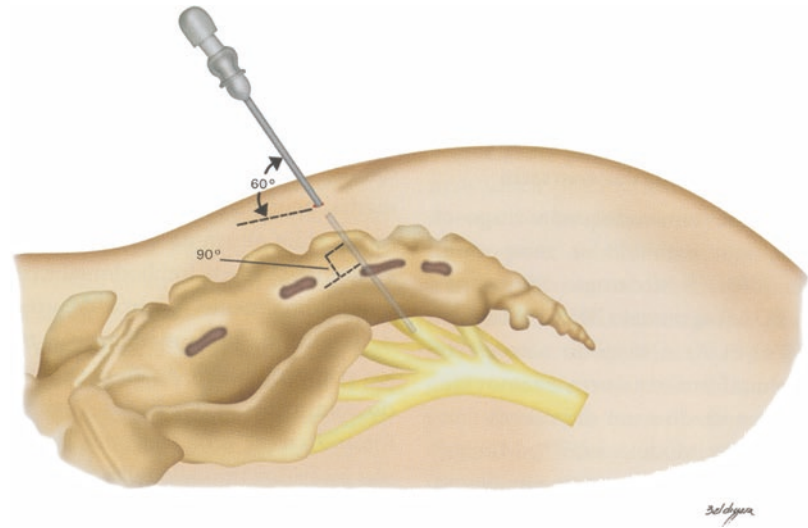

Fig. 36.2 The needle is inserted parallel to the foramina axes with an inclination to the skin of 60–80 degrees

ment of at least 50% compared to the previous clinical situation (reduction of 50% of days with incontinence and/or reduction of 50% of weekly incontinence episodes) reach this stage.

Classical Open Surgical Technique

Before incision, the sacral foramen is checked with an isolated needle. Once the sacral foramen is confirmed, an incision is made along the median line above the sacral spinous process, up to the level of the underlying lumbodorsal fascia. The lumbodorsal fascia is cut longitudinally, about one finger width from the median line. The paraspinous muscles underneath are divided sharply along the length of the fibers. The sacral foramen is checked, and the definitive electrode is inserted (model 3080, Minneapolis, MN, USA) and anchored to the periosteum (Fig. 36.3).

Each electrode is composed of four electrodes that can be selected individually through the programming of the neurostimulator. Once the tip is anchored, the rest of the electrode is channeled, with the aid of a tunneling tool, through the subcutaneous tissue layer, into a small incision made

on the patient's buttock and connected to the neurostimulator (Interstim 3023, Minneapolis, MN, USA).

This procedure has now replaced the tunneling of the electrode and the positioning of the IPG in the lower abdominal region. The IPG abdominal placement requires a longer operative time, and some patients complain of displacement or pain at the IPG site postoperatively [16]. The neurostimulator (impulse generator: IPG) can be activated using a control unit (N' VisionTM) which allows to set all parameters percutaneously via a radio frequency signal. Each stimulator is programmed in the most effective way to suit that individual patient.

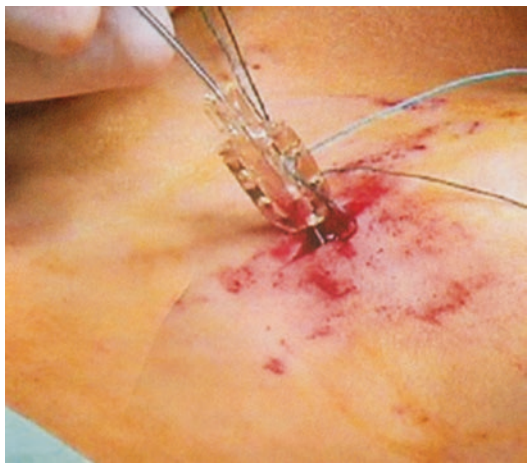

Fig. 36.3 The definitive electrode is anchored to the periosteum using not nonabsorbable thread

Minimally Invasive Technique

Recently, the introduction of the "tined lead" has made an important change in the surgical approach; the sacral electrode is now implanted with an approach only percutaneous. After insertion of the needle in the selected sacral foramen and test for nerve responses, a metal stylet (directional guide) is inserted through the needle. The needle is removed, two small incisions on either side of the guide are made, and a dilator is inserted on the guide of the directional guide and advanced into the sacral foramen. Leaving the introducer sheath in place, the chronic tined lead is inserted and advanced under fluoroscopic control (Fig. 36.4). Once the responses of the various electrodes are confirmed, the introducer sheath is removed, thereby deploying the tines and anchoring the lead [17].

Finally, the classical PNE and one-stage permanent implant could now be replaced by a two-stage procedure. Once the permanent lead is implanted, a percutaneous extension is used to

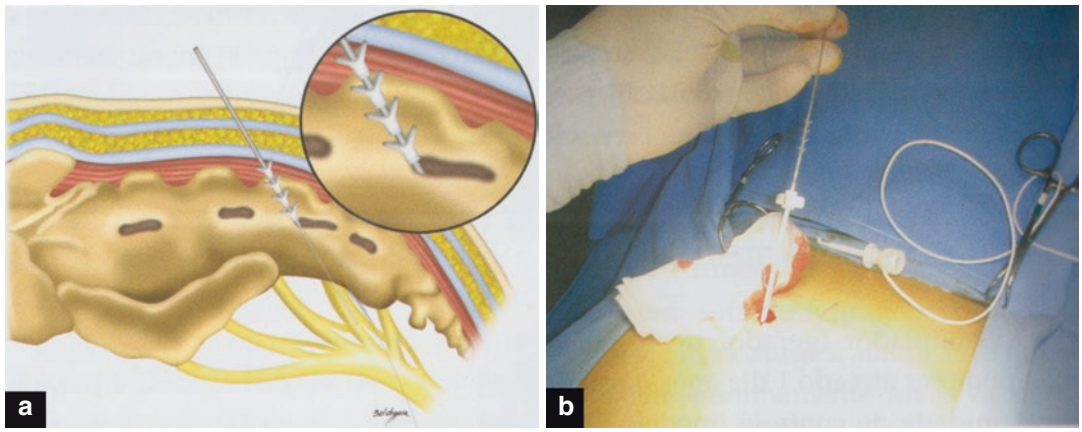

Fig. 36.4 (**a**) Quadripolar tined lead; the electrodes are shown. (**b**) After sacral foramen needle is inserted and location is verified by electrical stimulation to the needle and fluoroscopy, the plastic dilator is positioned. (**c**) The quadripolar lead is introduced through the dilator plastic sheath into position. Once the responses of the various electrodes are confirmed, the introducer sheath is removed, thereby deploying the tines and anchoring the lead

connect it to an external stimulator (Model 3065 U Medtronic™, Minneapolis, MN, USA, or Medtronic™ Model 3531 Verify) allowing a long period of evaluation (1–2 months) of the effectiveness of sacral neuromodulation. If the response is confirmed, the percutaneous extension will be removed and the lead directly connected to the IPG (Interstim 3023, Minneapolis, MN, USA). With the introduction of the minimally invasive technique, this two-stage modality has been proposed as alternative to the PNE itself.

Type of quadripolar lead stimulation is not standardized but should take the form of external settings of the stimulator around a pulse width of 210 ms, speed of 14–20 Hz, and an amplitude of <3 V for all four positions of the conductor answering by answer.

Prospective randomized data show that the two-stage implantation technique of SNM has a higher success rate when compared to the single-stage method despite a previous positive PNE response and effectively reduces the reoperation rate and overall procedural costs [18–19]. Spinelli reports that the success rate of this technique in patients selected for the permanent implant was significantly improved over a two-step technique initially using a temporary lead placement [20]. This allowed a longer test period with the permanent electrode before proceeding with the implantation of a definitive neurostimulator (IPG). In our experience with the use of the "tined lead" and the two-step technique, the percentage of successes to complete the procedure increased from 26.8% to 84.5%. In summary, the SNM technique has become somewhat standardized in recent years and has shifted from the placement of a temporary lead to a permanent one but remains a two-stage process of initial temporary stimulation pending a decision regarding the second-stage implantation of permanent pacemaker.

Indications

The lack in the knowledge of the exact mechanism makes difficult to give precise indications on the eligible patients. Two orders of considerations go advised: clinical and anatomical. It is a shared belief that the indication for neuromodulation is a severe incontinence not amenable to standard drugs or biofeedback therapy or that has failed conventional surgical management. Incontinence to solid or liquid feces at least once each week during the last 2 months, as reflected in a defecation diary kept by the patient, is a good practical criterion. Patients with only gas incontinence or minor staining are not a good candidate. If we consider the type of incontinence, patients with an urge incontinence (fecal loss at the first signs of the urge to defecate) show a better improvement if compared with passive incontinent patients (inadvertent and unpredictable fecal loss) [21].

Among anatomical considerations from the initial assertion of the need for integrity of the anal sphincters, an increasing worldwide application has shown that it is considered suitable for many cases of passive and urge AI as well as in those cases both with and without a disrupted anal sphincter ring [22]. More data are available to extend the use of neuromodulation in those patients normally destined for sphincteroplasty due to the presence of an EAS defect [23, 24], as well as in those cases with isolated IAS deficiencies in which a plant would normally be considered [25], in the incontinence and in the urgency associated to the syndrome of the low anterior resection (with or without the construction of a neorectal pouch) [26], and in those with partial lesion of the spinal cord [27, 28]. Patients with complete spinal cord lesion or complete peripheral nervous lesions such as spina bifida or iatrogenic nerve lesion are not candidate for sacral neuromodulation [21–22].

Patient's Evaluation and Impact on Gastrointestinal Physiology

Initial assessment included a complete clinical history and physical examination. Before applying the lead, patients usually perform anorectal physiological evaluation and an anal ultrasound to evaluate anal sphincter. Symptoms evaluated include the number of incontinence episodes,

fecal urgency, use of pads, and impact on lifestyle. To establish baseline function, all patients completed a 14-day fecal incontinence diary of episodes of fecal incontinence and bowel movements prior to PNE or first-stage implant. The same diary is used during the test period and eventually in the 2 weeks following PNE. The evaluation of the clinical diary is the only parameter that currently allows selecting the patients for definitive implant. Usually, PNE test or first-stage implant is considered positive if there is >50% improvement in FI symptoms compared with baseline and a rapid return to pre-PNE conditions when stimulation is turned off.

Other definitions and outcomes used included intention-to-treat (ITT) analysis which is based on measuring outcome based on the number of patients initially enrolled in the treatment as opposed to per-protocol analysis (PPA) which only measures the final outcome based on the number of patients who had a successful PNE or first stage and then went on to receive a permanent implant.

Primary failure is defined as those who never had a clinical response to PNE, while secondary failure refers to those patients who had a successful response to PNE but failed to subsequently achieve therapeutic benefit from the permanent implant. Physiological investigation includes anorectal manometry, specifically anal pressures (maximum resting and squeeze pressure (mmHg)), rectal sensory thresholds (balloon volumes in milliliters of air or water), small/large bowel motility, and neurophysiological study of the pelvic floor (including pudendal SEP, sacral reflexes, and PNTML).

Clinical Outcome

Incontinence

At a follow-up of 6 months, Matzel [9] in 1995 reported a complete recovery of continence in two cases and soiling in one patient with definitive implant of a sacral electrode with an improvement of resting and squeezing anal pressure. In July 2000, Malouf [29] reported an improvement on the Wexner incontinence scale from 16–20 to 3–6 in 5 patients followed for at least 16 months after definitive implant of a sacral electrode. The resting anal tone showed consistent improvement, but no variation was observed with the squeezing anal pressure. In 2001, Rosen [30] published the results of 16 permanent implant selected out of 20 (80%) incontinent patients tested over a period of 10–14 days with PNE. Three patients had their electrodes removed because of infection. All the 13 (81.2%) functioning implant had a significant improvement in fecal continence. Resting and squeezing anal pressure improved significantly only in patients with neurologic incontinence but not in those with idiopathic incontinence. For the first time, a dedicated quality of life questionnaire was used, showing clear improvement in all the four items investigated (lifestyle, coping behavior, depression, embarrassment).

In our first experience [21] with five patients implanted out of 23 PNE tests (22%), definitive electrical stimulation of sacral roots was associated with an improvement in fecal continence from a mean of 4.8 episodes/week to a complete cessation, reproducing at a median follow-up of 19.2 months (range 5–37) the clinical effect of the PNE test. A significant increase of the resting but not squeezing anal pressure was observed, and an earlier rectal sensation to balloon distension was observed in this first series of patients. Using isobaric rectal distention, the pressure applied for the first sensation threshold decreased significantly ($p = 0.012$) as did the pressure for the urge threshold ($p = 0.008$). The distension pressure decreases for the first sensation, and urge threshold is very important, because it states a better sensibility or a facilitation of the rectal receptors.

The first medium-term results of SNM for fecal incontinence have been published by Kenefick [31] in 2002, reporting good results in 15 incontinent patients followed up for a mean of 24 months with 11 patients fully continent. Episodes of fecal incontinence decreased from 11 (2–30) per week before stimulation to 0 (0–4) per week after permanent stimulation ($p < 0.001$). Urgency and ability to defer improved in all

patients. Resting and squeezing anal pressure significantly increased, and the volume requested for rectal sensitivity to initial distension was significantly lower ($p < 0.05$) than before SNM. There were no major complications. In these group of patients, the quality of life questionnaire [36-item Short Form Healthy Survey (SF36)] was administered before and after stimulation: "social function" and "role-physical" subscales of the SF36 improved significantly.

Medium-term results of a substantial series were presented by the GINS [32] group in the spring of 2002. Thirty-one patients had permanent implant out of 116 (27%) PNE tests, and PNE results were reproduced in all patients at a mean follow-up of 25.6 (range 1–56) months. The mean number of incontinence episodes for solid or liquid stools (per 14 days) decreased from 15 (range 2–22) at baseline to 3.2 (range 0–10) at 3 months follow-up ($p = 0.02$), to 2.9 (range 0–13) at 6 months, and to 0.3 (range 0–4) at 12 months follow-up. Again, anorectal manometry shows a positive trend in increasing sphincter pressure and rectal sensitivity. No local sepsis occurred. One patient complained of pain at the implant site when IPG case was used as anode (unipolar impulse) and another necessitated electrode repositioning for displacement after 3 months. In one patient, interruption of the electrode caused decreased effectiveness at 11 months post implant; the lead was changed and the patient recovered continence. SF36 was used in 18 of these patients before and after SNM. Improvement of continence had a positive impact on the health state, particularly in the reduction of physical limitations or disabilities. An overall analysis showed a significant improvement in patient's physical ($p < 0.05$) and mental health ($p < 0.05$) after implant.

Long-term results were reported first by Matzel in 2003 [33]. Functional improvement was achieved in 94% of 16 patients. At a median follow-up of 32.5 months (3–99), treatment was successful in 81%. Two of the electrodes were removed after 5 and 45 months for intractable pain. Mean squeeze pressure increased, but maximum squeezing pressure improved only in three of them. Resting pressure, perception, urge threshold, and maximum tolerable volume were not significantly changed. Using the disease-specific quality of life instrument (FIQL-ASCRS) before and during stimulation, the quality of life index was improved in all categories.

In a systematic review of the impact of sacral neuromodulation on clinical symptoms, Mirbagheri [34] with data obtained from 63 studies, the results demonstrated overall improvement in subjective and objective measures of FI in all studies, regardless of the design of the study. The PNE success rate, defined as >50% reduction in clinical symptoms over the evaluation period, ranged from 51.5% to 100%, with a median value of 81% on a per-protocol basis. The reported rates of "perfect continence" after permanent implant ranged from 13% to 88% (Table 36.1). Notwithstanding the inevitable heterogeneity of patient characteristics, pooling of these results ($n = 608$) gave a perfect continence rate of 36.5% on an ITT basis and 42.9% on a PPA.

The possibility of a placebo effect was investigated. Six trials assessed the effects of SNS for FI. In the crossover trial by Leroi [49], 24 participants while still blinded chose the period of stimulation they had preferred. Outcomes were reported separately for 19 participants who preferred the "on" and five who preferred the "off" period. For the group of 19, the median episodes of fecal incontinence per week fell from 1.7 during the "off" period to 0.7 during the "on" period; for the group of five, however, the median rose from 1.7 during the "off" period to 3.7 during the "on" period. In the crossover trial by Vaizey [50], participants reported an average of six and one episodes of fecal incontinence per week during the "off" and "on" periods, respectively, in two participants with FI. In another case crossover study by Kahlke [51], 14 participants with FI experienced significantly lower episodes of FI per week during the stimulator "on" (1 (SD, 1.7)) compared with the "off" period (8.4 (SD, 8.7)).

From 1996 to 2003, 94 patients affected by FI underwent the peripheral nerve evaluation (PNE) test for SNS in six Italian colorectal units [37]. Sixty of them (64%) had a good response to temporary SNS and therefore underwent a definitive

Table 36.1 Details of patients achieving full continence in 18 studies

Study	Sample size	Sacral neuromodulation (n)	% full continence	Full continence (per protocol) (n)
Leroi et al. [35][a]	34	34	5	15
Leroi et al. [36]	9	8	1	13
Altomare et al. [37][a]	52	38	9	24
Oom et al. [38]	46	37	8	22
Boyle et al. [39]	50	37	13	35
Hull et al. [40]	72	64	26	41
Oz-Duyos et al. [41]	47	28	14	50
Matzel et al. [42]	37	37	12	32
Jarret et al. [43]	59	46	19	41
Tjandra et al. [44]	59	54	25	46
Ganio et al. [13]	25	22	11	50
George et al. [45]	25	23	12	52
Matzel et al. [9]	3	3	2	67
Santoro et al. [46]	28	28	19	68
Kenefick et al. [31]	15	15	11	73
Kenefick [47]	19	19	14	74
Ganio et al. [21]	19	17	14	82
Vaizey et al. [48]	9	8	7	88
Total	**608**	**518**	**222**	**Pooled: 36.5[b]** **Range: 13–88[b]**

[a]Data after permanent implant only. [b]Intention-to-treat analysis (patient with perfect continence/total sample size). Per protocol analysis = 42.9%

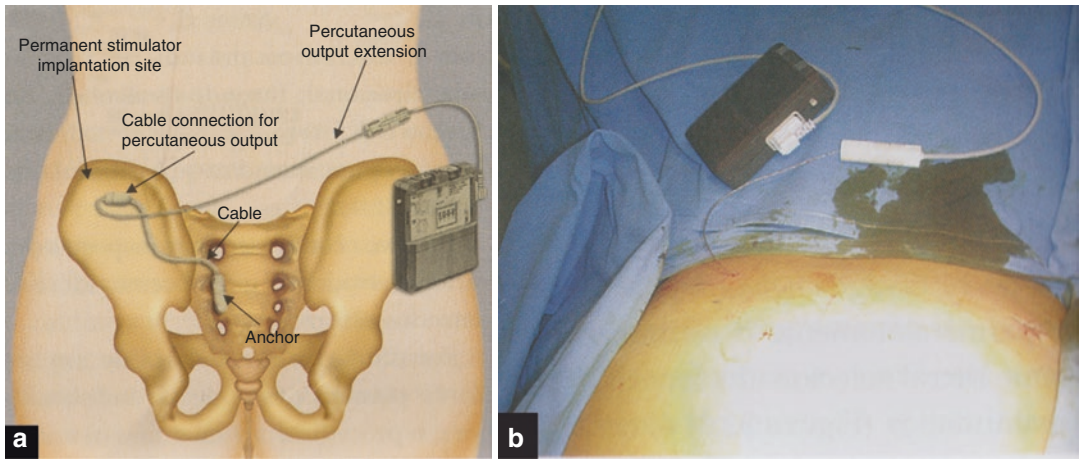

Fig. 36.5 Patient data of incontinent patients tested between 1999 and 2003

electrode(s) and electrostimulator implant. During a mean follow-up period of 74 ± 14 months (range 60–122 months), no patient was lost, but two died (3 and 4 years after the SNS implant) of diseases not related to FI or SNS, and six (10%) had the device removed because of complications or progressive failure of the therapeutic efficacy within the first 2 years of follow-up. Thus, 52 patients (86.7%) were available for the long-term evaluation (Fig. 36.5). Complications were reported in 15 patients (28.8%): pain at the site of implant in six cases (11.5%), electrode displacement (all implanted with the old technique) in eight patients (15.4%; all reimplanted, three using a tined lead),

and early battery rundown in one case (1.9%). Pain was managed by reducing the stimulation voltage or by repositioning the implantable pulse generator in another place, while electrode displacements and battery rundown required substitution of the devices.

In the 52 patients available for long-term evaluation, the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS) decreased significantly compared with baseline (from 15 ± 4 to 5 ± 5, $p < 0.001$). At least 50% improvement in continence was achieved in 74% of the patients, and at least 70% improvement (median value) was achieved in 50%. Full continence was achieved in 17% of the patients. The mean number of solid/liquid incontinence episodes decreased significantly from 0.5 (±0.5) to 0.1 (±0.3) per day ($p = 0.004$). Quality of life improved in all domains. The overall mean improvement in SF-36 scores was 39.8%. Both mean resting and squeeze anal pressures increased significantly, and maximum volume tolerated decreased significantly (Fig. 36.6).

A survey to review prospectively recorded data on all consecutive patients undergoing temporary testing for SNS from ten European centers with long-standing experience of SNS for FI was presented in 2015 [52]. From January 1998 to December 2006, a total of 407 patients underwent temporary stimulation, of whom

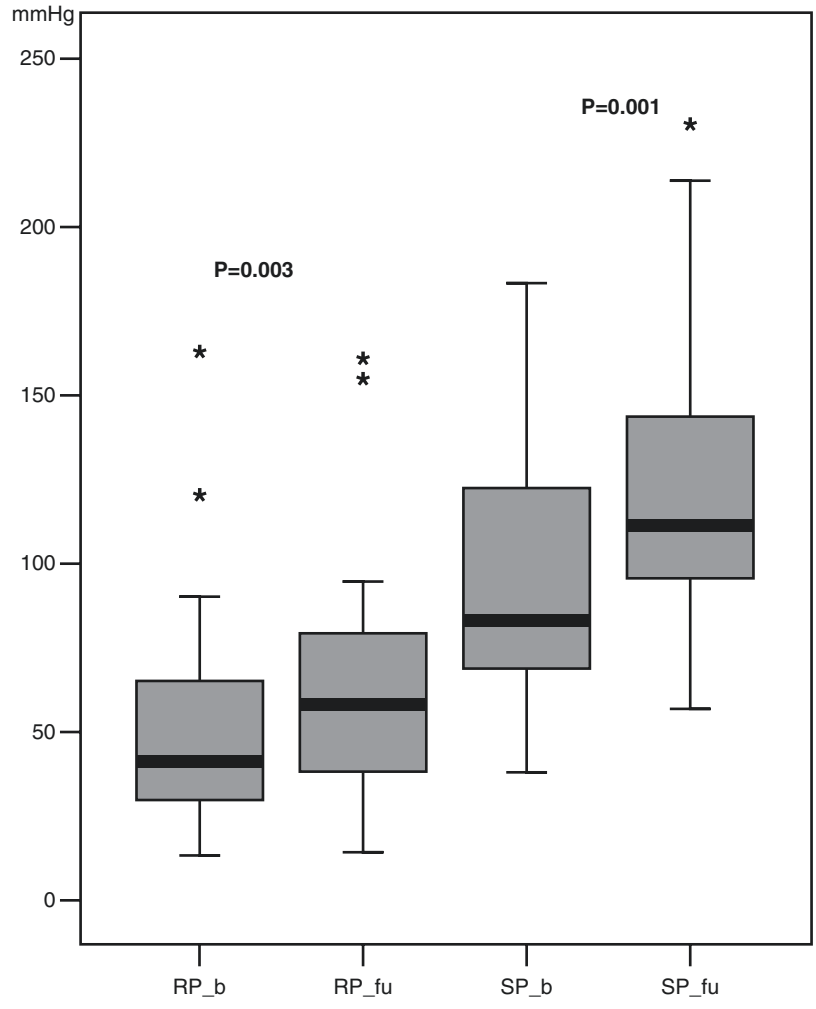

Fig. 36.6 Comparison between baseline (b) and last follow-up (fu) manometric data. RP resting pressure, SP squeezing pressure. ∗Outlier value

272 (66.8%) had an impulse generator implanted; 228 (56.0%) were available for long-term follow-up at a median of 84 (i.q.r. 70–113) months (Fig. 36.7).

Significant reductions in the number of FI episodes per week (from median 7 to 0.25) and summative symptom scores (median CCF-FIS from 16 to 7, St Mark's score from 19 to 6) were recorded after implantation (all $p < 0.001$) and maintained in long-term follow-up. In per-protocol analysis, long-term success was maintained in 71.3% of patients, and full continence was achieved in 50.0%; respective values based on intention-to-treat analysis were 47.7% and 33.4%.

A recent systematic review of data from published studies, although with differences in endpoints and reporting [34], reports overall an improvement in subjective and objective measures of FI across all studies, irrespective of study design. The PNE success rate, defined as >50% reduction in clinical symptoms over the evaluation period, ranged from 51.5% to 100%, with a median value of 81% on a per-protocol basis. The reported rates of "perfect continence" ranged from 13 to 88%, with a mean rate of complete continence of 36.5%. Notwithstanding the inevitable heterogeneity of patient characteristics, pooling of these results ($n = 608$) gave a perfect continence rate of 36.5% on an ITT basis and 42.9% on a PPA.

Incontinence and Sphincter Lesion

Initially, SNM was used only in FI of neurogenic origin, but subsequently, the indications have been extended to other conditions including incontinence in the presence of a sphincter defect, that represent the major cause of fecal incontinence, particularly in women.

Sphincteroplasty with overlap is the traditional treatment, but a significant reduction in benefits within 5 years of surgery has been reported. In a literature review [53] of SNM for FI in the presence of a sphincter defect, ten reports (119 patients) satisfied the inclusion criteria. All reported a lesion of the external anal and/or internal anal sphincter on endoanal ultrasound. A definitive implant was performed on 106 (89%) of the 119 patients who underwent a peripheral nerve evaluation test. The weighted average number of incontinent episodes per week decreased from 12.1 to 2.3, the weighted average CCF-FIS decreased from 16.5 to 3.8, and the ability to defer defecation, when evaluated, increased significantly. The features at anorectal manometry did not change. The quality of life improved significantly in almost all studies [54–59].

Similar resultas were observed in nine publications, where studies with less than 25 pactients were excluded [60]. All studies demonstrated highly improved function across all outcome

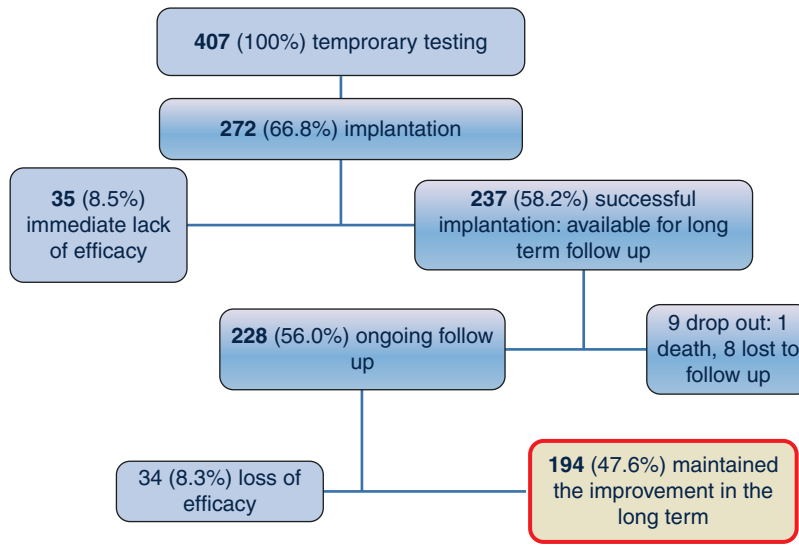

Fig. 36.7 Flow chart showing the long-term outcomes of all patients starting SNS treatment protocol in ten European centers according to intent-to-treat analysis

measures, and improvement was statistically significant in all, with sphincter gaps ranging from 17° to 180°. Outcomes remain stable at long-term follow-up. The size of the gap appears to have no impact on outcome.

Constipation

More recently, applications for sacral neuromodulation have been found in the treatment of chronic, intractable severe constipation. The Rome III criteria [61, 62] distinguish between functional constipation and constipation-predominant irritable bowel syndrome (IBS). The former is defined by the presence of two or more of the following symptoms, originating at least 6 months before diagnosis and currently active for 3 months: infrequent bowel movements (i.e., less than three stools/week), hard stools, excessive straining, a sensation of anorectal blockage, the use of manual maneuvers during evacuation, and a sensation of incomplete evacuation after defecation.

Two subtypes of functional constipation can be categorized: slow transit constipation (STC) and obstructed defecation (OD). However, in some cases, these two conditions overlap.

Kenefick [47] in 2006 reported of four women (aged 27–36 years) with severe, resistant idiopathic constipation for 8–32 years. Symptoms improved in all with temporary and in three with permanent stimulation at 8 months (range 1–11 months). Bowel frequency increased: 1–5 versus 6–28 evacuations/3 weeks. Symptom scores and quality of life improved.

A double-blind, crossover study was also performed to examine placebo effect and efficacy in two patients aged 36 years who had been implanted with a permanent stimulator 12 months previously. Once stimulation was removed in a blinded manner, symptoms, physiological parameters, and quality of life measures rapidly returned to baseline levels. In contrast, in the trial by Dinning [63] with 59 participants, SNS did not improve frequency of bowel movements.

Two open studies, performed on larger cohorts of constipated patients, have reported relatively satisfactory results of the SNM if we consider that the affected patients have a chronic, severe, and treatment-resistant pathology to usual medical conditions. The first, a multicenter prospective study including 62 constipated patients (81% with transit constipation) was published in 2010 [64]. Forty-five patients (73%) had a positive test after 3 weeks of stimulation and were implanted. Patients were followed for a median of 28 (1–55) months. Thirty-nine (87%) of the 45 implanted were significantly improved with respect to stool frequency, thrust efforts, incomplete defecation sensations, abdominal pain, and bloating. The CCF-FIS decreased from 18/30 to 10/30 at the last follow-up visit with a visual analogue scale of digestive symptoms that increased from 8 to 66/100 (0 was worst and 100 was best). Four out of 8 domains of the SF-36® quality of life score were also significantly improved after implantation.

The second study was retrospective and reported the results of the SNM in a population of 117 constipated patients [65]. Sixty-eight patients (58.1%) had a positive test and were implanted. At the last follow-up visit (median 37 months), 61 of the 68 (88%) implanted patients were still treated with SNM. The improvement appeared independent of the type of transit or distal constipation of the patients. After implantation, the results of the SNM seem to be maintained in the long term. Ratto et al. [66] evaluated 61 constipated patients (17 had transit constipation and 25 had distal constipation). Forty-two patients (68.9%) had a positive temporary test and were implanted. The average duration of follow-up was 51 ± 15 months. At the last follow-up visit, 47% of implanted patients had a significant improvement in their constipation scores. This improvement involved 64% of patients with distal constipation compared to 17% of patients with transit constipation suggesting that patients with evacuation difficulties would be better candidates than others for SNM treatment.

A prospective, open-label, multicenter study up to 5 years has been published so far [67]. Sixty-two patients (7 male, median age 40 years) underwent test stimulation, and 45 proceeded to permanent implantation. Twenty-seven patients exited the study and only 18 patients (29%)

attended 60-month follow-up. In 14 patients (23%) with Cleveland Clinic Florida Constipation Score, improvement was sustained at 60 months [17.9 ± 4.4 (baseline) to 10.4 ± 4.1, $p < 0.001$]. Benefit from sacral neuromodulation in the long term was observed in a small minority of patients with intractable constipation.

Finally, the results of a randomized, double-blind, French-controlled study were recently presented at the European Congress of Gastroenterology (UEGW 2015, Barcelona). This study mainly involved patients with distal constipation. Thirty-six patients underwent a temporary stimulation test and, in the case of a test response, were implanted. After implantation, two fairly long periods of 8 weeks of active or simulated stimulation were organized. Twenty patients (56%) were considered responders (improvement of symptoms by more than 50%) during the test period and were implanted. There was no significant difference between the percentages of responding patients during active stimulation versus simulated stimulation (60% vs. 55%, p = ns). After 1 year of follow-up, 11 of the 20 patients implanted (55%) were still responders.

In conclusion, although it seems that some patients are answering the SNM, without further details on the profile of its "good candidates," it seems difficult to validate this type of treatment in the management of constipated patients considering the limited success rate and the cost of this treatment.

Low Anterior Resection Syndrome

The proportion of rectal cancer patients undergoing sphincter-sparing operations ranged between 71% and 90%. Low anterior resection with end-to-end anastomosis is the most frequent procedure after mesorectal excision. Severe low anterior resection syndrome (LARS) developed in less than 40% of patients. The most important factor related to defecatory function impairment is the distance from the anal margin to anastomosis. Other factors thought to be involved were anastomotic leakage, preoperative radiation therapy, age, and postoperative radiotherapy. Lifestyle changes and dietary measures associated with or without drug treatment were the modalities of choice.

In a retrospective review, 12 patients (50% men) of a mean age of 67.8 (±10.8) years underwent sacral nerve test stimulation [68], and 10 patients (83%) proceeded to permanent implantation. Median time from anterior resection to stimulator implant was 16 (range 5–108) months. At a median follow-up of 19.5 (range 4–42) months, there were significant improvements in CCF-FIS and low anterior resection syndrome (LARS) scores ($p < 0.001$). In a systematic review, seven papers were identified including one case report and six prospective case series [69]. These included 43 patients with a median follow-up of 15 months. After peripheral nerve evaluation, definitive implantation was carried out in 34 (79.1%) patients. Overall, 32 (94.1%) of the 34 patients experienced improvement of symptoms which, based on intention-to-treat, was 32/43 (74.4%). The review suggests that SNS for fecal incontinence in LARS has success rates comparable to its use for other forms of FI.

Complications and Troubleshooting

A systematic analysis of published data on side effects of SNM reported adverse events and reoperation rates for 1954 patients, followed for 27 (1–117) months [70]. The majority of adverse events were reported within the first 2 years after stimulator implantation. Complications may broadly be divided into test-stimulation-related and implantation-related problems. Most relate to lead migration (about 12%), pain (3%), and infection (10%), with a 15% of reoperations for a combination of events including attenuated response, infection, IPG site pain, and lead migration [71].

Even though response to temporary stimulation is a prerequisite for permanent stimulator implantation, most of the concerns focused on lack or loss of benefit, which accounted for half of the primary problems described. Conceptually, one may question whether lack or loss of benefit

is truly an adverse event. Adjustment of stimulation parameters effectively resolved many of the reported problems, which could thus be seen as analogous to dosing changes in pharmacotherapy (Table 36.2). Similarly, any treatment based on electrical stimulation will require energy and will, therefore, deplete the battery over time. Unless the need for battery replacement surfaces very early after stimulator implantation, it may also be considered routine maintenance of electrotherapy.

Pain or paresthesia accounted for 14.9% of the complaints, with 35.1% of these reports specifically referring to the generator site as affected area. Lead-related problems accounted for 10.7% of the reports. Lead migration is usually resolved by reprogramming and usually does not require a new lead to be inserted.

In some cases, there is an accommodation to stimulation, which does not respond to an increase in stimulation amplitude, and this may ultimately require a repeat insertion or a contralateral lead insertion. Problems relating to response may occur as a result of impedance resistance, with attenuation of electron flow through the circuit; impedance describes the resistance to the flow of electrons through a circuit. Impedance measurement can act as a troubleshooting technique, checking the system's integrity in patients who lose SNM efficacy. In this setting, high-resistance levels (>4 K) indicate an open circuit, which is usually due to a fractured lead, loose connections, or both.

The pooled rate of infection was 5.1% (4.1–6.4). Device explants were largely due to infection but were also caused by generator erosion through the skin or other local complications at the pocket site and lack of benefit, thus leading to a higher rate of reoperation. A total of 39 studies, covering 1810 patients, provided information about explant rates at the end of their follow-up period, with an average of 10.0% (7.8–12.7) (I2 = 54.0%) and a significant increase with the duration of follow-up. Lead complications, battery depletion, or pain all contribute to additional intervention, with an overall reoperation rate of 18.6% (14.2–23.9) (I2 = 80.5%) based on cohorts with a total of 1784 patients. Reoperation rates rose with longer follow-up times. Overall, data would suggest that, when SNM is used for functional bowel disease, about half of the patients will experience at least one device- or treatment-related adverse event [72].

Impact on Anorectal Physiology

In evaluating the impact on anorectal physiological parameters, a consistent trend was noted, with an increase in both maximum resting pressure and squeeze pressure after SNM with a median difference of the mean of 5.9 (−11.8–21) and 14.8 mmHg (−12.5–96), respectively [34]. No correlation could be made between manometric findings and clinical symptoms after stimulation. Rectal sensitivity, as measured by the volume required to elicit sensory thresholds, tended to improve (as evidenced by a reduction in sensory threshold volumes) after SNM. Uludağ [73] used an isobaric phasic distension protocol to evaluate

Table 36.2 The most commonly described corrective actions for key concerns from Manufacturer and User Facility Device Experience (MAUDE) on adverse events related to the Interstim device

Primary concern	Sample	Conservative therapy	Operative therapy
Lack of benefit	325	Stimulation adjusted: 160	Explant: 22
	Medication: 3	Replacement: 17	
	System check: 7	Pocket revision: 3	
Pain of discomfort	97	Stimulation adjusted: 34	Explant: 8
	Medication: 4	Replacement: 1	
	System check: 2	Pocket revision: 7	
Lead problem	70	Stimulation adjusted: 3	Explant: 1
	System check: 2	Replacement: 36	
Programming problems	30	Stimulation adjusted: 11	
		Replacement: 1	

rectal filling sensations of first sensation (FS), earliest urge to defecate (EUD), and irresistible, painful urge to defecate (maximum tolerable volume (MTV)). Rectal wall tension and compliance could be calculated from these recordings. During stimulation, median volume thresholds decreased significantly ($p < 0.01$) for FS (98.1 vs. 44.2 ml), EUD (132.3 vs. 82.8 ml), and MTV (205.8 vs. 162.8 ml). The median reductions of the mean values for sensory volumes were 11.9, 16.4, and 6.6 ml for first sensation, sensation of urge, and maximum tolerated volume, respectively. Pressure thresholds tended to be lower for all filling sensations, and median rectal wall tensions decreased significantly ($p < 0.01$) for all filling sensations.

The effect of SNM on rectal compliance was measured in seven studies [21, 36, 48, 73–76], but none of these showed any statistically significant changes, although the sample size in each study was small ranging from 11 to 23 patients. Other rectal physiological parameters such as rectal stool retention test, rectoanal angle, and rectal motility were not affected by SNM [73, 77]. However, Michelsen [78] demonstrated a significant decrease in postprandial rectal tone during stimulation.

Mechanism of Action

Debate as to the mechanism of action for sacral stimulation in patients with FI is still ongoing.

Action on the striated sphincters and a facilitation of voluntary contraction have been suggested and attributed to direct alpha motor fiber stimulation [14]. Several studies have tried to show an improvement of the external anal sphincter during neuromodulation, but results are controversial.

In a systematic review of the impact of sacral neuromodulation on clinical symptoms, only a small number of factors were associated with outcome. Notably, age was a significant variable in more than one study [79, 80], and the younger the patient (<70 years old), the more likely a successful response to SNM. Anal sphincter defects and multiple PNE procedures were correlated with failures of SNM in two studies [81, 82]. The variables that were not predictive of outcome included baseline anorectal physiological parameters and colonic transit study, body mass index, gender, stimulation parameters, etiology of FI (idiopathic vs. organic), baseline quality of life, duration and severity of FI, and presence of anxiety or depression.

However, according to observations by Fowler [15], studies on the latencies of the pelvic floor contraction during peripheral nerve evaluation show that the muscle response is reflexly mediated with a minimum latency ranging from 50 to 57 milliseconds instead of the 4–5 milliseconds observed with sacral root magnetic depolarization [48]. Are these reflexes originated from a segmental level within the sacral spinal cord or from supraspinal neuronal centers involving spino-bulbospinal pathways? Schurch [83] recorded a reflex response of 41.2 ms (range 33.3–62 ms) which corresponds to a segmental reflex, similar to the pudendo-anal reflex, in three patients with complete spinal cord injury (SCI). The findings confirm that the anal contractions observed during peripheral nerve evaluation are reflex responses mediated by afferent pathways of spinal origin, since they were obtained in complete SCI patients in whom all spino-bulbospinal loops are supposed to be interrupted. The finding that neuromodulation is working in non-neurogenic patients but is not successful in complete SCI patients could give evidence that preserved spino-bulbospinal loops contribute to the positive effects of neuromodulation.

The reported trends toward an improvement in rectal sensitivity with a reduction in the threshold of perception of rectal distension are of particular interest, and an effect at the level of the central nervous system by afferent stimulation may be hypothesized.

Some experimental animal studies seem to confirm the hypothesis that neuromodulation has an effect on the central nervous system via afferent sensory fibers. A double-blind randomized study with spinally transected rats has evaluated the role of neuromodulation on C-afferent fibers that form the afferent arc of the pathological reflex responsible of bladder hyperreflexia after

spinal cord trauma. T10 spinal transection developed bladder hyperreflexia after 3 weeks associated to an increase in the neuropeptide content (substance P, neurokinin A, and calcitonin gene-related peptide (CGRP)) in L6 dorsal root ganglions. The electrical stimulation of S1 reduces the increase of neuropeptide in L6 and abolished bladder hyperreflexia suggesting that the blockade of C-afferent fibers is one of the mechanisms of action of sacral neuromodulation [84].

Recently, Chan [84] showed an increase of nerve fibers immunoreactive to vanilloid receptor subtype 1 (VR1) in the mucosal, submucosal, and muscle layers of patients with rectal hypersensitivity and fecal urgency. The VR1, present in A-delta and C-fibers and postsynaptic sites within the spinal cord dorsal horn, is known as an integrator of noxious stimuli. VR1 is activated by heat, protons, and capsaicin (an alkaloid, extractable from red pepper) and induces a flow of cations (especially Ca+ and Na+). Intravenous injection of capsaicin has produced dose-dependent sensations in the rectum of healthy people, indicating a high density of functional VR1 in this organ [27]. An increased density of VR1 fibers could lead to hyperexcitability of the dorsal spinal cord that results in a dysregulation of the sacral reflexes. These efferent reflexes include neurogenic inflammation and increase in the sympathetic tone which produces vasospasm, tissue hypoxia, and reflexive striated muscular spasticity [28].

An interesting contribution to the comprehension of the mechanism of action of the SNM comes from Hamdy [85]. He showed that the anal sphincter contraction induced by magnetic cortical stimulation was facilitated when this stimulation was preceded by repetitive stimulation of the pudendal or sacral nerve, suggesting that repetitive stimulation of a sacral nerve could cause sensory-motor interactions with better control of the sphincter function. Specific action of SNM on the primary sensory cortical area was evaluated by Malaguti [86] using somatosensory-evoked potentials (SEPs) of the pudendal and posterior tibial nerves in patients implanted with a monolateral permanent quadripolar electrode. In all patients, SNM produced a significant decrease in pudendal SEP latency at different pulse rates at the ipsilateral and contralateral implant sites. This finding was evidence of the effect of SNM on the cortical sensory area.

In a prospective trial, the latency (ms) of somatosensory-evoked cerebral potentials (SEP) induced by stimulation of the pudendal nerve was compared before (T0) and at 1 month during peripheral nerve evaluation (PNE) of SNM at frequencies of 21 Hz (T1) and 40 Hz (T2) [87] in patients with constipation or fecal incontinence. The results were correlated with the clinical outcome at 6 months. Twenty-eight (66.7%) of 42 patients had a good clinical result ("success") at 6 months.

In 16 (69.6%) of 23 incontinent patients with clinical "success" from SNM at 6 months (CCF-FIS $\leq$7), there was a significant difference between P40 latency at T0 and T2 (38.81 ms T0, 37.49 ms T2, $p = 0.049$). In the seven incontinent patients with "failure" at 6 months, there was no change between T0 and T2.

In 12 (63.2%) of 19 constipated patients with "success" at 6 months (Wexner constipation score $\leq$15), there was no difference between baseline (T0) and T2 P40 latency (39.28 ms T0, 38.25 ms T2, $p = 0.374$). In the seven constipated patients with "failure," there was a significant fall in P40 latency (41.20 ms T0, 39.30 ms T2, $p = 0.047$) but not into normal range.

The T0 P40 latency in incontinent patients having "success" was significantly higher than in the normal population ($p = 0.044$), and success was also associated with a fall in the SEP P40 latency after SNM at 40 Hz at 1 month to within the normal range (Fig. 36.8). In constipated patients, success of SNM appears to be associated with an SEP P40 latency at T0 marginally at the upper limit of normal but not falling significantly after SNM at 40 Hz at 1 month. Failure of SNM was associated with an SEP P40 latency at T0 very significantly higher than the normal value (approximately 2 SD) and falling significantly on SNM at 1 month at 40 Hz but not to within the normal range.

These results can be interpreted to indicate that clinical success in incontinent patients is associated with a reduction of P40 latency from elevated

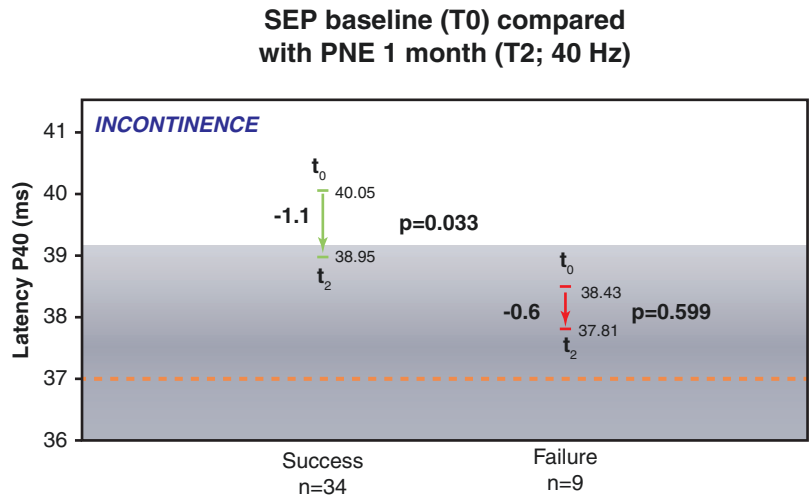

Fig. 36.8 SEP baseline (T0) compared with PNE 1 month (T2; 40Hz) for fecal incontinent patients

values to within the normal range. In the case of constipation, there was clear statistically significant evidence that those who failed had high P40 latencies at T0, and despite a reduction on SNM, they continued to have P40 values which still remained above the upper limit of normal.

These results support that SNM acts on the cortical level via the afferent pathway. Furthermore, the modifications to SEP induced by SNM seemed to be a prognostic factor for the clinical outcome.

Laurberg [88] used positron emission tomography to evaluate regional cerebral blood flow before and after 30 minutes of continuous stimulation and repeated this procedure after 2 weeks of continued stimulation before and 30 minutes after arrest of the stimulation in nine women and one man. The initial stimulation activated a region of the contralateral frontal cortex that normally is active during focused attention. After 2 weeks of stimulation, this activation had been replaced by activity in parts of the ipsilateral caudate nucleus, a region of the brain thought to be specifically involved in learning and reward processing. These changes may contribute to the improved continence, which is an acquired result of the stimulation.

A recent review of relevant studies on the central mechanism of SNM in FI confirms that the initial assumption of peripheral motor neurostimulation is not supported by increasing evidence, which reports effects of SNM outside the pelvic floor [89]. The new hypothesis states that afferent signals to the brain are essential for a successful therapy. In a total of eight studies on the central mechanism of SNM for FI, a variety of (sub)cortical and spinal changes after induction of SNM are described, and the corticoanal pathways, brainstem, and specific parts of the spinal cord are involved.

Summary

Sacral neuromodulation appears to be clinically efficacious for patients with fecal incontinence. Overall, the published series demonstrate a high effectiveness with a median 90.8% successful rate in the medium term at the cost of a reduced morbidity. Again, the long-term results are encouraging with a 76–81% of positive results, with up to 42% achieving full continence and the majority experiencing improvement in symptoms.

The possibility to select patients on the basis of a preliminary PNE makes, till now, sacral neuromodulation a unique technique in the spectrum of the possible treatments for fecal incontinence.

Given the low morbidity, reversibility, and minimal invasiveness of this procedure, the results provided by SNM therapy supersedes other surgical interventions for FI.

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