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Prospective Study

Multi-waveform Spinal Cord Stimulation with High Frequency Electromagnetic Coupled (HF-EMC) Powered Implanted Electrode Array and Receiver for the Treatment of Chronic Back and Leg Pain (SURF Study)

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Background: Externally powered spinal cord stimulation technology can be fully implanted when trialing the effectiveness of the therapy, since no percutaneous leads are needed, and the trial period lasted 30 days. Multiple tests of different stimulation modalities and parameters are possible, thus improving the chances that the therapy will lead to effective pain reduction.

Objectives: The objective of this study was to analyze the effectiveness of the Freedom Spinal Cord Stimulator System (Stimwave LLC, Pompano Beach, FL) for the treatment of failed back surgery syndrome due to postlaminectomy syndrome utilizing multiple waveforms.

Study Design: This was a prospective, single cohort study. Patients were enrolled and implanted with up to 2 permanent, 8-contact neurostimulators (electrode arrays and separate receivers). Pain and overall improvement were evaluated at 3 months and 6 months following an initial one-month implanted trial period.

Settings: A variety of frequency stimulation waveforms (tonic as well as subthreshold) at frequencies of 10 Hz to 1500 Hz* and 50 to 800 µs pulse width, were provided. (*Note: While 1500 Hz was utilized in the study, Stimwave Technologies is currently only permitted to provide spinal cord stimulation therapy at frequencies below 1500 Hz, therefore pulse rates used in this study are not commercially available on Stimwave Technologies' products).

Methods: Endpoints evaluated included the Visual Analog Scale (VAS) for pain intensity, Oswestry Disability Index (ODI) for functionality, Patient Global Impression of Change (PGIC) for overall health improvement, and quality of life as measured by the European Quality of Life 5 Dimension questionnaire (EQ-5D-5L).

Results: Thirty-nine patients completed the study. At 6 months, the responder rate (≥ 50% reduction VAS for back pain) was 33/39 = 85%. Mean VAS for back pain decreased 62%. The mean ODI decreased 46% from 54 to 29.2, indicating a reduction from severe to moderate disability. The median satisfaction as measured with the PGIC was 6 out of 7. The mean EQ-5D-5L utility score increased from 0.54 to 0.75. At the 6-months endpoint, 44% (17/39) of patients preferred tonic stimulation with a back pain per protocol responder rate of 82%; 41% (16/39) preferred surge with a responder rate of 56%; and 15% (6/39) preferred high density, with a responder rate of 83%. Fifteen patients reported 28 adverse events. Migration of the electrode array (n = 10) was the adverse event most reported. Two serious adverse events related to infection were reported.

Limitations: This study had several limitations. Trial failures were excluded from the analysis, there was a small sample size, and there was a lack of blinding due to the suprathreshold nature of tonic stimulation.

Conclusion: The study demonstrates that spinal cord stimulation with multiple stimulation patterns demonstrates clinical and functional efficacy when using an externally powered stimulation system.

Key words: Chronic back pain, chronic leg pain, lumbar postlaminectomy syndrome, postlaminectomy syndrome, neuromodulation, externally powered spinal cord stimulation, HF-EMC

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Chronic pain affects more than 90 million Americans and causes direct and indirect costs of over $635 billion annually (1). Repeated spine surgery may lead to chronic pain, which can have a significant effect on quality of life (QoL) due to physical impairment, functional disability, and long-term psychological insults resulting in depression and emotional distress (2). Chronic pain significantly contributes to loss of work (1). Low back and neck pain are leading causes of disability worldwide, with pain conditions among the top 10 causes of disability (3-5).

Physiotherapy and nonsteroidal anti-inflammatory drugs are among the initial treatments of choice for chronic pain patients. Other pharmacotherapy, including opioids, can result in dependence, addiction, abuse, overdose, constipation, hormone imbalance, hyperalgesia, respiratory or immune dysfunction, and death (6). Interventional pain procedures such as injections of local anesthetics and steroids can be an effective tool but are often limited by a short duration of effect and have no predictive value when considering other irreversible therapies such as radiofrequency ablation (7). Traditional spinal cord stimulation (SCS) has consistently demonstrated effectiveness for the management of chronic pain due to postlaminectomy syndrome (7).

Many SCS devices include an implanted pulse generator (IPG) or a receiver with external transmitter (externally powered SCS), that delivers a stimulation pulse with a programmable amplitude, pulse duration, and pulse frequency to a neural tract innervating discrete pain areas (8). Historically, tonic stimulation necessitated overlapping paresthesia in areas affected by pain (9). More recent stimulation patterns with higher frequencies have demonstrated success with paresthesia-free subthreshold algorithms (10).

Externally powered technology with high-frequency electromagnetic coupling (HF-EMC) can be fully implanted during a trial, eliminating the need for a percutaneous electrical connection, thereby allowing for an extension of the trial phase as long as necessary, and enabling testing of as many settings and waveforms as needed to achieve and confirm success of treatment (11,12). If the patient is a responder, the device can then be left in permanently; there is no need to remove or implant different hardware components such as a pulse generator and extension leads, which obviates additional discomfort to patients and eliminates additional cost to payers (12-14).

This study was prospective, including patients at multiple centers with chronic low back pain or back and leg pain due to postlaminectomy syndrome (PLS). Patients were implanted with the externally powered Freedom SCS System (Stimwave LLC, Pompano Beach, FL); multiple stimulation modalities were used.

Methods

Device Description

The Freedom SCS system (Fig.1) treats chronic intractable pain by targeting the central nervous system.

Fig. 1. *The Freedom-8 SCS and 4 PNS neurostimulator electrode arrays have 8 or 4 contacts.*

The technology uses a wireless energy transfer with high frequency electromagnetic coupling (HF-EMC) from the Wearable Antenna Assembly to the implanted electrode array and receiver. Each electrode array contains 4 or 8 contacts (1.3 mm in diameter with 4 mm spacing) with an embedded chip, circuitry, and is connected to a separate receiver. The Wearable Antenna Assembly is composed of a flexible fabric, antenna, and rechargeable transmitter worn as needed. The neurostimulator device relieves pain by sending electrical stimulation to specific nerve locations where the pain is present and then blocks those pain signals from reaching the brain.

In this study, pulse rates of up to 1500 Hz* were tested. (*Note: While pulse rates at 1500 Hz were utilized in this series, stimwave is only permitted to provide spinal cord stimulation therapy at frequencies below 1,500 Hz, therefore pulse rates used in this series are not commercially available on Stimwave Technologies products.)

Study Design

Seven sites participated in the study after approval of the respective investigational review boards. After informed consent, patients with chronic back pain or back and leg pain refractory to conservative management for at least 12 months following spinal surgery were offered participation. Patient selection criteria included: men or nonpregnant women diagnosed with chronic back pain or back and leg pain with an average baseline back pain visual analog scale (VAS) ≥ 5 (on an 11-point scale) during the last 14 days in their pain diary; a chronic back pain or back and leg pain diagnosis resulting from PLS; stable pain medication regimen; no anatomic contraindications to the placement of the device; able to operate the patient programmer, recharge the equipment or manage the diary; able to undergo study assessments and provide accurate responses; suitable surgical candidacy for implant; ability to attend follow-up visits; neurologically and psychosocially appropriate for the implant according to the assessment of a clinical psychologist; capacity to give informed consent; and living reasonably near to the study site.

Exclusion criteria included: mechanical instability related to pain; unresolved malignancies; postherpetic neuralgia; active systemic infection or immunocompromised; a psychological diagnosis such as psychosis, suicidal tendencies, borderline personality disorder, somatization, narcissism, or health conditions (e.g., substance abuse, another chronic condition requiring the regular use of opioid medication); uncontrolled diabetes through diet and/or medication; bleeding complications or coagulopathies; life expectancy of less than one year; any active implanted device whether turned off or on; previous spinal cord stimulation experience; or any conditions requiring magnetic resonance imaging evaluation or diathermy procedures.

Patients received multiple waveform stimulation parameters (5 Hz–1500 Hz*, n = 49) during the study (Fig. 2). Thirty days after the implantation of the device, patients were classified as trial responders or trial nonresponders. Trial responders achieved a > 50% VAS change for back pain and were then evaluated subsequently at one, 3, and 6 months. Trial nonresponders exited the study. This study design was selected to allow nonresponding patients to seek alternative treatment options. (*Note: While 1500 Hz was utilized in the study, Stimwave Technologies is only permitted to provide spinal cord stimulation therapy at frequencies below 1500 Hz, therefore pulse rates used in this study are not commercially available on Stimwave Technologies' products).

The primary endpoint was the percentage of patients with ≥ 50% pain relief as measured by VAS compared to baseline at the end of an additional 6 months of follow-up without an increase or change in type of pain medication. The following secondary endpoints were evaluated at the end of 6 months: percentage VAS change from baseline for back pain and leg pain, change from baseline functionality using the Oswestry Disability Index (ODI) score, percentage of patients who

Fig. 2. *Stimulation schemes used during the study. The patients could choose between the 3 stimulation schemes shown: Tonic (suprathreshold), Burst and high density* (subthreshold). (*Note: While 1500 Hz was utilized in the study, Stimwave Technologies is currently only permitted to provide spinal cord stimulation therapy at frequencies below 1500 Hz, therefore pulse rates used in this study are not commercially available on Stimwave Technologies' products).*

responded to SCS therapy at the end of the one-month trial period, patient therapy satisfaction measured by the Patient Global Impression of Change (PGIC), changes from baseline in the European Quality of Life 5 Dimension questionnaire (EQ-5D-5L), frequency of sleep disturbances, and trial responder rate. Incidence of device-related adverse events were also recorded.

Implant Technique and Programming

One (or 2) individual externally powered neurostimulators (electrode array and separate receiver) were implanted through a first incision leading to the patients and were anatomically positioned with the distal electrodes midline at the T8 and T9 vertebral levels (Fig. 3). The electrode arrays were implanted through a first incision leading to the epidural space using a 13G Tuohy needle and standard technique. Intraoperative testing was done to verify functionality of the system(s). The steering stylet(s) were removed and separate receiver(s) connected to the electrode array(s). Receiver pocket(s) were created using a second incision, and the electrode array(s) were tunneled beneath the skin from the first incision to the receiver pocket(s). A knot was tied to permanently connect the separate receiver(s) and electrode array(s). The proximal portion of the neurostimulator(s) were coiled, sutured to itself while eliminating any sharp ends, and then the coil sutured to the fascia within the pocket(s) to prevent migration. The pocket(s) were then closed with subcutaneous and then subcuticular sutures. There was no temporary percutaneous trial; instead, all patients received a permanent neurostimulator system. At the 30 day follow-up, nonresponders (defined as having < 50% relief of back pain while stimulated) could request the explant of the neurostimulators (electrode array and separate receiver) or opt for leaving in situ.

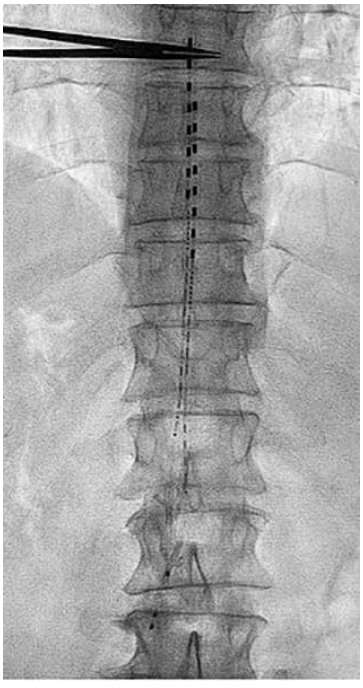

Fig. 3. *AP image showing distribution of 2 8-contact neurostimulator electrode arrays with the receiver spanning the T8-T11 vertebral levels in the epidural space representative of the positioning for all patients in the study.*

The devices were programmed immediately following the implant to provide multiple waveforms (5 Hz–1500 Hz* and 50 μs–800 μs). Figure 2 shows the stimulation schemes that were used:

- Tonic: 60 Hz-120 Hz; 50 μs -500 μs, mA outcome based (paresthesia).
- Surge: 500 Hz; 4 pulses; 800 μs; 40 Hz burst frequency; passive-active combination recharge phase, mA outcome based (subthreshold).
- High density: 1000 Hz-1500 Hz*; 30-44 pulses; 30 μs; 33 Hz burst frequency, active recharge phase, mA outcome based (subthreshold). While pulse rates at 1500 Hz were utilized in this series, stimwave is only permitted to provide spinal cord stimulation therapy at frequencies below 1,500 Hz, therefore pulse rates used in this series are not commercially available on Stimwave Technologies products.

Patients were sequentially exposed to all 3 stimulation schemes throughout the trial period and selected the waveform that provided optimal analgesia. Once they chose a waveform, therapy was customized based on patient feedback.

Patients received 2 external rechargeable transmitters. This allowed patients to switch out their externals when the battery depleted, thus not losing therapy. The antenna was placed over the area where the receiver was implanted (over one clothing layer) to transmit the power to the implanted neurostimulator for a minimum of 8 hours per day without an IPG. No patients reported any issues or difficulties related to antenna placement.

Data Collection and Analysis

Data were recorded at baseline and throughout the study on case report forms or questionnaires. The integrity and quality of the data were assessed periodically by an independent research organization and a data safety monitoring board. VAS data were reported as raw scores, means, and percent change from baseline. Additionally, the ODI, the PGIC, the EQ-5D-5L, and

the frequency of sleep disturbances were recorded. Stata 16 (StataCorp LLC, College Station, TX) was used for all analyses. Trial nonresponders were excluded from the per protocol population. Secondary endpoints were also evaluated. Post hoc analyses were performed to test for comparisons of the 3 waveforms and compare responder rate and average VAS back pain and leg pain with a historical control based upon key literature.

Adverse events (AEs) were reported in the modified intent-to-treat population (mITT - patients who received an implant) and classified as serious AEs or nonserious AEs, and as related or nonrelated AEs.

Results

Sixty-eight patients failed screening and 49 were implanted with one or 2 8-electrode arrays within the dorsal epidural space, with the most distal electrode positioned at the T8 and T9 vertebrae levels. After the receiver was advanced through the lumen of the electrode array and mated with the electrodes, the stimulator was then tunneled subcutaneously.

At the 30-day visit, 40 patients were considered primary endpoint responders. In 8 patients, the devices were explanted, since the therapy was ineffective, even though the device is magnetic resonance imaging compatible and could in fact remain in situ to prevent further surgery. One patient was allowed by the medical monitor to continue in the study since the device yielded a 46% decrease in back pain and a 74% decrement in leg pain. At one month after the trial period (60 days following implant), 37 patients completed the data collection. One patient withdrew consent due to lack of efficacy, and 3 patients presented with missing data (all 3 patients presented at 3 months). At 3 months after the initial trial period, 39 patients completed data collection. An additional patient withdrew consent due to lack of efficacy. At 6 months after the trial, 39 completed data collection (Fig. 4).

Table 1 presents baseline demographics and characteristics for all implanted patients. The mean age of the patients was 59.96 ± 11 years, and 22 of the patients were women. The patients' average pain duration was 12.48 ± 10 years prior to entering the study. Four out of 49 (8%) patients reported back pain only.

Trial Phase Result

The trial responder rate (≥ 50% VAS reduction for back pain compared to baseline) was 40/49 = 82% ($P < 0.001$), giving 95% confidence that the rate is no lower than 71%.

Primary Endpoint

The patients were classified as primary endpoint responders if they achieved > 50% back pain reduction at 6 months compared to baseline. Eighty-five percent (33/39) of the patients responded to the stimulation ($P < 0.001$), giving 95% confidence that the rate is no lower than 72%. At the 6-months endpoint, 44% (17/39) of patients preferred tonic stimulation with a back pain per protocol responder rate of 82%; 41% (16/39) preferred surge with a responder rate of 56%; and 15% (6/39) preferred high density with a responder rate of 83% (Fig. 5).

Secondary Endpoints

Figure 6 shows the mean back/leg pain VAS scores. At 6 months, mean VAS for back pain decreased 62%. At 6 months, mean VAS for leg pain decreased 60%. Additionally, back pain remission, defined as VAS for back pain of 25 mm or less, was analyzed. Patients with a preference for tonic stimulation reported a back pain reduction of 69% and leg pain reduction of 66%. Patients preferring surge had a back pain reduction of 50% and leg pain reduction of 49%. Patients choosing high density reported a back pain reduction of 64% and leg pain reduction of 58% (Fig. 5). Post-hoc com-

Fig. 4. *Patient flowchart.*

Table 1. *Basic demographics and characteristics (n = 49).*

LF (n = 49)	
Age (Mean, SD)	59 (11)
Gender (n, %)	Male: 27 (55%), Female (22 (45%)
Height (Inch) (Mean, SD)	66.7 (3)
Weight (Pound) (Mean, SD)	181 (44)
Primary Region of Pain (n, %)	Lower Back: 34 (69%), Leg: 13 (27%), Equal: 2 (4%)

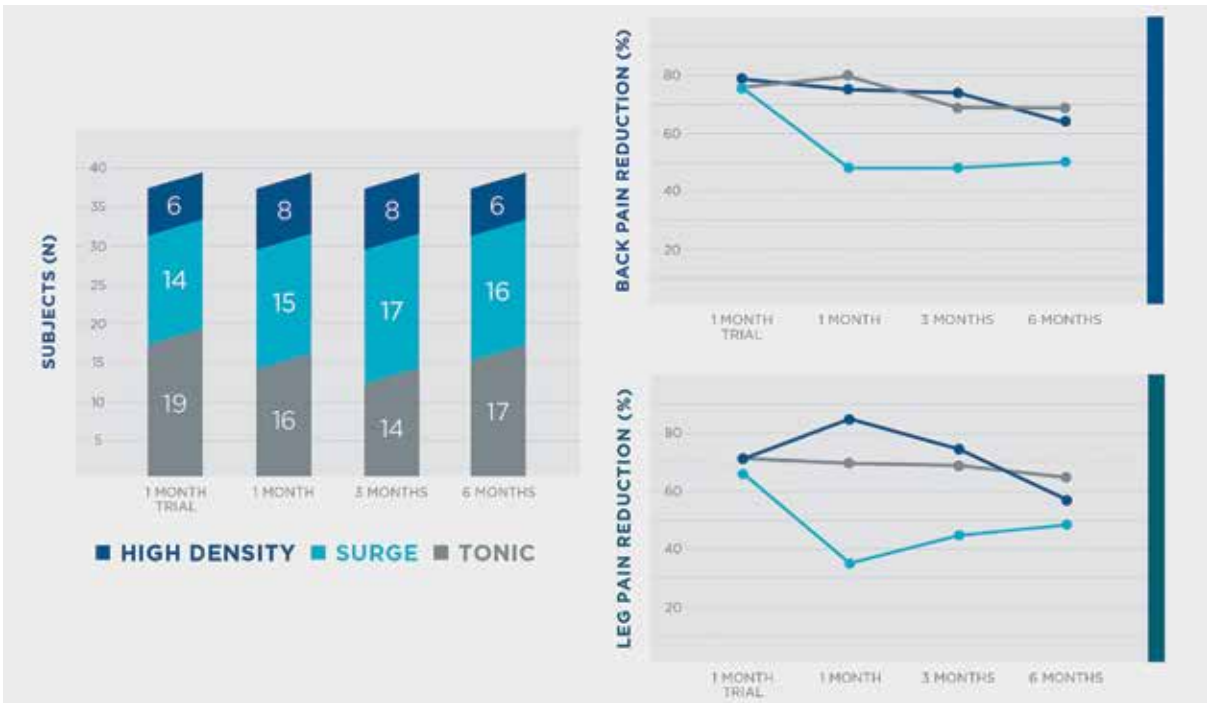

Fig. 5. *Preferred waveforms back pain/leg pain VAS.*

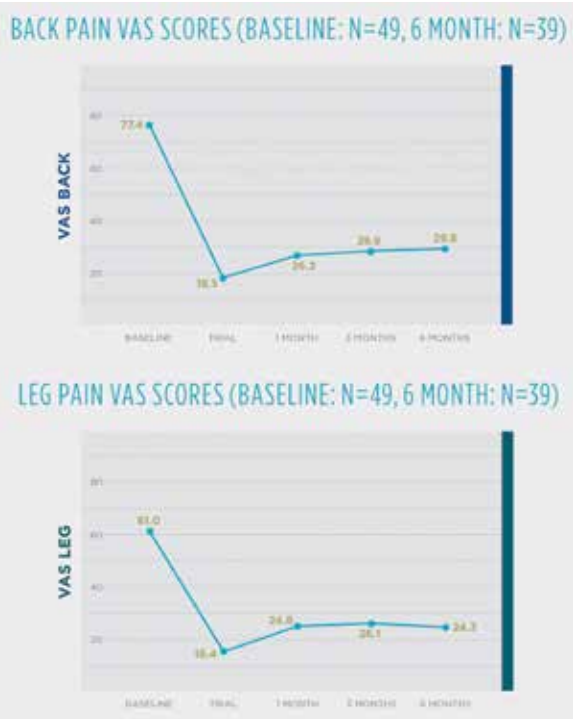

Fig. 6. *Back/leg pain VAS scores (baseline: n = 49, 6-month: n = 39).*

parisons of baseline, 6 month, and average improvement at 6 months in VAS back pain relief did not vary among the 3 waveforms ($P > 0.25$) and suggest all 3 are effective at reducing pain. Rates from recent literature of SCS trials (15-17) were used to generate estimated performance for other SCS treatments, with an expected proportion of responders of 67% at 6 months, and an average improvement in low back pain and leg pain of 3.6 and 2.7 respectively. Post-hoc tests for superiority and 95% confidence intervals demonstrated that externally powered spinal cord stimulation performed better than the derived control ($P < 0.02$, Table 2).

Forty-one percent of all patients experienced back pain remission (Fig. 7).

Figure 8 shows the decrease in disability with the ODI score. At 6 months, mean ODI decreased 46% from 54 to 29.2, indicating a reduction from severe to moderate disability. The median satisfaction as measured with the PGIC was 6 out of 7.

The mean EQ-5D-5L utility score at 6 months increased from 0.54 to 0.75 (Fig. 8).

Quality of sleep improved dramatically with patients reporting sleeping 18% longer on average. Similarly, sleep disturbances (awakenings) were reduced 17%.

Safety Results

In the intention-to-treat population, 2 patients reported treatment-related serious AEs: 2 infections that required hospitalization. These 2 serious AEs resolved after removing the system and administering antibiotic therapy. One patient was reimplanted once the infection cleared. Fifteen of 49 implanted patients reported 28 AEs. The most common adverse event reported was migration of the electrode array. Other AEs included incisional pain (n = 4, 8%), and uncomfortable stimulation (n = 2, 4%). Table 3 shows the serious AEs and AEs recorded by treatment group. Upon the discovery of migrations, locking anchors were subsequently employed for the rest of the study. In addition, it was observed that adverse event rates decreased with increased implanter experience. The highest recruiting sites noted the smallest AEs and revision rates (Fig. 9) After the introduction of a locking anchor and increased implanter experience, AE rates drastically reduced (Q2 2017). The same was observed for revisions as a result of the above-mentioned AEs (Fig. 10).

Discussion

Pain Reduction

Eighty-five percent of patients achieved at least 50% pain reduction at 6 months following implant of the externally powered Freedom SCS System. These analgesic outcomes exceed those demonstrated by traditional SCS with an IPG. De Vos (18) reports that 71% of patients experienced > 50% pain relief for leg pain and 51% of patients experienced > 50% pain relief for back pain after SCS. Single-stage Freedom SCS System implants enable the treating physician to test different schemes and waveforms during a trial period that can be as long as required. There was a high rate of successful trials using multiple waveforms customized to the needs of the patients. The need for individualization is supported by the results of the PROCO study (16). That study, while not using the Freedom SCS System, demonstrated that the efficacy of SCS is independent of the stimulation frequency (1 kHz, 4

Table 2. *Comparison of SURF with historical control data.*

Endpoint	Summary	95% Confidence Interval	Historical Control Rate (HC)	*P* Value
6M Responder rate (≥ 50% improvement in back pain)	84.6% (33/39)	(69.5%, 94.1%)	67%	<0.001
6M Improvement in back pain (scaled down to 0-10)	4.8±2.7	(4.0, 5.7)	3.6	0.0070
6M Improvement in leg pain (scaled down to 0-10)	3.8±2.8	(2.9, 4.7)	2.7	0.0193

* Exact binomial confidence interval (CI) for responder rate, CI for the mean for improvement in back and leg pain

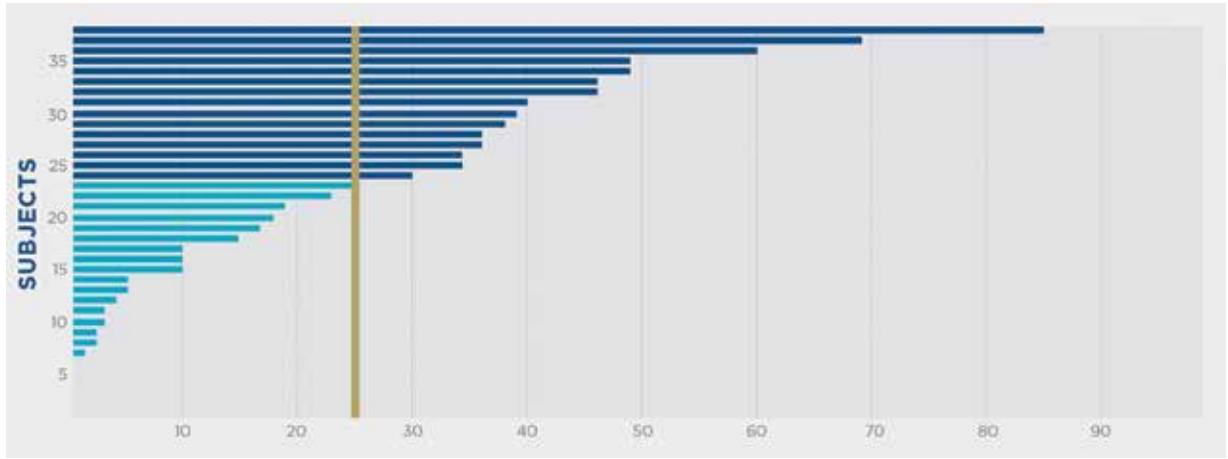

Fig. 7. *At 6 months, the remitter rate was 41%.*

Fig. 8. *Functionality (measured by Oswestry Disability Index) and EQ-5D-5L utility score.*

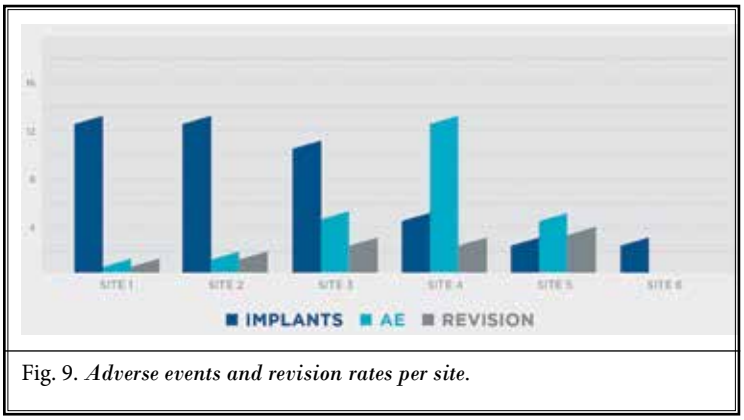

Fig. 9. *Adverse events and revision rates per site.*

Table 3. *Adverse events mITT (n = 49).*

AE's Treatment Related (n)	2
Events (n)	28
Patients (n)	15
Type of Adverse Event	
Stimulator Migration	10
Incisional Pain	4
Device Failure	4
Increased Stimulation	2
Stimulator Breakage	2
Infection	2
Other	2
Erosion	1
Unintended Stimulation	1

kHz, 7 kHz, and 10 kHz) and a titration of pulse-width and amplitude are required to obtain optimal results at different frequencies.

ODI and QoL

We observed changes in quality-of-life instruments, including the EQ-5D-5L. It is very difficult to show improvement in a generic quality-of-life instrument like the Short-Form (SF-36) Health Survey or EQ-5D-5L when a single condition is treated (19). Others have similarly shown that when addressing a single diagnosis, condition-specific quality-of-life instruments like the ODI are more sensitive to interval changes.

Safety Profile

The most common AE reported was stimulator migration. This was thought to be attributed to inadequate tensile strength of the passive silicone anchor that was used during the study. Upon the discovery of these early migrations, locking anchors were then employed for the remainder of the study. With increasing implanter experience, AE rates and revisions were inversely affected and stabilized. Since the end of the study, an injectable anchor has been introduced to market and postmarket data have confirmed that migration rates have significantly reduced since the introduction of using this anchoring device with the Freedom SCS System.

Subperception, Stimulation, Patient Preferences, and Longevity of the System

Kapural et al (20) published the results of the SENZA RCT trial demonstrating that subperception SCS at 10 kHz was superior to supraperception paresthesia-based SCS for the treatment of chronic back pain and leg pain, having as a primary advantage not producing paresthesia, which might be annoying for patients.

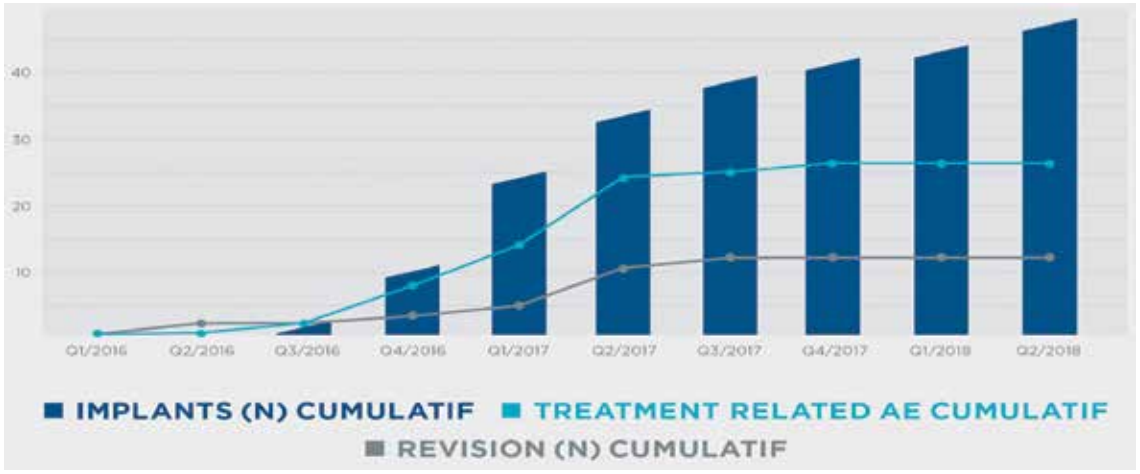

Fig. 10. *Adverse events and revision rates compared to implant dates.*

Similar results concerning subperception and supraperception were reported by North et al in the WHISPER study (15). This was a prospective, multicenter, randomized controlled crossover trial designed to demonstrate the safety and effectiveness of subperception SCS at frequencies up to 1.2 kHz. The authors compared the results of subperception stimulation to supraperception paresthesia-based stimulation in 140 patients with severe disabilities or crippling conditions with chronic pain of trunks and/or limbs and that had been previously implanted with SCS. Ninety-three of the 140 patients preferred subperception stimulation compared to 35 patients who preferred supraperception stimulation.

But it should be pointed out that according to the PROCO study (16), the longevity of traditional SCS systems is influenced by the stimulation frequency; stimulating at 10kHz (subperception stimulation) consumes 3 times more energy than when stimulating at 1 kHz (subperception stimulation). Thus, it is also in the interest of the patient, and to avoid frequent battery replacements, to use lower frequencies at subperception levels that do not cause paresthesia, and/or systems that do not require an implanted energy source, such as the system used in this study.

Limitations

This study presents several limitations. Analysis was completed on an enriched population. Nonresponding patients were excluded from the study after the initial one-month trial to allow them to pursue alternative treatment options. AEs rates were inversely related to the implanters' experience, with the highest enrolling sites reporting the lowest incidence rates of AEs. Surveillance x-ray images were assessed to determine the electrode array position at defined intervals throughout the study. Asymptomatic device migration was registered and reported. Additional limitations include the absence of blinding due to the nature of low frequency stimulation and the industry sponsoring of the study. Post-hoc tests for superiority demonstrated that externally powered spinal cord stimulation performed better than the derived control. Analyses suggest more responders and better improvement in back pain and leg pain than comparable treatment options, but the sample size is small and further research should be done to confirm these post-hoc results.

Summary and Perspective

This was the first multicenter, prospective study analyzing the effectiveness of multiple waveforms with the externally powered Freedom SCS System for the treatment of refractory chronic back or back and leg pain associated with PLS. This report is divergent from the substantial body of SCS literature, which historically required 2 procedural episodes, including an initial temporary lead placement, subsequently followed by a permanent implant. Externally powered SCS with only one procedural episode facilitated a 30-day trial period during which the best stimulation parameters settings could be evaluated. This opportunity to streamline care may represent an opportunity to foster the cost effectiveness of externally powered SCS (21).

This study has shown the opportunity to enhance

results by improving procedural techniques, focusing on both placement and fixation. Utilization of a fixation device offers the potential of reducing complications, especially device dislocation.

The results of this study demonstrate that externally powered stimulation with the opportunity to employ multiple stimulation patterns is an efficacious treatment for patients with PLS.

Authorship Statement

Drs. Bolash, Creamer, Rauck, Vahedifar, Calodney, Fox, and Özaktay treated patients and collected the data at the study sites. Niek Vanquathem prepared the manuscript. All authors reviewed the manuscript critically and approved the final version.

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