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High-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back Pain Patients: Results of a Prospective Multicenter European Clinical Study

Jean-Pierre Van Buyten, MD[1]*, Adnan Al-Kaisy, MD[1†], Iris Smet, MD*, Stefano Palmisani, MD[†], Thomas Smith, MD[†]

Objective: The objective of this prospective, open-label, multicenter European clinical trial was to quantify the efficacy and safety of a spinal cord stimulation (SCS) system that utilizes high-frequency (up to 10 kHz) waveforms, which do not produce paresthesia, for the treatment of chronic, intractable pain of the back and/or limbs.

Material and Methods: Eighty-three patients, with significant back pain, were recruited for a trial of high-frequency stimulation through two percutaneous eight-contact epidural leads. Patients' pain ratings, disability, sleep disturbances, and satisfaction, as well as complication rates, were assessed for up to six months.

Results: After a trial period, 88% (72 out of 82) of patients reported a significant improvement in visual analog scale (VAS) scores and underwent permanent implantation of the high-frequency SCS system. Mean back pain VAS of 8.4 was reduced to 2.7 at six months ($p< 0.001$). Mean leg pain VAS of 5.4 was reduced to 1.4 at six months ($p< 0.001$). Seventy-four percent of patients had greater than 50% back pain relief at six months. There were significant improvements in Oswestry disability score and sleep, and reductions in pain medication use. Adverse events observed were those seen with conventional SCS therapy—lead migration, wound infection, and pain around implant site.

Conclusions: In a cohort of patients with difficult-to-treat chronic back pain, high-frequency SCS provided significant and sustained low back pain and leg pain relief to more than 70% of treated subjects. Notably, this was achieved without paresthesia. Patients also experienced significant improvement in disability and sleep. Overall, the results confirm a favorable safety and efficacy profile of the high-frequency SCS system.

Keywords: axial back pain, failed back surgery syndrome, high-frequency stimulation, low back pain, spinal cord stimulation

Conflict of Interest: Drs. Van Buyten, Al-Kaisy, and Smet received fees related to the presentation of study results at scientific congresses from Nevro Corp. The other authors reported no conflicts of interest.

INTRODUCTION

For more than four decades, spinal cord stimulation (SCS), as proposed by Shealy et al. (1), has been used in treating different pain conditions. SCS has gained wide acceptance for the management of chronic pain secondary to failed surgery (failed back surgery syndrome [FBSS]) as recently described in a review by Van Buyten and Linderoth (2). The PROCESS (Prospective Randomised Controlled Multicentre Trial of the Effectiveness of Spinal Cord Stimulation) study, a randomized clinical trial, demonstrated the superiority of SCS combined with conventional medical management (CMM) over CMM in FBSS patients. Mean pain intensity, as measured using visual analog scales (VAS), decreased with SCS from 7.6 at baseline down to 4.0 at six months for leg pain and from 5.5 down to 4.1 for back pain. However, patients with predominant low back pain were excluded from this study and lower pain reduction was observed in back than in leg pain in the enrolled patients. Despite advances in SCS technology and techniques that allow improved paresthesia coverage, pain relief for patients with predominant chronic back pain has been elusive and patients with predominantly neuropathic leg pain are still widely accepted to be the best candidates for SCS.

The novel Senza™ system (Nevro Corp., Menlo Park, CA, USA) allows high-frequency stimulation (up to 10 kHz) to be delivered to the spinal cord without inducing paresthesia. Preclinical work has

Address correspondence to: Jean-Pierre Van Buyten, MD, AZ Nikolaas, Department of Anesthesia and Pain Management, Moerlandstraat, 1, 9100 Sint-Niklaas, Belgium. Email: vanbuyten@skynet.be

* Department of Anesthesia and Pain Management, AZ Nikolaas, St Niklaas, Belgium; and

† The Pain Management and Neuromodulation Centre, Guy's and St. Thomas' Hospital, London, UK

[1] Both authors contributed equally to the conduct, analyses, and writing of this study.

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Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria

To participate in the study, the patient must meet all of the following criteria:
- Candidate for commercial SCS device
- VAS back pain score > 5 cm (on a 10-cm scale)
- Capable of giving informed consent
- 18 years of age or older
- Able to comply with the requirements of the study visits, follow-up phone visits, and self-assessment questionnaires (e.g., meets language requirements and lives within reasonable distance from the study site)

Exclusion criteria

Patients are excluded from study participation if they meet any of the following criteria:
- Obvious mechanical instability related to pain (diagnosed by imaging taken within the past 12 months)
- Malignancies
- A life expectancy of less than one year
- A systemic infection
- Any active implanted device whether turned off or on
- Already participating in another clinical study
- Pregnant/lactating or not using adequate birth control
- Untreated major psychiatric comorbidity, serious drug-related behavior issues
- Bleeding complications or coagulopathy issues
- Immunocompromised patients at risk for infection or other issues
- Insulin-dependent diabetic who is not controlled through diet and/or medication (determined by the physician)

SCS, spinal cord stimulation; VAS, visual analog scale.

demonstrated that high-frequency stimulation of wide dynamic range (WDR) neurons, which are hyperactive in chronic pain conditions, results in decreased output of these cells (desensitization) and brings them closer to preinjury states (data on file at Nevro Corp.). Control of the "wind-up" phenomena in WDR neurons may be one of the ways this therapy provides pain relief. Preclinical work also was performed to confirm the safety of continuous high-frequency stimulation. Twelve goats were implanted with eight-contact linear percutaneous leads, fitted with an external stimulator, and randomized to receive either no stimulation (control group) or continuous high-frequency SCS (test group) for 10 $\pm$ 1 days. At the end of the test period, the animals were sacrificed and tissue samples were isolated. Microscopic evaluations of the samples performed by veterinary pathologist concluded that there were no morphologic differences between the test and the control groups (3). These findings led to a five-center prospective clinical trial in the United States in which 24 patients completed a temporary trial with high-frequency SCS after they were trialed with conventional SCS. The study showed a reduction of back pain VAS from 8.1 at baseline to 1.9 at end of trial without paresthesia. Furthermore, 88% of the patients preferred high-frequency SCS over conventional SCS (4).

This paper reports the findings from a prospective, multicenter, open-label European clinical study evaluating the safety and efficacy of high-frequency SCS system in the treatment of chronic back pain at six-month follow-up.

METHODS

This study was conducted in two European centers (Belgium and United Kingdom). Both centers obtained ethics committee approvals and all patients provided informed consent prior to engaging in any study-related procedures and assessments. The study was conducted in accordance with local regulations, good clinical practice guidelines (ISO 14155 and U.S. Food and Drug Administration), and the Declaration of Helsinki.

Device Description

The Senza™ rechargeable SCS system received CE Marking in May 2010 for use as an aid in the management of chronic intractable pain of the trunk and/or limbs. Similar to other commercially available SCS systems in design and function, this high-frequency SCS system delivers electrical stimulation to the spinal cord via a pulse generator and one or two leads. However, unlike conventional systems, the high-frequency SCS system is capable of delivering stimulation pulse rates up to 10 kHz.

Patient Selection

To be included in the study, patients had to meet the following criteria: 18 years or older at the time of enrollment; have a primary diagnosis of chronic back pain (defined as lumbosacral pain) with or without leg pain with intensity of at least 5.0 out of 10.0 (average score over the last 30 days) on the VAS; have failed to respond to at least six months of conventional treatment including pharmacologic treatment, physical therapy, epidural injections, and/or radiofrequency therapy (2); able to provide consent; and able to comply with study procedures, visits, and assessments.

Patients were excluded from the study if they met any of the criteria listed in Table 1.

Study Design

Patients who had provided informed consent underwent a baseline evaluation. Within 30 days of the baseline visit, each patient was implanted with either percutaneous trial (United Kingdom) or tunneled trial (Belgium) leads, as per the center's practice, which marked the beginning of the trial phase. The leads were connected to an external trial stimulator and the device was programmed to deliver optimal pain relief (bipolar stimulation up to 10 kHz and current amplitude in the range of 1–5 mA based on patient's preference). Pain severity and level of relief were assessed at the end of the trial

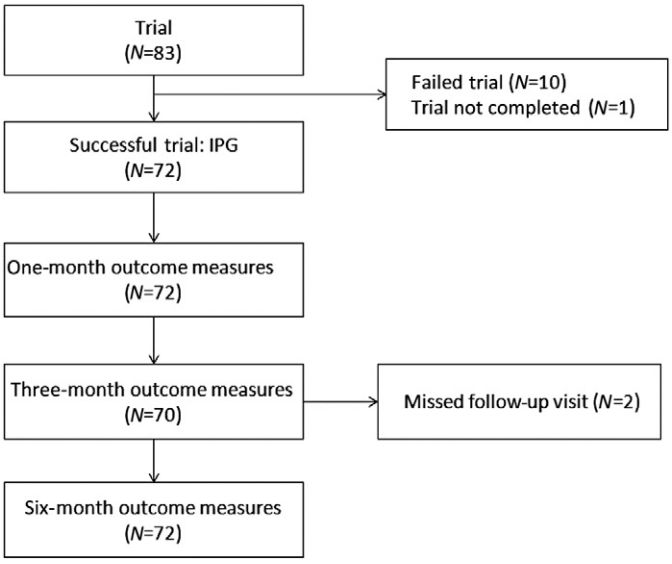

Figure 1. Patient flow. IPG, implanted pulse generator.

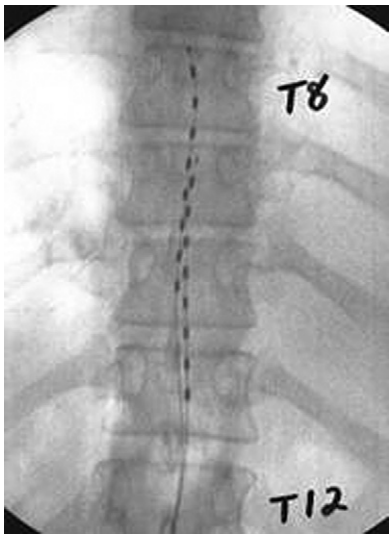

Figure 2. X-ray—dual lead placed at levels T8–T11.

period. Only those patients experiencing a successful outcome during trial stimulation, as determined by the patients and investigators (at least a 50% reduction in pain intensity and able to cope with the requirements of SCS), proceeded to the next phase of the study: permanent implantation of an implanted pulse generator (IPG).

The IPG implant marked the beginning of the permanent implant phase of the study. The IPG was connected to the leads and implanted subcutaneously in the abdominal wall or gluteal area based on patient and physician preference. Permanent lead implantation involved either replacement of the trial leads with permanent leads or internalization of the trial leads, thus making the trial leads permanent. Patients were assessed at one, three, and six months following permanent implant (Fig. 1). Changes in pain medications and adjustment of stimulation parameters were permitted throughout the trial.

Procedures

The trial and implantation procedures followed each center's established method for conventional SCS. For the trial period, the leads were implanted in the epidural space using modified Tuohy needles. In this study, every patient was implanted with two leads, located between the T8 and T11 vertebral levels, staggered to have a maximum number of electrodes over the T9–T10 area (Fig. 2). The IPG was placed in the conventional site of buttock or abdominal wall. Compared with conventional SCS trial and implant procedures, the high-frequency SCS surgical procedure has two key differences: The leads are always inserted at the same vertebral level for both back and leg pain, and there is no need for intraoperative paresthesia testing and programming. The leads were placed between T8 and T11, approximately at the midline, without confirmation for physiologic midline placement. Intraoperative paresthesia programming was performed neither during lead placement of the trial phase nor during the permanent implant, allowing sedation from start to end, providing maximum comfort to the patient.

Therapy was delivered either through the external stimulator or the IPG by continuous bipolar high-frequency constant current stimulation.

Data Collection and Analysis

Baseline data were collected at the time of consent and prior to stimulation with the SCS system. They included VAS rating for back, leg, and overall pain, sleep disturbance as assessed by the number of awakenings per night, and Oswestry Disability Index (ODI). Patients also were asked to rate their satisfaction with the therapy and whether they would recommend it to others, both using a five-point scale. All data were gathered on preprinted case report forms. The administration/collection of the data was performed by the study personnel of each center. The forms were collected and their information was verified during regularly scheduled monitoring visits at each study site.

Descriptive statistics were calculated for each analyzed variable. These include number of observations, mean, median, and standard deviation. Two-tailed paired *t*-test was used to analyze relevant metrics such as VAS. Adverse events (AEs) are reported descriptively for all patients. A *p*-value less than or equal to 5% was considered to be statistically significant.

RESULTS

Between August 2009 and February 2011, a total of 83 patients were enrolled and entered the trial phase of the study, with one patient withdrawing from the study during this phase. Of the 82 patients who completed the trial, 88% (72 patients) had a successful trial and, consequently, underwent permanent implant.

The demographics of the patients at enrollment and permanent implant are summarized in Table 2. The majority of patients enrolled in the study (81% or $N = 67$) had a diagnosis of FBSS, including 14 patients who had previously failed conventional SCS (Fig. 3). Of the 67 FBSS patients who were enrolled, 66 completed the trial with the external pulse generator. Among these 66 patients with FBSS, 57 (86%) had a successful trial. Patients with predominant back pain comprised 87% of the enrolled patients ($N = 72$). Sixty-two of the 72 patients with predominant back pain (86%) had successful trials. The mean duration of the pain condition was 9.7 years for all enrolled patients, 8.9 years for patients with a successful trial, and 15.9 years for patients with a trial failure. Mean baseline back pain VAS score for enrolled patients was 8.4 (out of 10), 8.4 for patients

Table 2. Baseline Patient Characteristics.

	Enrolled (*N* = 83)	Discontinued from study before permanent implant* (*N* = 11)	Permanent implant (*N* = 72)
Gender—*N* (%)			
Female	48 (57.8%)	6 (54.5%)	42 (58.3%)
Male	35 (42.2%)	5 (45.5%)	30 (41.7%)
Diagnosis—*N* (%)			
Failed back surgery syndrome	67 (80.7%)	10 (90.9%)	57 (79.2%)
Chronic pain without prior surgery	16 (19.3%)	1 (9.1%)	15 (20.8%)
Pain type—*N* (%)			
Primary back pain	72 (86.7%)	10 (90.9%)	62 (86.1%)
Primary leg pain	11 (13.3%)	1 (9.1%)	10 (13.9%)
Age—(mean [years] ± SD)	50.4 ± 9.5	47.8 ± 11.1	50.8 ± 9.2
Years since diagnosis—(mean [years] ± SD)	9.7 ± 8.1	14.7 ± 9.6	8.9 ± 7.6
Baseline VAS scores (mean ± SD)			
Back pain	8.4 ± 1.2	8.1 ± 1.1	8.4 ± 1.2
Leg pain	5.4 ± 3.2	5.2 ± 3.3	5.4 ± 3.2

*Ten patients discontinued due to trial phase failure. One patient did not complete trial phase.
SD, standard deviation; VAS, visual analog scale.

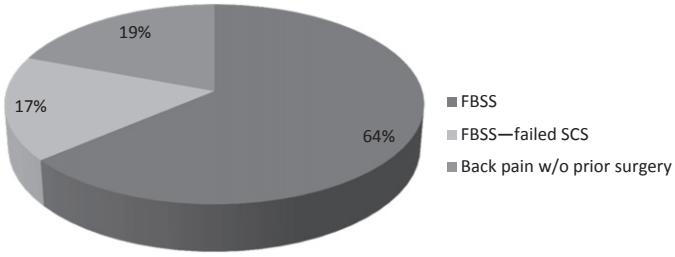

Figure 3. Distribution of back pain diagnoses. FBSS, failed back surgery syndrome; SCS, spinal cord stimulation.

who had a successful trial stimulation, and 8.0 for patients who had trial failure. Mean baseline VAS score for enrolled patients who had leg pain was 5.4 (out of 10).

The 72 implanted patients were evaluated at one-, three-, and six-month postpermanent implant.

At six months, the reported VAS score for back pain was 2.7 compared with 8.4 at baseline (Fig. 4), a 78% median reduction. VAS scores corresponding to leg pain also decrease from 5.4 at baseline to 1.4 at six months, yielding an 83% median decrease. The reduction in back and leg pain was statistically significant ($p< 0.001$). Seventy-four percent of patients had greater than 50% pain relief and 47% of the patients had greater than 80% pain relief.

ODI and sleep disturbances at six months postimplant were significantly lower as compared with baseline. Mean ODI values decreased from 55 at baseline down to 37 ($p< 0.001$), and 57% of patients had an improvement of 14 points or more (Fig. 5). Mean sleep disturbances decreased from 3.7 at baseline to 1.3 at six-month follow-up ($p< 0.001$, Table 3).

While opioid use was widespread among patients prior to the study (86%), it was reduced in 62% and eliminated in another 38% of patients during follow-up.

Eighty-five percent of patients were satisfied or very satisfied with the high-frequency SCS system, and 85% of them would recommend or highly recommend it to others with similar pain.

Among the 83 patients who had undergone trial and/or permanent implants, a total of 51 AEs were reported in 38 patients (46%). A summary of these AEs is provided in Table 4. The most commonly occurring AEs were pocket pain (31% of events) and lead migration (22% of events). Thirteen patients required re-interventions to solve these AEs. Both centers performed neurologic assessments at baseline and during the follow-up period on their patients, without any indication of neurologic deficit. Additionally, a comprehensive medical review of the neurologic data was conducted by a panel of four neurologists not involved in the study. This Neurological Advisory Panel concluded that there was no evidence of clinical signs or symptoms of spinal cord neurologic deficit or dysfunction that could have been caused by the spinal cord stimulator implant and/or its use.

DISCUSSION

This prospective multicenter study, one of the largest prospective SCS studies conducted to date, shows that high-frequency SCS provides significant pain relief in patients with chronic back pain. Notably, there are limited data supporting the use of conventional SCS in low back pain patients. However, in this study, 72 out of 82 patients (88%) trialed with high-frequency SCS had positive results and underwent permanent implantation. At six-month follow-up, 74% of the patients experienced at least 50% pain reduction (VAS score back pain). The ODI decreased significantly, sleep disturbance was improved, and patient satisfaction with the therapy was high. The safety profile of this novel therapy is similar to the one of conventional SCS, with pocket pain and lead migrations being the most common AEs.

It is a commonly accepted fact that when using conventional SCS, paresthesia must cover the pain area to alleviate pain. Creating adequate paresthesia coverage during the lead implantation is often a lengthy process that requires a cooperative patient and repeated cycles of creating stimulation patterns, checking for adequate paresthesia coverage, and adjusting lead locations. Additionally, in FBSS patients, anatomic paresthesia coverage is required (5–8) but is often not sufficient to provide adequate low back pain relief, leading to disappointing clinical benefits (9,10).

The lead positioning for high-frequency SCS is straightforward: Two leads are placed staggered under fluoroscopic control between

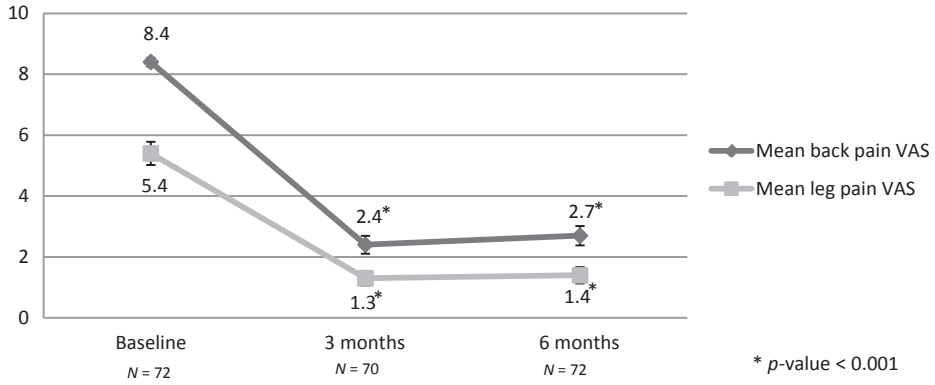

Figure 4. Back and leg VAS scores, change from baseline by visit with ± standard error of the mean. VAS, visual analog scale.

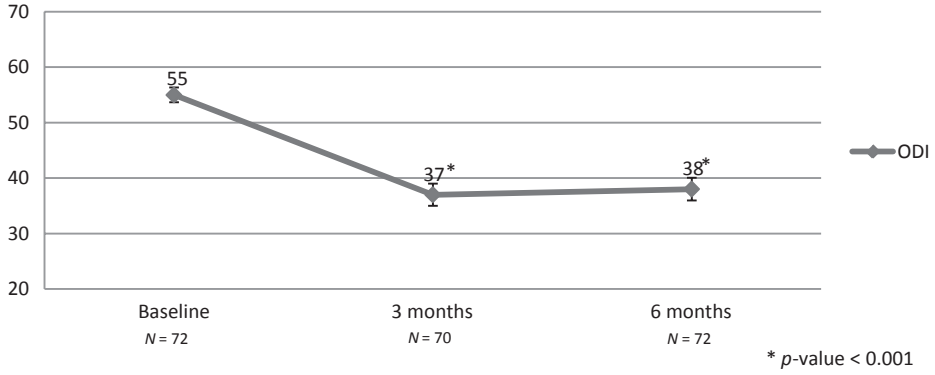

Figure 5. Oswestry Disability Index (ODI), mean change from baseline by visit with ± standard error of the mean.

Table 3. Sleep Disturbance Mean Change From Baseline by Visit.

	Month 3 (*N* = 69) Baseline Mean ± SD	Change from baseline Mean ± SD	*p*-Value	Month 6 (*N* = 70) Baseline Mean ± SD	Change from baseline Mean ± SD	*p*-Value
Sleep disturbances	3.8 ± 3.1	−2.4 ± 3.4	<0.001	3.7 ± 3.1	−2.4 ± 2.9	<0.001

SD, standard deviation.

T8 and T11 approximately at the midline without confirmation for physiologic midline placement. There is no need for intraoperative paresthesia testing and patient feedback. This not only makes the procedure time predictable and shorter compared with conventional SCS but also allows the use of deep sedation during the whole procedure, making it more comfortable to the patient.

Lack of paresthesia translates into significant clinical benefit for the high-frequency SCS system. In an independent patient survey, 71% of conventional SCS users reported uncomfortable stimulation with position change and 66% adjust or turn off stimulation (11). This jolting and uncomfortable stimulation associated with postural changes and physical activity, commonly seen in conventional SCS, is not a concern for patients using high-frequency SCS. Moreover, paresthesia-free stimulation allows for comfortable nighttime use and restoration of sleep quality. Lastly, in contrast to conventional SCS, it also may allow patients to drive automobiles as jolting and uncomfortable stimulation associated with paresthesia is not a concern.

In addition to these significant clinical benefits, the lack of paresthesia opens the possibility of conducting double-blind placebo controlled studies of SCS.

While it is performed in patients with neuropathic pain and in the FBBS population, the conventional SCS therapy is focused on leg pain due to the difficulty of treating back pain (12,13). This study enrolled mainly a population of FBSS patients with predominant back pain. The high trial success rate (88%) and the significant clinical benefits observed in treating both back and leg pain offer an exciting new option in this difficult and large group of patients.

While most of the patients in this study were FBSS, 19% of the enrolled patients had no prior back surgery. Fifteen of these 16 patients passed the trial, which represents a 94% trial success rate. The mean VAS back pain for this cohort was 8.1 at baseline and was

Table 4. Complications.

Device-related adverse events	# of events (serious)	# of patients with event	% of patients with serious event
Pocket pain	16 (5)	15	6.0%
Lead migration	11 (2)	11	2.4%
Wound infection*	5 (4)	5	4.8%
Muscle cramps/spasms	5	5	0%
Hematoma/seroma/implant site edema	5	5	0%
Temporary nerve irritation	2	2	0%
Skin irritation†	2	2	0%
Loss of therapy effect	1 (1)	1	1.2%
Suboptimal lead placement‡	1 (1)	1	1.2%
Thrombosis	1	1	—
Other	2	2	—
Total	51 (13)	38	15.7%

*Four infections were in the trial phase and one in permanent phase.
†Due to bandages postprocedure.
‡Occurred in trial phase.

reduced to 2.6 at six months, an 81% median reduction. The mean VAS leg pain for this cohort was 5.9 at baseline and was reduced to 1.2 at six months. If these results are verified in additional studies, high-frequency SCS may represent an earlier therapeutic option, ahead of spine surgery, in the treatment algorithm for chronic back pain given it is a less invasive and fully reversible procedure.

Patients who have failed conventional SCS also constitute a notable subset. A significant number of patients fail SCS trials each year or lose efficacy after IPG implant. The key causes have been noted to be inadequate paresthesia coverage over the pain area, lack of pain relief despite paresthesia coverage, and dislike of paresthesia (14). For these patients, few therapy choices remain. Fourteen patients who had previously failed conventional SCS were trialed with the high-frequency SCS system in this study. Eleven of the 14 patients (79%) had a successful trial, suggesting different mechanisms of action for the two SCS modalities. The mean VAS back pain was 8.9 for this cohort but was reduced to 2.0 at six months. The mean leg pain score was 7.7 but was reduced to 1.9. High-frequency stimulation seems to offer promise for this difficult-to-treat cohort with very limited therapeutic options.

Future studies in this and other patient populations are warranted to investigate whether the observed efficacy and paresthesia-free pain relief benefits observed in this study could be applied to other patient cohorts not fully served by conventional therapy.

Many studies have shown that SCS is a safe therapy for chronic pain. These studies have reported complications in 20–75% of patients, which were generally minor and correctable (15–17). The AEs with high-frequency stimulation reported in this study are similar to those observed with conventional SCS. Pocket pain, the most common AE, may be related to the shape of the device as observed with conventional SCS devices from other manufacturers. A differently shaped IPG is likely to decrease the incidence of such events.

Eighty-five percent of the patients were satisfied with the therapy and would recommend it to others. Feedback from the study patients indicates that the need for more frequent charging compared with conventional SCS does not impact patient satisfaction. Recharging typically takes about an hour and patients seem happy to accept this in view of the benefits derived from high-frequency stimulation. Despite more frequent charging, no battery-related device failures or malfunctions were observed during the study.

The major limitation of this study lies in the fact that this was a single arm study, without a concurrent control group. Therefore, the placebo effect cannot be quantified (18). However, the return of pain in patients, either during trial due to lead disconnection or during follow-up due to lead migration (as documented by x-ray), and the recovered pain relief upon the resolution of these issues provide evidence for a real physiologic effect of high-frequency stimulation.

CONCLUSION

The results from this clinical study demonstrated that patients with chronic, intractable back and leg pain had significant pain relief after six months with the high-frequency SCS system. The decreased VAS pain rating for both back and leg was consistent throughout the study and was associated with improvements in disability with no perception of paresthesia. The high-frequency SCS system appears to be efficacious in many back pain patients that fail to benefit from conventional stimulation. The number and types of AEs reported in this study were similar to those previously published for conventional SCS devices. The high-frequency system delivered substantial benefits and would be a valuable therapeutic option for this group of chronic pain sufferers in whom conservative medical management has failed. Longer-term data are being collected to confirm the sustained efficacy and safety profile of this novel therapy.

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Authorship Statements

Drs. Van Buyten and Al-Kaisy designed and conducted the study, including patient recruitment, data collection, and data analysis. Drs. Smet, Smith, and Palmisani recruited patients and collected data. Drs. Van Buyten and Al-Kaisy prepared the manuscript with

important intellectual input from Drs. Smet, Palmisani, and Smith. All authors approved the submitted version of the manuscript.

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