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Original Research Article

Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome

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Abstract

Objectives. Spinal cord stimulation (SCS) for patients with failed back surgery syndrome (FBSS) show variable results and limited to moderate evidence. In the last years the stimulation of high frequency (HF) has been considered as a better alternative in this pathology for its supposed benefits compared to the stimulation with conventional frequency (CF). To compare in one year follow-up, the efficacy of high-frequency SCS (HF) versus conventional frequency SCS (CF) on the patients with FBSS.

Design. Prospective, Randomized blind trial.

Setting. Academic University Pain Medicine Center.

Subject. Seventy eight patients with FBSS diagnosis based on internationally recognized criteria, and refractory to conservative therapy for at least 6 months, have been initially recruited, and

Methods. Sixty subjects met the eligibility criteria and were randomized and scheduled for the trial phase.The patients were randomly assigned in either, one of the two groups: CF SCS or HF SCS. Within the study methods, special attention was paid to standardizing patient programming, so that these parameters would not impact the results.The trial period was considered successful if there was ? 50% reduction in the NRS from baseline.

Results. A total of 55 subjects successfully completed all assessments during one year follow-up. Change patterns in scores do not differ based on high versus conventional frequency, with significant global average reduction at 1year similarly for both groups. Among all the items included in the Short Form-12 questionnaire (SF-12), only the variations in the social function score between the instants t1 and t2 are somewhat higher in the high frequency group.

Conclusion. The evolutionary pattern of the different parameters studied in our patients with FBSS does not differ according to their treatment by spinal stimulation, with conventional or high frequency, in one year follow-up.

Key Words. Chronic Pain; Disability; Failed Back Surgery Syndrome; Lumbar; Outcome Assessment; Spinal Cord Stimulation

Introduction

Spinal cord stimulation (SCS) is a commonly established therapy to treat chronic neuropathic pain (NeP) of various etiologies [1,2]. One of the most common indications for SCS is failed back surgery syndrome (FBSS) or a persistent or recurrent complex chronic pain syndrome, with mixed neuropathic and nociceptive (e.g., mechanical, inflammatory) elements, that afflicts between 10% and 40% of patients who undergo lumbosacral spine surgery for the alleviation of pain [3,4].

The systematic review of the literature cited by Taylor et al. [5] concluded that the level of evidence for the efficacy of SCS in chronic back and leg pain secondary to FBSS remains "moderate." More recent systematic reviews confirm there is level I to II evidence of the efficacy of SCS in lumbar FBSS [1,6], whereas there is moderate (level II to III) evidence for high-frequency stimulation [6].

The final therapeutic outcome of SCS,is the result of a complex interaction between the anatomy of the spinal cord and the electrical characteristics of the structures involved. The electric field generated and its interaction with the underlying neural tissue will likewise be the result of the conductivity of the intraspinal elements in relation to the lead position and the "global" programming applied to the implanted system. In FBSS, the NeP component has been markedly more responsive to conventional SCS than the midline nociceptive low-back pain component [7,8].

Conventional low-frequency (CF) tonic stimulation has been considered the standard for programming in SCS. Although programming parameters depend on each individual patient, they are usually within the following ranges: amplitude, 3–10 mA; frequency, 10–40 Hz; and pulse width, 60–450 ms [9–11]. Most studies base their analysis of outcomes on self-reported pain relief and patient satisfaction. Beyond the description of the system implanted, very little or no information is given on the variables selected for programming, either at baseline or in long-term follow-up.

Stimulation with ultra-high frequencies (10 KHz) has generated, perhaps, the largest number of publications over the last few years [12–17]. In terms of methodology, the articles only present the T9-T10 offset coverage and the manufacturer's programming algorithm as the optimal combination for HF therapy. However, available scientific evidence shows that other aspects have not been addressed. Furthermore, even though most published articles report better results than with conventional stimulation, at present little is known about the physiological mechanisms behind the effects of high-frequency SCS (HF) compared with conventional-frequency SCS (CF). According to published basic studies based on computer models, HF stimulation blocks large-diameter fibers preferentially, while medium-diameter and small-diameter fibers are recruited, together with an inhibition of wide dynamic range (WDR) cells in the underlying dorsal horn [18,19]. The demonstration of some effect with both monophasic and biphasic pulses, together with the lack of effect on the impulse traffic in the DCs in a rat model, point to a putative mechanism at the segmental level [20,21].

What is manifestly attracting the interest of researchers is the study of frequency variation in the programming of SCS and its impact on the final results of therapy in patients with NeP. The variable response to conventional SCS among patients with pain may stem from the fact that different types of pain arise from different nerve activities. Using a rat NeP model, Shechter et al. [21] showed that different frequencies may suit different clinical settings involving different pain syndromes, although Guan et al. [22] previously showed that 50-Hz dorsal column stimulation inhibited both spontaneous and induced activity in WDR neurons of nerve-injured rats. Nevertheless, although the mechanisms of SCS have been widely investigated in animal studies, the literature still lacks controlled clinical studies comparing CF and HF SCS in humans.

Considering the facts presented above, the objective of our study was to demonstrate, in the long term, whether frequency has an effect on clinical results and on the outcome of spinal cord stimulation therapy in patients with FBSS.

Methods

This prospective, randomized blind trial was conducted at the Multidisciplinary Pain Management Department of the General University Hospital of Valencia, Spain. Approval was obtained from the Research Commission and the Clinical Research Ethics Committee of the Department of Health of Valencia General Hospital, Valencia, Spain, and the project was reviewed by the Spanish Regulatory Drug Agency (AEMPS) and classified as a "study with products for healthcare use." The study complied with local regulations, Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and the applicable law and regulations governing personal data protection and rights and responsibilities regarding information and documentation in health care.

Patient Selection

We enrolled patients age 18 years and older who underwent one or more back surgeries and later developed FBSS [1,3,4,23,24], defined as chronic, intractable pain of the trunk and/or limbs that has remained refractory to conservative therapy for at least six months. All patients had a minimum pain intensity of 5/10 on the numeric

rating scale (NRS). Pain was mainly axial low back pain or radiating leg pain that failed to respond to other treatment options—both conservative (medical, physical therapy) and invasive (epidural blocks, radiofrequency, epidural adhesiolysis)—and had no further surgical indication.

The exclusion criteria were as follows: mechanical low back pain; coexisting chronic pain condition or neurological disease; coexisting conditions that would increase procedural risk (e.g., sepsis, coagulopathy); history of laminectomy or posterior fusion at the thoracolumbar junction, where percutaneous electrode end tips are routinely placed; abnormal pain behavior; unresolved psychiatric illness; unresolved issues of secondary gain or inappropriate medication use.

Before eligibility for the study was confirmed, all patients underwent a session with our psychologist to consider the adequacy of the treatment to be used and to determine the influences of psychosocial issues on their pain complaints [25,26]. A negative evaluation was considered a key exclusion criterion.

Patients were told to keep their drug doses stable throughout the study (anti-inflammatory drugs, muscle relaxants, and narcotics) and were advised not to deviate from the prescribed regimens.

Study Design

This study was designed as superiority trial to verify that a new treatment is more effective than the standard treatment from a statistical point of view and from a clinical point of view.

According to a computerized list of randomized numbers, the patients were assigned to one of two groups: the CF group or the HF group. The list of randomized assignments was concealed from the investigators, who did not know which group the following patient would be assigned to until he or she had been chosen for randomization. The same clinician placed the implants in all the study subjects, but did not take part in any further assessments.

The evaluators who collected pain ratings and other outcome measures were blinded to the subjects' group allocations throughout the process. As such, they were disinterested third parties who were not involved in patient care at any time during the study process.

The study was introduced to patients by informing them that there were two groups and that treatment was equally effective in both. It was explained that according to their random assignment, they might experience paresthesia as part of their treatment, but that this did not affect the final outcome of therapy. They also received strict instructions not to discuss which of the different evaluations they were to undergo, the group in which they were included, and, therefore, whether or not they experienced paresthesia as part of their therapy.

Implant Procedure

In order to maximize the homogeneity of our sample and optimize the comparisons between groups, the same number of leads and contacts was used for both SCS systems.

- In the HF group, two percutaneous leads with eight electrodes were implanted. The end tip of one of the leads was placed at T8 and the other one at T9, both near the anatomical midline. The leads were placed in such a way that the electrodes were staggered at T9 in order to achieve coverage in the T8-T11 segment with all 16 electrodes. The leads were connected directly to a rechargeable impulse generator (Senza System, Nevro Corp., Menlo Park, CA, USA).
- In the CF group, two percutaneous leads were implanted with eight electrodes (Vectris Compact Surescan, Medtronic, Minneapolis, MN, USA), placing the end tips at T8, both near the anatomical midline. The final position was decided after a stimulation test for identification of paresthesias overlapping the main pain area in the trunk and lower limbs. The leads were connected directly to a rechargeable impulse generator (Surescan RestoreSensor, Medtronic, Minneapolis, MN, USA).

The implant procedures were performed under local anesthesia following our standard clinical practice. As patients are required to interact during anesthesia, "Monitored anesthesia Care" (Local anesthesia and sedation) was implemented according to the physician's judgment to optimize patient adaptation to the procedure.

The first part of the procedure, or the trial SCS phase, involved implantation of the electrodes with the patient in the prone position. Under fluoroscopic guidance, the most suitable intervertebral lumbar space was chosen as the entry point for the percutaneous procedure, and tissues were dissected up to the interspinales muscle. A modified Thuoy needle was then inserted using a paraspinal access to prevent the electrode from brushing against the spinous processes during trunk extension maneuvers. Once the epidural space was found using the loss of resistance technique, the electrode was introduced under fluoroscopic vision up to T8. The procedure was then repeated for positioning of the second electrode according to the protocol. We always make sure that each lead clearly stimulates its corresponding side as the anatomical midline (fluoroscopy guidance) and physiological midline do not necessarily coincide. The transverse separation between the two parallel leads was usually between 0.5 and 5 mm, depending on the patient's response to the intraoperative stimulation test.

Correct positioning of the leads was confirmed using anatomical landmarks. In the CF SCS group, stimulation

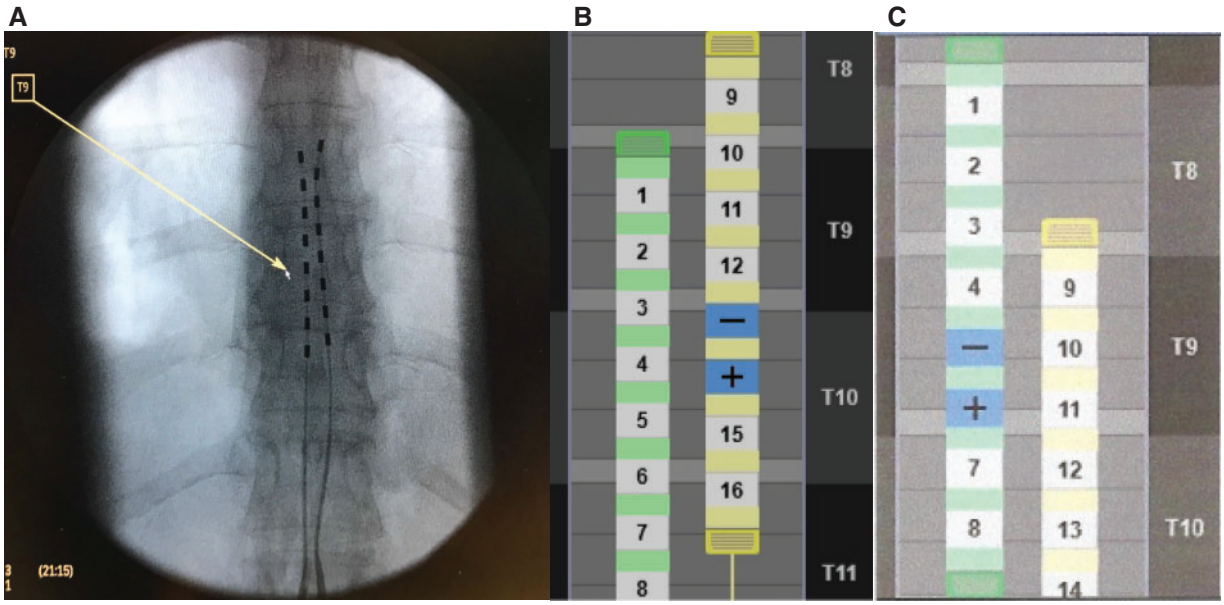

Figure 1 Shows (**A**) the position of the leads on the screen of the fluoroscopy device (T9 marked). (**B**) Image of the screen of the programming computer of Nevro showing the position of the leads according to superimposed vertebral levels. (**C**) Same as (**B**), with leads positioned differently.

patterns were tested for optimal overlap between paresthesia and the region of the subject's back and leg pain by adjusting the position of the electrodes until the paresthesia was identified and covering the entire area of pain [27,28]. In the HF group, this step was skipped, and only correct impedance was tested in both implanted leads.

Leads were then anchored to the supraspinous ligaments and connected to extension lines tunneled subcutaneously to use the external stimulator during the trial period, which lasted two weeks.

The trial period was considered successful if there was $\geq$50% reduction in the numeric rating scale (NRS) from baseline. Permanent implantation was scheduled, with creation of a subcutaneous pocket in the abdominal wall, where the implantable pulse generator (IPG) was placed. The extension lines were removed and the leads were tunneled subcutaneously and connected to the IPG. Impedance was tested intraoperatively before closing to verify the electrical integrity of the implanted system.

Stimulation Parameter Programming

Special attention was paid to standardizing patient programming so that differences between programming personnel and their interactions with patients would not affect the results.

In the HF group, the system has its own algorithm to optimally select the anodes and cathodes required to confine the electric field in a specific stimulation point. The programming ranges for the different parameters are as follows: frequency, 2 Hz to 10,000 Hz; pulse width, 20 μs to 1 ms; amplitude, 0 mA to 15 mA [9,10]. The same protocol was followed for all subjects: 1) Mimic the actual position of the electrodes (fluoroscopy) within the programming software. During the implant procedure, the final position of the electrodes was taken from the fluoroscopic image and reproduced in the programming computer (Figure 1). 2) Pulse width: The initial pulse width was 30 μs. If the patient had good coverage except for a small percentage (toe, lower back), pulse width was increased. 3) Amplitude: Minimal initial amplitudes were always 1.5 mA, whereas maximal amplitudes were 5 mA and always adjusted to obtain the optimal analgesic response. 4) Frequency: 10,000 Hz.

In the CF stimulation group, we used a specific algorithm for intraoperative stimulation and subsequent adjustment during the trial phase. This algorithm is based on our previous experience and on the results of several reports of electric field effect modeling in the activation of myelin fibers [27–29] and clinical experience with stimulation parameters in patients with predominant back pain [30]. In the leads used in the study (Vectris Compact Surescan, Medtronic, Minneapolis, MN, USA), each electrode was 3 mm in length, the insulation between the electrodes was 4 mm, and the interelectrode spacing was 7 mm (center to center), thus providing

Table 1 Data collected for each patient enrolled

	BASAL	1 TRIAL	2 IPG Implant	3 3rd MONTH	4 6th MONTH	5 12th MONTH
ECG, blood sample, baseline pathologies, medication intake	✓					
Pain Detect	✓	✓	✓	✓	✓	✓
DN4	✓	✓	✓	✓	✓	✓
Oswestry discapacity index	✓	✓	✓	✓	✓	✓
SF-12	✓	✓	✓	✓	✓	✓
Sleep Scale (MOS)	✓	✓	✓	✓	✓	✓
HAD	✓	✓	✓	✓	✓	✓
PGI-I				✓	✓	✓

good longitudinal coverage and an electric field sufficiently oriented to preferential stimulation of the posterior columns vs posterior roots. Initially, the central poles were always selected in both electrodes. Because many dermatomes need to be stimulated in these pain conditions, a guarded cathode polarity (+−+) was selected initially to favor stimulation of the posterior columns. If abnormally high impedance values were obtained in the intraoperative test, then a double-guarded cathode array (+− −+) was used, as this widens the field and reduces the threshold [29]. As both amplitude and pulse width are related by the strength-duration curve for a specific fiber, we tried to stay on a straight line to optimize consumption. Therefore, we began with a pulse duration of 300 μs (monophasic pulses) while increasing the amplitude to reach the stimulation threshold. If the threshold was not reached at 4.5 to 5 volts, pulse duration was increased to 390 ms. If no stimulation was attained at 8 volts, then pulse duration was increased to 450 ms. The latter cases occur mainly because of the subject's prone position and, occasionally, because of a temporary increase in impedance. Nonetheless, when the stimulation threshold was above 8 volts, we moved the poles longitudinally as needed to look for lower values. With respect to frequency, we used the minimal frequency to avoid patient discomfort. The initial value was 40 Hz per program. Except for subjects with exclusively unilateral pain, we always used two programs for the intraoperative test. During the trial period, we used the same stimulation pattern as in intraoperative stimulation and, if needed, we moved the poles longitudinally as much as required.

All programming sessions were run by a team comprising a staff physician not involved in the implant process or in-patient follow-up and by a representative of the device manufacturer. The system was reviewed at the five assessment points of the study after the system was implanted, and additionally if the patient reported changes in the quality of perceived analgesia. In the CF stimulation group in particular, the system was reviewed if changes were observed in the overlap between the area of paraesthesia and the area where the patient reported pain.

Data Collection and Outcome Assessment Analysis

Baseline and follow-up data were collected for both groups (Table 1). The tests and questionnaires used in the study are the same as we routinely performed in all patients scheduled for SCS implantation in our department. Data were collected for all patients at six time points, as follows: 1) at randomization (baseline), 2) at the time of the trial SCS phase, 3) at permanent IPG implantation, 4) at three months, 5) at six months, and 6) at 12 months postimplantation. Therefore, all variables were collected at the same time points and in the same way.

The baseline evaluation included a pain assessment, a psychological assessment, and an assessment of functional capacity with currently used questionnaires to provide a quantitative and qualitative measurement of pain and an overview of how pain affected the patients' everyday lives.

Below we provide a brief description of the questionnaires used and how they were scored to correlate with the results obtained. Pain intensity was measured on an 11-point pain intensity numeric rating scale, where 0 represents no pain and 10 represents the worst possible pain [31]. The Pain Detect Questionnaire (PD-Q) [32] and Douleur Neuropathique 4 (DN4) [33] have good discriminant validity for detecting the neuropathic pain component in patients with chronic back and leg pain and for differentiating between neuropathic and nociceptive pain in daily practice. Item-specific scores provide important information in addition to the total score [34]. PD-Q has a total score ranging from –1 to 38. The total score is divided into three PD-Q categories, including unlikely NeP (<13), unclear NeP (13–18), and likely NeP (>18). In the DN4 questionnaire, scores ≥4/10 indicate NeP. The Oswestry Disability Index (ODI) is one of the main condition-specific outcome measures used in the management of spinal disorders [35,36]. The

score can be interpreted as follows: <20%, minimal disability; 20–40%, moderate disability; 40–60%, severe disability; and >60%, wheelchair-bound. The Short Form-12 (SF-12) questionnaire demonstrated good internal consistency, reliability, construct validity, and responsiveness in patients with back pain [37,38]. The results are expressed in terms of two meta-scores: the physical component summary (PCS) and the mental component summary (MCS). A high score on the SF-12 indicates better physical functioning. The Medical Outcomes Study Sleep (MOS-Sleep) Scale is a self-report instrument including 12 items to measure six sleep dimensions [39]. The score range for the 12-item version is 12 to 71. The Hospital Anxiety and Depression (HAD) scale is a self-assessment scale that was developed to detect states of depression, anxiety, and emotional distress [40–42]. Higher scores on each individual subscale or the entire scale indicate greater anxiety, depression, or mood disorders. The Patient Global Impression of Improvement (PGI-I) scale is a simple, direct, easy-to-use seven-point Likert scale that requires the clinician to assess how much the patient's illness has improved or worsened from baseline [14,43,44].

The study methodology included the detection and collection of possible complications or adverse events (AEs), which were usually related to the implant or the hardware used [45]. Reporting was performed at scheduled visits (baseline, 1, 3, 6, 9, and 12 months)

In order verify that HF stimulation is more effective than CF stimulation from a clinical point of view, the primary end point was a reduction of at least 50% in pain intensity in the NRS score in the 12-month evaluation within each group (intragroup analysis) and between the groups. Other key outcome measures were ODI, PD-Q, and HAD. The remaining measurements—SF12, MOSS, and PGI-I—were considered secondary objectives.

Statistical Analysis

The primary purpose of this study was to assess, in subjects who successfully completed the trial phase, whether there was an association between the frequency applied in SCS programming (HF or CF) and the level of improvement in pain and pain-related functional psychological variables. The study was also intended to determine the level of clinical improvement over one year according to the frequency and to compare the effects achieved in each group as assessed with the instruments described above.

This study had a general mixed design to assess group differences (intersubject effect, type of frequency) and change over time (intrasubject effect, including five levels or five measurement time points), with a dependent variable (each one of the parameters to be assessed).

The method used to compare differences between patient groups in changes of parameters over time (compare the effects of either frequency type) is based on intergroup comparison of changes at measurement time points and not on direct comparison of values at each time point. This is the best approach to preclude baseline value deviations from biasing interpretation of the study results. For instance, if two subjects have the same final value and are compared, we would conclude that there are no significant differences between them; however, if the values are compared with the baseline values, it may be concluded that one subject experienced a significant improvement and the other did not; that is, one subject shifts (there is an effect) while the other subject does not (there is no effect).

Given the diversity of the evaluation instruments, each required a specific method adapted to its nature. The Shapiro-Wilks test was used as an adjustment test to normal distribution of continuous variables. A P value >0.05 on the Shapiro-Wilks test implied acceptance of the normality hypothesis.

Therefore, the methods used in our study followed parametric and nonparametric approaches:

- Parametric approach: for normally distributed variables, a repeated-measures general linear model (GLM) was used for dependent variables, with the intrasubject factor time including five levels and the intersubject factor frequency group (high vs low). This model provided a preliminary global result of the effect of time and its comparison between groups. Detailed comparisons were then made between each pair of time points.
  - A Student's t test for independent samples was used to contrast the equality of means in two normally distributed, independent continuous samples.
- Nonparametric approach: Wilcoxon tests for comparison of distributions for two related samples were applied to non-normally distributed variables between time points in order to assess changes in each patient group (effect of the procedure). Subsequently, Mann-Whitney tests for comparison of distributions of two independent samples were used to compare these changes between the groups (comparison of effects).
  - Pearson's nonparametric chi-square test was used as an association or dependency test between two categorical variables, as long as the expected cell frequency in the contingency table was more than five cases. Otherwise, the Fisher exact test was used (only for dichotomous variables).

Sample size was calculated based on the percentage of success, at least 50% pain relief, and patient satisfaction with treatment—as reported in previous studies with CF SCS [46,47] and HF SCS—a reduction of at least 50% in pain intensity and ability to cope with the requirements of SCS [13–16]. Our calculation was based on the minimum difference to be detected between groups and between time points for the NRS scale. The sample size was not defined as a success rate but as a mean difference. With

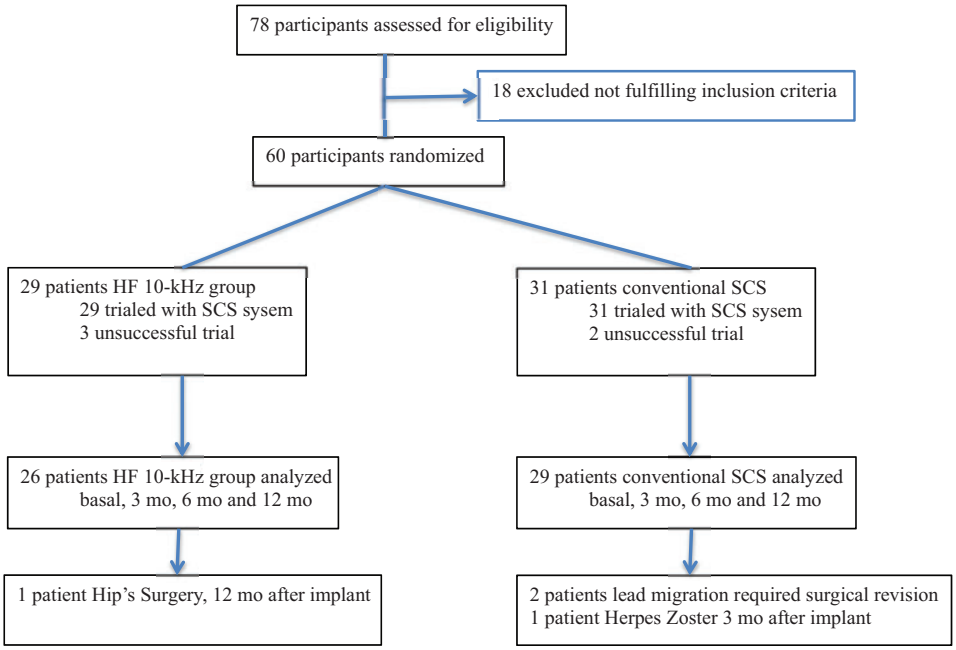

Figure 2 Study subject flow. HF10 = 10-kHz high-frequency; SCS = spinal cord stimulation.

Table 2 Baseline demographics and clinical characteristics

	Conventional SCS group (N = 29)	HF 10 kHz SCS group (N = 26)	Difference*
Age, mean (SD), y	53.79 (11.46)	51.62 (9.31)	0.446
Male/female, %	37.9/62.1	57.7/42.3	0.116
Pain diagnosis, %			
Failed back surgery syndrome	100	100	
Previous back surgery, %	100	100	
Baseline NRS, mean (SD)	7.60 (1.06)	7.69 (1.17)	0.33
Baseline pain detect, mean (SD)	18.86 (7.17)	16.23 (6.85)	0.329
Baseline ODI, mean (SD)	27.18 (5.21)	26.96 (5.18)	0.33

HF = high frequency; NRS = numeric rating scale; ODI = Oswestry Disability Index; PD-Q = Pain Detect Questionnaire; SCS = spinal cord stimulation.

a total sample of 60 cases (30 cases per group, minimum sample size of 54 [27/27], possible 10% of losses assumed), a statistical power of 85% would be obtained. Therefore, a comparison of means would lead to a minimum difference of one point on the NRS scale between the groups (and some dispersions of data), all with a significance level of $P < 0.05$.

The statistical analyses were designed and performed by an independent biostatistician.

Results

A total of 78 subjects were recruited initially. Of these, 60 subjects met the eligibility criteria and were randomized and scheduled for the trial phase. A total of 55 subjects had a permanent implant placed and attended all assessments, thus successfully completing the trial phase (Figure 2).

The demographic profiles of both subject groups were comparable. Therefore, no effects on subsequent outcomes may be attributed to baseline demographic differences (Table 2).

Numeric Rating Scale

We used the NRS to assess whether there were any significant improvements in pain over time (up to month 12) and whether the SCS frequency had any effect on

Table 3 Data on numeric rate scale, PainDETECT questionnaire, Oswestry Disability Index, and Hospital Anxiety and Depression Scale

		t1	t2	t3	t4	t5	t2-t1		t3-t2		t4-t3		t5-t4		Global t4-t1		Global t5-t1	
		Mean* (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean of the Difference	*P* Value (F Test†)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)
NRS	Conv. freq.	7.69 (1.27)	5.10 (2.09)	5.71 (1.70)	5.78 (1.97)	5.86 (2.46)	−2.59 (1.85)	0.000*	0.60 (1.73)	0.001*	0.07 (1.92)	0.898	0.23 (2.30)	0.513	−1.67 (2.69)	0.000*	−1.44 (2.28)	0.000*
	HF	7.50 (1.52)	4.48 (2.14)	5.98 (2.61)	5.83 (2.23)	6.06 (2.13)	−3.02 (2.41)		1.50 (2.47)		−0.15 (2.70)		0.17 (2.07)		−1.91 (2.09)		−1.82 (2.45)	
	P value (Student's *t*)	0.617	—‡	—	—	—	*P* value (F test§)	0.521	*P* value (F test)	0.123	*P* value (F test)	0.726	*P* value (F test)	0.907	*P* value (F test)	0.711	*P* value (F test)	0.560
PD-Q	Conv. freq.	18.41 (6.90)	13.45 (7.80)	13.97 (8.62)	13.52 (9.03)	14.89 (7.36)	−4.97 (4.89)	0.000*	0.52 (5.17)	0.299	−0.45 (5.71)	0.337	1.75 (6.64)	0.515	−4.89 (7.47)	0.000*	−3.14 (6.50)	0.002*
	HF	16.35 (7.26)	11.50 (7.14)	12.35 (8.25)	14.19 (8.49)	13.54 (8.53)	−4.85 (5.03)		0.85 (4.32)		1.85 (4.85)		−0.65 (5.54)		−2.15 (4.52)		−2.08 (6.77)	
	P value (Student's *t*)	0.284	—	—	—	—	*P* value (F test)	0.911	*P* value (F test)	0.814	*P* value (F test)	0.126	*P* value (F test)	0.156	*P* value (F test)	0.110	*P* value (F test)	0.853
ODI	Conv. freq.	26.45 (5.85)	21.93 (7.92)	20.55 (8.32)	21.07 (9.90)	22.07 (7.86)	−4.52 (6.50)	0.000*	−1.38 (6.12)	0.779	0.52 (5.80)	0.377	1.57 (7.48)	0.408	−5.38 (10.36)	0.000*	−4.14 (8.76)	0.000*
	HF	27.00 (5.39)	20.96 (7.56)	21.85 (8.59)	22.92 (6.85)	22.96 (7.06)	−6.04 (6.64)		0.89 (6.06)		1.08 (5.71)		0.04 (6.63)		−4.08 (6.00)		−4.04 (5.77)	
	P value (Student's *t*)	0.719	—	—	—	—	*P* value (F test)	0.453	*P* value (F test)	0.187	*P* value (F test)	0.632	*P* value (F test)	0.430	*P* value (F test)	0.577	*P* value (F test)	0.959
HAD anxiety	Conv. freq.	10.72 (4.60)	8.07 (4.54)	8.24 (5.37)	8.45 (6.16)	8.54 (5.67)	−2.67 (3.92)	0.000*	0.17 (4.14)	0.199	0.21 (4.39)	0.403	0.50 (4.00)	0.913	−2.28 (6.05)	0.022*	−2.04 (5.82)	0.010*
	HF	10.31 (4.03)	7.46 (4.12)	8.35 (5.18)	9.31 (5.99)	8.69 (5.08)	−2.85 (3.50)		0.89 (3.08)		0.96 (2.97)		−0.62 (3.67)		−1.00 (3.83)		−1.62 (4.07)	
	P value (Student's *t*)	0.724	—	—	—	—	*P* value (F test)	0.953	*P* value (F test)	0.619	*P* value (F test)	0.260	*P* value (F test)	0.294	*P* value (F test)	0.361	*P* value (F test)	0.761
HAD depression	Conv. freq.	9.45 (4.31)	6.34 (4.05)	7.03 (5.52)	6.93 (5.81)	7.21 (4.97)	−3.10 (3.55)	0.000*	0.69 (4.09)	0.096	−0.10 (3.09)	0.413	0.71 (4.02)	0.208	−2.52 (6.35)	0.009*	−2.00 (5.38)	0.046*
	HF	8.96 (4.04)	5.69 (3.51)	6.69 (4.86)	7.54 (5.45)	8.19 (5.00)	−3.27 (4.04)		1.00 (2.67)		0.85 (3.75)		0.65 (3.85)		−1.42 (4.07)		−0.77 (4.50)	
	P value (Student's *t*)	0.668	—	—	—	—	*P* value (F test)	0.959	*P* value (F test)	0.747	*P* value (F test)	0.333	*P* value (F test)	0.955	*P* value (F test)	0.456	*P* value (F test)	0.368

HF = high frequency; HAD = Hospital Anxiety and Depression; NRS = numeric rating scale; ODI = Oswestry Disability Index; PD-Q = Pain Detect Questionnaire; SCS = spinal cord stimulation.

*In a two-factor design, the marginal means for each level in a factor are the means for that factor averaged through the levels of the other factor; i.e., the means corrected to remove the effect of other factors (masked effects). As this is a one-factor model, the marginal means coincide approximately with the sample means. For this reason, the sample means are shown.

†This *P* value is derived from the F test for the post hoc contrasts of the repeated-measures analysis of variance. It tests whether there were significant changes between two specific time points overall, without distinguishing between groups (a *P* value <0.05 indicates a significant change in the parameter between these two time points).

‡Values are not compared between the groups at each measurement time point (except at t1). The approach of this study focuses on comparing changes between time points in order to avoid introducing bias for potential deviations in the baseline values or the previous time point values.

§This *P* value is derived from the F test for the post hoc contrasts of the repeated-measures analysis of variance. It tests whether the significant changes between two specific time points overall differ between the groups (a *P* value <0.05 indicates that the significant changes in the parameter between these two time points differ significantly between the groups).

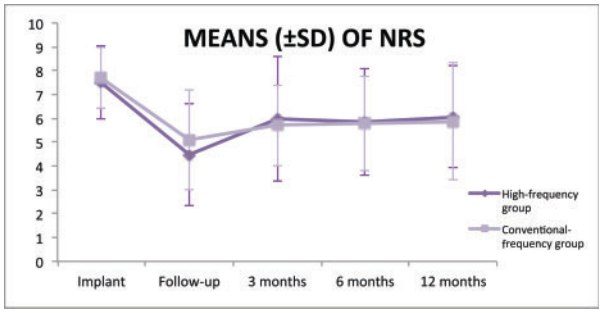

Figure 3 This graph shows the significant decrease in numeric rating scale at the first follow-up, the slight increase at three months, and then a constant level of pain until the year. The overall reduction of pain is also observed as there is no group effect following the same pattern in both groups of patients (parallel lines; any observed deviation is purely random).

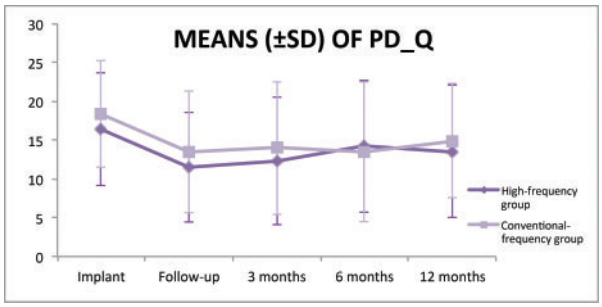

Figure 4 This graph shows how the Pain Detect Questionnaire significantly decreases in the first review and then gradually increases—not significantly—until translated into an overall reduction of three points that, because there is no group effect, follows the same pattern in both groups of patients (parallel lines; any observed deviation is purely random).

this improvement. The intersubject factor was defined by the subject group (CF SCS vs HF SCS), and the intrasubject factor was defined by time. The significance value for Box's M test was used to analyze the null hypothesis that covariance matrices observed for dependent variables were equal in both groups (0.107, >0.05); consequently, the GLM repeated-measures approach was applied. The results of the analysis showed that changes in NRS score patterns did not differ regardless of whether frequency was high or conventional. Overall, there was a significant reduction in average NRS scores at the different assessments (approximately three points, that is, an average reduction of 30–40% with respect to the initial value) and a slight increase in average NRS scores at three months (0.5–1.5 points, i.e., a significant global average reduction at one year of about 1.5–2 points, which corresponds to a 20–25% reduction with respect to the starting value). These values were similar for both groups (Table 3). The significant

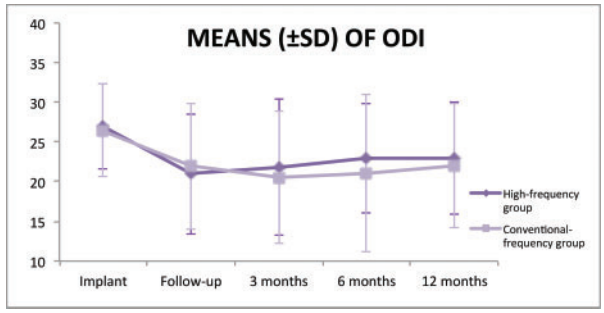

Figure 5 This graph shows how Oswestry Disability Index significantly decreases in the first review and then moves—not significantly—until translated into an overall reduction of four points that, because there is no group effect, follows the same pattern in both groups of patients (parallel lines; any observed deviation is purely random).

improvement in pain over 12 months followed the same pattern in both groups (conventional SCS and HF SCS) (Figure 3).

PainDETECT Questionnaire

We assessed whether there were any significant changes in the mean PD-Q scores (Figure 4). The significance value for Box's M-test was 0.329 (>0.05); consequently, the GLM repeated-measures approach was applied. The results of the analysis showed that changes in PD-Q score patterns did not differ, regardless of the type of frequency (CF or HF). Overall, there was a significant reduction in average PD-Q scores (about five points) when data were collected. At six months, the reduction in PD-Q scores was almost five points, compared with only two points in the HF group. This difference was not significant, although the proximity to the *P* value acceptance threshold (0.110) indicates a trend toward differentiation. In the 12-month assessment, the global average reduction became similar in both groups and was about 2–3 points (Table 3).

Oswestry Disability Index

Changes in ODI score patterns did not differ, regardless of frequency (CF or HF), and any deviations were purely fortuitous (Figure 5). Thus, there was a significant mean reduction of 5–6 points in the ODI scores when the data were collected (Table 3), that is, a global average reduction of 4 points in both groups at the 12-month assessment.

Short Form-12

The SF-12 subdomains were evaluated independently in the statistical analysis (Table 4).

Table 4 Data on Short Form-12 questionnaire

		t1	t2	t3	t4	t5	t2-t1		Global t4-t1		Global t5-t1	
		Mean (SD)*	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean of the Difference	*P* Value (F Test†)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)
SF-12 mental health	Conv. freq.	38.28 (24.79)	53.79 (25.41)	50.34 (27.32)	53.79 (27.70)	49.64 (24.26)	15.52 (24.29)	0.000*	15.52 (24.43)	0.001*	10.36 (32.01)	0.042*
	HF	42.69 (20.70)	56.54 (21.53)	50.38 (31.17)	51.54 (25.09)	48.46 (24.77)	13.85 (22.99)		8.85 (27.76)		5.77 (23.86)	
	P value (Student's *t*)	0.464	—‡	—	—	—	*P* value (F test§)	0.733	*P* value (F test)	0.347	*P* value (F test)	0.556
		Mean¶ (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean of the difference	*P* value (Wilcoxon)	Mean of the difference	*P* value (Wilcoxon)	Mean of the difference	*P* value (Wilcoxon)
SF-12 physical functioning	Conv. freq.	13.79 (29.57)	27.59 (41.37)	18.97 (33.84)	22.41 (39.16)	18.75 (33.76)	13.79 (42.04)	0.103	8.62 (48.31)	0.374	4.46 (41.97)	0.521
	HF	0.00 (0.00)	23.08 (38.03)	28.85 (42.83)	17.31 (31.44)	23.08 (40.57)	23.08 (38.03)	0.010*	17.31 (31.44)	0.014*	23.08 (40.57)	0.014*
	P value (MW)	0.015*	—	—	—	—	0.490		0.510		0.118	
SF-12 role-physical	Conv. freq.	18.97 (21.81)	35.34 (22.68)	27.59 (29.39)	31.03 (33.18)	25.00 (28.87)	16.38 (26.96)	0.004*	12.07 (29.60)	0.042*	5.36 (34.93)	0.561
	HF	14.42 (18.94)	32.21 (24.54)	35.10 (25.99)	28.85 (24.18)	28.37 (27.28)	17.79 (25.04)	0.003*	14.42 (27.54)	0.019*	13.94 (27.46)	0.023*
	P value (MW)	0.472	—	—	—	—	0.587		0.444		0.293	
SF-12 bodily pain	Conv. freq.	20.69 (24.15)	40.52 (28.67)	36.21 (31.75)	43.97 (34.50)	37.50 (32.98)	19.83 (30.89)	0.002*	23.28 (37.16)	0.003*	16.96 (32.67)	0.012*
	HF	25.96 (20.59)	41.35 (28.23)	40.38 (28.35)	37.50 (27.619	32.69 (27.17)	15.38 (30.30)	0.020*	11.53 (30.19)	0.056	6.73 (25.05)	0.185
	P value (MW)	0.204	—	—	—	—	0.655		0.202		0.239	
SF-12 general health	Conv. freq.	18.10 (17.55)	36.21 (23.70)	33.62 (26.11)	33.62 (26.11)	38.39 (22.03)	18.10 (19.93)	0.000*	15.52 (27.88)	0.007*	19.65 (28.35)	0.002*
	HF	18.27 (25.06)	33.65 (27.33)	26.92 (25.42)	29.81 (27.40)	26.92 (26.38)	15.39 (23.54)	0.005*	11.54 (27.60)	0.040*	8.66 (19.93)	0.039*
	P value (MW)	0.592	—	—	—	—	0.638		0.623		0.163	
SF-12 vitality	Conv. freq.	22.07 (25.27)	40.69 (37.22)	37.93 (38.30)	40.00 (37.80)	27.14 (33.65)	18.63 (34.61)	0.011*	17.93 (37.17)	0.018*	5.00 (34.27)	0.462
	HF	20.00 (18.76)	40.00 (29.93)	36.15 (32.99)	27.69 (31.54)	26.15 (26.39)	20.00 (31.49)	0.005*	7.69 (32.53)	0.304	6.15 (29.27)	0.385
	P value (MW)	0.943	—	—	—	—	0.649		0.347		0.971	
SF-12 social functioning	Conv. freq.	51.03 (33.20)	58.62 (34.20)	53.79 (37.46)	55.52 (36.80)	53.93 (32.58)	7.59 (35.63)	0.246	4.48 (39.96)	0.579	2.50 (45.51)	0.863
	HF	36.15 (29.40)	64.62 (24.20)	62.69 (31.44)	55.38 (30.62)	51.15 (29.44)	28.46 (33.07)	0.001*	19.23 (35.54)	0.011*	15.00 (38.49)	0.064
	P value (MW)	0.104	—	—	—	—	0.036*		0.231		0.345	
SF-12 role-emotional	Conv. freq.	41.38 (50.12)	64.66 (42.00)	62.24 (45.58)	50.86 (47.47)	54.46 (48.14)	23.28 (46.26)	0.011*	9.48 (58.41)	0.364	13.08 (64.36)	0.352
	HF	36.54 (48.08)	50.00 (48.99)	57.96 (48.36)	61.54 (47.56)	50.00 (50.99)	13.46 (36.21)	0.068	25.00 (57.00)	0.026*	13.46 (55.78)	0.178
	P value (MW)	0.737	—	—	—	—	0.473		0.402		0.930	

HF = high frequency; MW = Mann-Whitney; SF-12 = Short Form-12.

*In a two-factor design, the marginal means for each level in a factor are the means for that factor averaged through the levels of the other factor, i.e., the means corrected to remove the effect of other factors (masked effects). As this is a one-factor model, the marginal means coincide approximately with the sample means. For this reason, the sample means are shown.

†This *P* value comes from the F test for the post hoc contrasts of the repeated-measures analysis of variance. It tests whether there were significant changes between two specific time points overall, without distinguishing between groups (a *P* value <0.05 indicates a significant change in the parameter between these two time points).

‡Values are not compared between the groups at each measurement time point (except at t1). The approach of this study focuses on comparing changes between time points in order to avoid introducing bias for potential deviations in the baseline values or the previous time point values.

§This *P* value is derived from the F test for the post hoc contrasts of the repeated-measures analysis of variance. It tests whether the significant changes between two specific time points overall differ between the groups (a *P* value <0.05 indicates that the significant changes in the parameter between these two time points differ significantly between the groups).

¶This parameter does not follow a normal distribution. Therefore, nonparametric statistical tests were used to analyze changes and compare them between the groups. The most appropriate statistic for nonparametric results is the median; however, given the particular nature of some parameters (semicontinuous variables with only three or four values), the mean and the SD are shown, as this will facilitate the interpretation of results.

SF Mental Health

Progression of SF mental health did not differ according to the frequency (CF or HF). Thus, there was a significant average increase in this component of around 14–15 points at the time of the assessment. At six months, the average increase was 15 points for CF and 9 points for HF; however, these values must be considered statistically equal. At the 12-month assessment point, the average increase was 10 points for CF and 6 points for HF, although statistical significance was equal for both.

SF Physical Function

Progression of physical function did not differ according to CF or HF. However, although not significant, certain tendencies (*P* values close to 0.05) were observed for the difference in progression between the groups, such as the average global increase observed in both groups during the year: For the HF group, the difference was significant and high, while for the CF group it was much lower and nonsignificant. The main difference in progression between the groups was the deviation in the initial values: The HF group started from a baseline value of 0.

SF Role (Physical)

Progression of role (physical) did not differ according to CF or HF. Thus, in general, there was a significant average increase of around 16–18 points for this component at the time of the first follow-up. At six months, the average increase was 12–14 points. At 12 months, the average increase was 5 points for CF (not significant) and 13 points for HF (significant); however, these values were statistically equal.

SF Bodily Pain

Progression of bodily pain did not differ according to CF or HF. Thus, in general, there was a significant average increase of around 15–20 points for this component at the time of first follow-up. At six months, the average significant increase was 24 points for low frequency and 12 points for HF (significant), although these values were statistically equal. At 12 months, the average significant increase was 17 points for CF and seven points for HF (not significant); these values were statistically equal.

SF General Health

Progression of general health did not differ according to CF or HF. Thus, in general, there was a significant average increase in this component of around 15–18 points at the time of the first follow-up. At six months, the overall average increase was 12–16 points. At 12 months, the increase was 20 points for the CF group and 9 points for the HF group. These findings were statistically similar.

SF Vitality

Progression of vitality did not differ according to CF or HF. Thus, in general, there was a significant average increase of around 19–20 points in this component at the first assessment. At six months, the mean increase was 18 points for the CF group and 8 points for the HF group. These findings were statistically equal. At 12 months, the overall average increase was 5–6 points, although this was not statistically significant. Therefore, vitality values at the end of the year were similar to those recorded at baseline.

SF Social Functioning

Progression of social functioning in the HF group was variable, whereas in the CF group it was stable. However, the only statistically significant differences between the groups for this component were recorded at the first follow-up. Therefore, there was no significant progression for the CF group. In the HF group, however, a significant progression was observed, with an average increase of 28 points.

SF Role (Emotional)

Progression of role (emotional) did not differ according to CF or HF. Thus, in general, there was a significant average increase in this component of around 15–23 points at the time of the first follow-up. At six months, the mean increase for the CF group was 9 points, although this was not significant. In the HF group, the increase was significant (25 points), although the values were statistically equal in both groups. At 12 months, the general average increase was 13–14 points, although this was not significant, indicating that after 12 months, values were similar to those recorded at baseline.

Medical Outcomes Study Sleep Scale

There was no group effect (intersubject) in the Medical Outcomes Study Sleep Scale (MOS-SS), suggesting that, generally, subjects receiving CF and HF SCS had similar annual average scores (Table 5). There was, however, a time effect (intrasubject), with parameters changing over the intervention period. There was no group-by-time effect, and changes in the HF and CF SCS groups were similar. Overall, average MOS-SS somnolence scores increased significantly (6–7 points) at the assessment point. At six months, the average increase was 7–8 points. At 12 months, the average

Table 5 Data on Medical Outcomes Study Sleep Scale

		t1	t2	t3	t4	t5	t2-t1		Global t4-t1		Global t5-t1	
		Mean* (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)	Mean of the Difference	*P* Value (F Test)
MOS-SS somnolence	Conv. freq.	53.10 (28.87)	60.46 (20.31)	62.99 (18.05)	60.92 (19.58)	63.10 (24.98)	7.36 (18.29)	0.014*	7.82 (31.12)	0.058	10.00 (27.06)	0.001*
	HF	51.79 (23.04)	57.95 (23.53)	58.21 (24.19)	58.97 (23.38)	67.18 (19.95)	6.15 (21.07)		7.18 (25.57)		15.39 (21.65)	
	P value (Student's *t*)	0.854	—[†]	—	—	—	*P* value (F test[‡])	0.787	*P* value (F test)	0.935	*P* value (F test)	0.367
MOS-SS sleep disturbance	Conv. freq.	27.20 (25.24)	40.39 (27.13)	39.31 (24.98)	41.38 (30.52)	37.32 (29.71)	13.19 (21.55)	0.000*	14.18 (31.29)	0.000*	10.12 (27.95)	0.005*
	HF	29.66 (25.13)	53.94 (27.84)	45.82 (29.56)	50.63 (28.49)	41.25 (25.95)	24.28 (25.59)		20.96 (28.11)		11.59 (24.92)	
	P value (Student's *t*)	0.719	—	—	—	—	*P* value (F test)	0.096	*P* value (F test)	0.404	*P* value (F test)	0.784
MOS-SS sleep quantity	Conv. freq.	5.03 (1.37)	5.83 (1.14)	5.57 (1.29)	5.52 (1.28)	5.48 (1.54)	0.79 (1.25)	0.000*	0.48 (1.27)	0.000*	0.41 (1.63)	0.037*
	HF	5.25 (1.17)	6.40 (1.17)	5.79 (1.54)	6.10 (1.27)	5.73 (1.11)	1.15 (1.30)		0.85 (1.23)		0.48 (1.40)	
	P value (Student's *t*)	0.535	—	—	—	—	*P* value (F test)	0.252	*P* value (F test)	0.289	*P* value (F test)	0.867
		Mean[§] (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean of the difference	*P* value (Wilcoxon)	Mean of the difference	*P* value (Wilcoxon)	Mean of the difference	*P* value (Wilcoxon)
MOS-SS awakening short of reath	Conv. freq.	57.93 (34.37)	64.83 (29.60)	68.28 (31.86)	65.52 (33.37)	65.00 (31.09)	6.90 (26.87)	0.236	7.59 (40.50)	0.331	7.07 (43.16)	0.462
	HF	57.69 (31.15)	68.46 (27.23)	73.85 (24.50)	76.15 (27.14)	76.92 (29.77)	10.77 (26.07)	0.056	18.46 (34.84)	0.017*	19.23 (35.09)	0.015*
	P value (MW)	0.938	—	—	—	—	0.531		0.630		0.425	
MOS-SS snoring	Conv. freq.	34.48 (36.12)	44.14 (38.31)	45.52 (36.99)	38.57 (36.01)	41.43 (35.25)	9.66 (41.62)	0.233	2.76 (41.30)	0.738	5.71 (24.25)	0.177
	HF	43.08 (38.65)	53.85 (39.51)	51.54 (38.02)	48.46 (41.25)	51.54 (41.63)	10.77 (19.78)	0.005*	5.39 (23.01)	0.313	8.46 (31.07)	0.218
	P value (MW)	0.356	—	—	—	—	0.734		0.885		0.903	
MOS-SS sleep adequacy	Conv. freq.	31.03 (26.23)	44.83 (27.47)	42.07 (33.21)	44.48 (36.15)	37.86 (32.01)	13.79 (25.41)	0.004*	13.45 (36.87)	0.049*	6.83 (38.63)	0.511
	HF	27.42 (24.51)	55.00 (28.74)	46.92 (32.59)	48.08 (33.94)	40.00 (29.53)	27.58 (30.86)	0.000*	20.65 (42.60)	0.022*	12.58 (34.16)	0.060
	P value (MW)	0.548	—	—	—	—	0.100		0.628		0.325	

HF = high frequency; MOS-SSS = Medical Outcomes Study Sleep Scale; MW = Mann-Whitney; SF-12 = Short Form-12.

*In a two-factor design, the marginal means for each level in a factor are the means for that factor averaged through the levels of the other factor, i.e., the means corrected to remove the effect of other factors (masked effects). As this is a one-factor model, the marginal means coincide approximately with the sample means. For this reason, the sample means are shown.

[†]Values are not compared between the groups at each measurement time point (except at t1). The approach of this study focuses on comparing changes between time points in order to avoid introducing bias for potential deviations in the baseline values or the previous time point values.

[‡]This *P* value is derived from the F test for the post hoc contrasts of the repeated-measures analysis of variance. It tests whether the significant changes between two specific time points overall differ between the groups (a *P* value <0.05 indicates that the significant changes in the parameter between these two time points differ significantly between the groups).

[§]This parameter does not follow a normal distribution. Therefore, nonparametric statistical tests were used to analyze changes and compare them between the groups. The most appropriate statistic for nonparametric results is the median; however, given the particular nature of some parameters (semicontinuous variables with only three or four values), the mean and the SD are shown, as this will facilitate the interpretation of results.

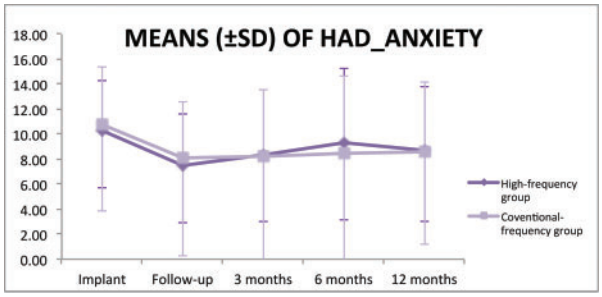

Figure 6 Hospital Anxiety and Depression questionnaire. Anxiety scores.

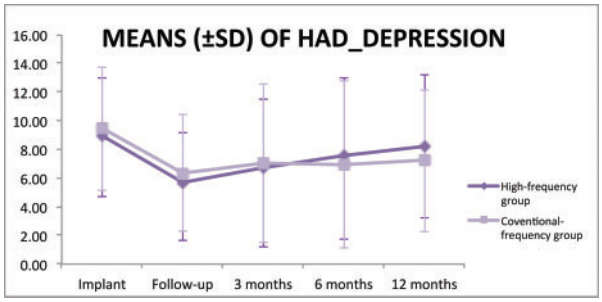

Figure 7 Hospital Anxiety and Depression questionnaire. Depression scores.

increase was 10–15 points. Overall, average MOS-SS sleep disturbance scores increased significantly (by 15–25 points) at the assessment point. Between month 3 and month 6, there was a significant reduction in the score (4–9 points), which translates into a significant average increase of 14–20 points at six months and 10–12 points at 12 months. Overall, there was a significant increase in average MOS-SS sleep quantity scores of about 0.8–1.2 hours at the assessment point. At three months, there was a slight reduction in the number of hours by about 0.3–0.6 hours. This translates into a significant average increase of 0.5–0.9 hours at six months and 0.5 hours at 12 months. Overall, there was a significant average increase of 14–28 points in MOS-SS sleep adequacy scores at the assessment point (proximity to the Mann-Whitney *P* value acceptance threshold indicates a trend toward a greater increase in the HF group compared with the CF group). The significant average increase was 14–20 points at six months. This was sustained at 12 months.

Hospital Anxiety and Depression Scale

The anxiety and depression dimensions were normally distributed for the HAD scale (Table 3). Therefore, a doubly multivariate GLM was used. There was no group effect (intersubject), suggesting that subjects receiving either CF or HF SCS had similar HAD parameter values in the annual average scores. There was, however, a time effect (intrasubject), with parameters changing over the intervention period.

Overall, there was a significant reduction in the average HAD anxiety scores (about 3 points) at the assessment point. At six months, the average reduction was 1–2 points. At one year, the average reduction was 2 points in both groups (Figure 6).

Change patterns in HAD depression scores did not differ based on frequency (HF vs CF). Overall, there was a significant reduction in the average HAD depression scores (about 3 points) at the assessment point. At six months, the average reduction was 1.5–2.5 points. At one year, the average reduction was 1–2 points. This was similar in both groups (Figure 7).

Patient Global Impression of Improvement and Clinical Global Impression–Improvement Scales

In both groups and for both parameters, changes were observed between assessment points t2 and t4 and between t2 and t5 (Table 6; Figures 8 and 9). Additionally, in the HF group, there was a change from t1 to t2 in both parameters. Changes in PGI score patterns did not differ based on frequency (HF vs CF). Overall, there was a significant increase in average PGI scores at month 3 (0.5–0.7 points). At six months, the average increase was 0.6–0.9 points overall. At one year, the average increase was similar (Figure 8).

Change patterns in Clinical Global Impression (CGI) scores did not differ based on frequency (HF vs CF). Overall, there was a significant increase in average CGI scores at month 3 (about 0.3–0.6 points). At six months, the average increase was 0.5–0.7 points overall. At one year, the average increase was similar (Figure 9).

The system was reviewed at the five data collection points, and the mean number of programming sessions in each group was 6.05 ± 0.69 in the CF group and 5.97 ± 0.79 in the in the HF group. There were no clinical or statistical differences between the groups.

Complications

A summary of the device-related AEs is provided in Table 7. The most common AE was lead migration, which was significantly more frequent in the HF group during the trial period and required surgical revision at the same time as the IPG implant ($P < 0.05$). Lead migration during the follow-up year was similar in both groups. No patients had infection of the implant site or complained of implant site pain. There was no evidence of neurologic deficit or dysfunction in any patient.

Discussion

Treatment of disabling NeP remains a challenging issue. Many efforts have been made to understand the mechanisms underlying this clinical condition, whose complexity stems from the contribution of numerous

Table 6 Data on Patient Global Impression of Improvement scale and Clinical Global Impression of Improvement scale

		t2	t3	t4	t5	t3-t2		Global t4-t2		Global t5-t2	
		Mean* (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean of the Difference	*P* Value (Wilcoxon)	Mean of the Difference	*P* Value (Wilcoxon)	Mean of the Difference	*P* Value (Wilcoxon)
PGI	Conv. freq.	2.55 (0.87)	3.00 (1.16)	3.17 (1.56)	3.11 (1.42)	0.45 (1.27)	0.088	0.62 (1.18)	0.010*	0.64 (1.28)	0.014*
	HF	2.35 (0.80)	3.08 (1.55)	3.23 (1.24)	3.31 (1.12)	0.73 (1.34)	0.012*	0.89 (1.39)	0.003*	0.96 (1.45)	0.003*
	P value (MW)	0.367	—†	—	—	0.643		0.611		0.246	
CGI	Conv. freq.	1.66 (0.67)	1.93 (0.92)	2.10 (1.08)	2.07 (1.12)	0.28 (0.88)	0.112	0.49 (0.87)	0.011*	0.50 (0.96)	0.010*
	HF	1.62 (0.50)	2.27 (1.25)	2.27 (0.92)	2.23 (0.82)	0.65 (1.13)	0.010*	0.65 (1.09)	0.007*	0.62 (0.98)	0.005*
	P value (MW)	0.805	—	—	—	0.341		0.659		0.482	

CGI = Clinical Global Impression of Improvement; HF = high frequency; MW = Mann-Whitney; PGI = Patient Global Impression of Improvement.
*This parameter does not follow a normal distribution. Therefore, nonparametric statistical tests were used to analyze changes and compare them between the groups. The most appropriate statistic for nonparametric results is the median; however, given the particular nature of some parameters (semicontinuous variables with only three or four values), the mean and the SD are shown, as this will facilitate the interpretation of results.
†No se comparan los valores entre grupos en cada instante de medición (salvo en t1) pues el enfoque de esta investigación centra su interés en comparar las variaciones entre instantes con el fin de evitar la introducción de sesgo por posibles desviaciones en los valores iniciales o del instante previo.

Figure 8 Patient Global Impression of Improvement (PGI-I) scale. The boxes corresponding to assessment points t4 (six months) and t5 (12 months) in both groups are filled above the median, whereas the box for t2 (follow-up) is not, thus indicating generally higher values of PGI at t4 and t5. In addition, for high-frequency (HF) stimulation, these differences are also seen between t2 and t3 (three months). Fifty percent of the conventional-frequency stimulation group at t5 had better scores than 95% of that cohort at t2, and with the HF group, 95% of them had higher scores than their own group at t2.

Figure 9 Clinical Global Impression–Improvement (CGI-I) scale. It is observed that the boxes corresponding to the instants t4 and t5 in both groups are filled above the median and the box of the instant t2 is not, which indicates, in general, higher values of CGI in the instants t4 and t5. In addition, for high frequency, these differences are also seen between t2 and t3.

Table 7 Complications and side effects

	Conventional SCS Group (N = 29)	HF 10 kHz SCS Group (N = 26)	Standard Difference*
Unsuccesful trial, No. (%)	2 (6.45)	3 (10.34)	ns, 0.446
Lead migration from trial to permanent, No. (%)	0 (0)	4 (10.34)	<0.05
Lead migration with replacement 12 mo, No. (%)	2 (6.45)	1 (3.44)	ns

SCS = spinal cord stimulation.

neurotransmitters and neurological pathways. In FBSS patients, this complexity is further aggravated by the frequent coexistence of nociceptive pain.

In recent years, there has been increasing interest in the neurophysiology underlying the clinical results obtained with new SCS approaches, whose method of operation is beyond the basic mechanism of the gate control theory [48]. Considering that SCS has been used in clinical practice for over 50 years, it is surprising that there is a clear lack of interest in programming parameters other than the perception of paresthesia over the area of pain (assuming an overlap of the therapeutic current field in the metameric area of nociceptive conduction). As expressed by Clark [49], for clinicians, electrophysiological data may be less relevant than the basic conclusion that different stimulation frequencies can provide different levels of benefit in different clinical settings involving different pain syndromes.

A recent article by Miller et al. [50] clearly establishes the idea that programming and clinical outcomes are not based on a single parameter, but on an optimal combination that ultimately generates the effective dose that reaches the critical neural targets and exerts the desired pain-relieving effect. The starting point for the analysis should be the difference between a model with low frequency and high charge per pulse and a model of high frequency with low charge per pulse and high charge per second. There is evidence that frequency is an important determinant for activating specific pain-relieving mechanisms that were associated with endogenous opioid release or activation of dorsal horn GABAergic neurons [50]. On the other hand, weak electric fields can inhibit neurons in the hyperactive state or exert effects on dorsal horn neurons that are inactive or previously active and subsequently sensitized after injury [51–54].

Very little is known about the efficacy of SCS for neuropathic pain in FBSS patients. North et al. [47,55] reported that in patients with postsurgical lumbar arachnoid or epidural fibrosis, SCS is superior to repeated surgical intervention or dorsal ganglionectomy. In their 1991 study [55], the authors report results for a series of 50 FBSS patients (averaging 3.1 previous operations) who underwent SCS implantation. A successful outcome (at least 50% sustained pain relief and patient satisfaction with the result) was recorded in 53% of patients at 2.2 years and in 47% of patients at 5.0 years. The same authors also conducted a prospective study [47] randomizing patients with FBSS to either repeat back surgery or SCS implantation. The six-month cross-over point shows SCS to be effective as a treatment for persistent root pain after lumbosacral spine surgery. In addition, the statistically significant difference ($P = 0.018$) gives SCS the advantage over reoperation.

Kumar et al. [56, 57] randomized 100 FBSS patients with predominant leg pain of neuropathic/radicular origin to receive SCS plus conventional medical management (SCS group) or conventional medical management alone (CMM group) for at least six months. In the intention-to-treat analysis at six months, 24 SCS patients (48%) and four CMM patients (9%, $P < 0.001$) achieved the primary outcome (>50% leg pain relief). Compared with the CMM group, the SCS group experienced improved relief from leg and back pain, quality of life, and functional capacity and expressed greater satisfaction with their treatment ($P \leq 0.05$ for all comparisons) [57]. At the 24-month follow-up, selected FBSS patients reported sustained pain relief, clinically important improvements in functional capacity and health-related quality of life, and satisfaction with treatment [8].

A recent review and meta-regression analysis [58] that attempted to define the predictors of pain relief following SCS in FBSS patients found no strong evidence of an influence of patient-related factors (such as age, gender, initial level of pain and location [i.e., predominant back pain, predominant leg pain, or mixed]), except for mean duration of pain ($P = 0.011$): indeed, each 12-month increase in the duration of pain reduced the degree of pain relief by ~2%.

Considering the foregoing, we must recognize that few variables have been analyzed in published clinical studies on SCS (CF and HF) and that those assessed are generally physical function and disability. Hence the importance we placed on including uncommon but relevant variables in the assessment of functionality, impairment of mood and character, and sleep quality in individuals with FBSS treated with SCS, even though retrospective evidence (level C) from the study by Kelly et al. [59], showed an improvement in physical function and no differences in sleep pattern or quality in terms of

the number of hours of sleep or the ability to fall asleep (level D). Ramineni et al. [60] analyzed the impact of SCS on sleep quality in patients with FBSS and found improvements in the Insomnia Severity Index (ISI) at six months of follow-up (improved pain control).

Appropriate patient selection is essential if we are to establish realistic goals and patient expectations regarding treatment and thus ensure that SCS is successful [61]. Studies are not very homogeneous in terms of their populations, including very different population groups under the umbrella term "back pain" or "back and leg pain," with such diverse origins as degenerative disc disease, spondylosis, spinal stenosis, facet-mediated back pain, or spondylolisthesis. In the study by Kapural et al. [16], only about 85% of subjects in both groups had undergone spinal surgery. Van Buyten et al. [13] and Al Kaisy et al. [15] analyzed the same group of patients, of whom 79.2% had FBSS. The study by Perruchoud et al. [14] included patients with symptoms of chronic low back pain radiating in one or both legs, without specifying their clinical diagnosis and underlying disease. In our study, the inclusion criterion was very restrictive and is unique in the diagnosis of FBSS based on internationally recognized criteria [1,23,24]. Patients with neuropathic pain from FBSS very often had failed conservative treatment, were in greater pain, and had poorer functioning compared with other painful conditions [1,51–53]. This leads us to the key area of patient selection for chronic radicular pain studies and the increasingly notable differences established in the mechanisms of action involved in potential SCS therapies. Such an approach precludes a consistent analysis of groups of patients with mixed and complex patterns involving multiple biological and biophysical elements.

The recent study by Bicket et al. [62] points to the gaps in research on HF SCS for chronic pain. Of the eight articles that these authors selected for their analysis, only two were randomized blinded studies [14,16], whereas the rest were nonrandomized, prospective, open-label studies [13,15,30,63–65]. Van Buyten et al. [13] treated 72 patients with HF SCS at 10 kHz and assessed for up to six months. More than 70% of treated subjects reported significant and sustained relief from back and leg pain without paresthesia. Moreover, there was an improvement in the ODI score and in sleep, as well as a reduction in pain medication use. The AEs observed were the same as those seen with conventional SCS. The same authors recently reported the 24-month follow-up results for these patients [15], and data were available for 65 of the 72 patients (90%). Back and leg pain relief was significant and sustained at 24 months ($P < 0.001$ when the 24-month NRS was compared with baseline): 60% of the implanted patients had at least 50% relief from back pain, and 71% had at least 50% relief, as well as a significant decrease in mean ODI values, subjective sleep disturbances, and opioid intake. A possible limitation of this study is the lack of a control group, which makes it impossible to exclude some placebo effect. The study conducted by Perruchoud et al. [14] included 40 patients who achieved stable pain relief with CF SCS and who were randomized to receive either HF SCS at 5 kHz or a sham control (no stimulation after achieving paresthesia-free stimulation). Complete data were available for 33 patients: the proportion of patients responding under HF SCS was 42.4% (14/33 patients) vs 30.3% (10/33 patients) in the sham group. At the two-week follow-up, the authors found no statistically significant difference between the two stimulation techniques in the PGIC scale, the NRS, and the EuroQoL five-dimensional (EQ-5 D) index. The small sample and the short follow-up limit the interpretation of these data; however, they do suggest that different frequencies may have different effects.

CF SCS for treatment of FBSS has been studied by various groups in recent years; however, the literature on HF SCS for the treatment of FBSS remains scarce. In a recent systematic review [6], of an initial examination of 175 potentially viable articles, 63 were eventually selected. Of these, only six fulfilled the evaluation criteria. Among the randomized controlled trials analyzed, only four reported effectiveness for short- and long-term treatment with CF [46,57] and with HF SCS [14,16]. Given the wide variation in inclusion criteria and lack of clinical homogeneity, no meta-analysis was performed. As the same articles are used in other systematic reviews [6,62,66,67], the results, obviously, are invariably similar.

We think that the methodological issues raised previously are the main reason for the discrepancy between modest pain relief in either arm of this study and the much larger pain relief reported in other studies that have shown delta VAS reductions of 4–6 [13,15,16]. In addition, our approach was progressive: We compared changes over 12 months within the group (intragroup analysis) and compared t1-t5 between the groups (intergroup analysis). In fact, in our study, none of the variables studied revealed differences between the groups, except for variations in the social function score between t1 and t2, which were somewhat higher in the HF group. We are unable to provide an explanation for this result or discuss any specific significance it may have.

In a recent study by Meier et al. [68], patients undergoing permanent SCS treatment of neuropathy were examined using quantitative sensory testing. The authors found no significant changes in perception expressed as sensory detection thresholds and pain, suggesting that active SCS treatment does not change sensory perception. Moreover, SCS effects may be different in short-term and long-term SCS approaches. In their rat NeP model, Shechter et al. [21] suggest that different frequencies may suit different clinical settings involving different pain syndromes. These data, and perhaps the differences between our results and those of previously published studies, indicate that SCS analgesia depends on both the intensity and the frequency of stimulation by

peripheral and spinal segmental mechanisms, although the exact mechanism and final clinical effect need further explanation [7,48].

We observed differences between our study and other studies of reference, such as that of Van Buyten et al. [13], who permitted changes in pain medications and adjustment of stimulation parameters throughout the trial without providing specific data on the protocol or mean number of programming attempts in each group.

Complications were remarkable in the study by Kapural et al. [16], the most common AEs being implant site pain (11.9% of the HF group and 10.3% of the CF group). The only information reported by the authors was the creation of a subcutaneous pocket using a standard surgical technique for placement of the IPG. Van Buyten et al. [13] implanted the IPG subcutaneously in the abdominal wall or gluteal area based on patient and physician preference and reported pocket pain in 31% of patients. In our study, no patients complained of implant site pain, bearing in mind that in all cases, the subcutaneous pocket for placing the IPG was made in the abdominal wall [69–71]. Finally, uncomfortable paresthesia was reported in 11.3% of the CF group in the study by Kapural et al. [16]. In our series, no patients experienced problems with the perception of paresthesia in the CF group. It is difficult to compare our results as the information provided in published studies does not explain how the therapy modalities were presented to patients. In addition, the protocol was not followed in the adjustment of programming performed based on patient feedback at standard clinical visits.

The conclusions of two randomized controlled trials for chronic low-back pain [14,16] were very different when CF SCS was compared with HF SCS. One of the problems for analyzing and comparing the available literature, other than the paucity thereof, concerns the large number of differences in methods, information on stimulation parameters, and lack of standardized evaluation and reporting of events. In many published papers, variables are not tested for normality, and the same statistical tests—usually parametric (*t* test)—are used for all variables. When assessing the patterns of changes in each group, studies directly compare time points between groups; however, we believe that this may not be entirely appropriate. It is our understanding that, in order to ensure an objective evaluation of therapy, instead of comparing the values for each time point between groups, we should compare the changes occurring from time point to time point, so as to exclude potential artifacts introduced by differing baseline values. We also believe that a multivariate approach should be used (repeated-measures analysis of variance). The parametric multivariate approach assesses whether there are changes over time (all time points and by pairs) and whether these are different between groups. The nonparametric approach is truly bivariate: First, it assesses whether there are changes in each group between pairs of time points (Kruskal-Wallis), and then it compares the changes occurring between time points in one group vs another (Mann-Whitney).

The same is true of other waveforms, for example, "burst," which might have mechanisms in common with HF. Burst stimulation, which was recently introduced as a new stimulation modality, combines characteristics of HF stimulation and CF stimulation. The technique uses five high-frequency pulses at 500 Hz (500 Hz = peak frequency) that occur 40 times per second (40 Hz = burst frequency). The pulse width was set at 1 msec, and the amplitude was optimized for each individual patient. Recently, published articles with various methodologies and comparisons showed that burst stimulation proved to be significantly better than placebo stimulation and better for overall pain than CF SCS [72,73] and was equal to HF SCS [65] or superior to it [74]. The new data reported for intractable FBSS warrant more refined, better-designed investigations to determine their efficacy.

Ours was a single-center study with a small sample but an adequate power calculation. It was funded from our departmental resources. We made a special effort to reduce observer bias by blinding outcome evaluators, who can be considered disinterested third parties. Nevertheless, our study is subject to limitations. Given that the sample size of the groups is small, we assumed an alpha error in the detection of results that can serve as a basis or guide for confirmation in subsequent studies with larger samples in which the level of significance could be adjusted for multiple comparisons. It should also be pointed out that according to the statistical methodology we used, the lack of crossover data should not lead us to conclude that therapy that failed at one frequency will not necessarily have failed SCS completely; the patients might still respond to the other frequency (despite the fact that the lead configurations used here were specific to each waveform), and this study would not identify them. Further study, for example, with crossover design, will be necessary to address this.

In conclusion, our results show that the progression of the parameters studied in patients with FBSS does not differ according to whether the frequency of stimulation is conventional or high. In general, in all the parameters, a significant average reduction occurs at the time of the first assessment and a significant global mean reduction occurs at one year, although in a similar way for both groups.

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