

10 kHz High-Frequency Spinal Cord Stimulation for Chronic Axial Low Back Pain in Patients With No History of Spinal Surgery: A Preliminary, Prospective, Open Label and Proof-of-Concept Study

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Objective: To explore the effectiveness of 10 kHz high frequency spinal cord stimulation (HF10 therapy) treatment of chronic low back pain in patients who have not had spinal surgery.

Methods: Patients with chronic low back pain without prior spinal surgery were evaluated by a team of spine surgeons to rule out any spinal pathology amenable to surgical interventions and by a multidisciplinary pain team to confirm eligibility for the study. After a successful (>50% back pain reduction) trial of HF10 therapy, enrolled subjects underwent permanent system implantation and were followed-up one year post-implant.

Results: About 95% of the enrolled subjects (20/21) received the permanent system. At 12 months post-implant, both back pain VAS score and ODI were significantly reduced compared with baseline values (by 73% and 48%, respectively); an estimated quality-adjusted life year gain of 0.47 and a reduction in opioid use by 64% was observed. Four more patients among those unable to work at baseline due to back pain were employed at 12 months post-implant. There were no serious adverse events.

Conclusion: HF10 therapy may provide significant back pain relief, reduction in disability, improvement quality of life, and reduction in opioid use in chronic low back pain not resulting from spinal surgery.

Keywords: 10 kHz, chronic back pain, high frequency stimulation, spinal cord stimulation

Conflicts of Interest: Adnan Al-Kaisy received travel sponsorship and speaker fees from Medtronic and Nevro Corp, he is the principal investigator in separate studies sponsored by Medtronic and Nevro Corp., and he has financial interest in Micron Device LLC. Stefano Palmisani received speaker fees and/or sponsorships to attend professional meetings from Nevro Corp and Medtronic; David Pang received sponsorship to attend professional meetings from Nevro Corp and Medtronic; Thomas E. Smith received consultancy fees and sponsorship to attend professional meetings from Nevro Corp. The remaining authors have no conflicts of interest to disclose.

INTRODUCTION

Chronic low back pain causes more disability globally than any other medical condition (1,2). If conservative management fails, patients are left to self-manage their symptoms and surgery is indicated only in selected cases (3–5).

Spinal cord stimulation (SCS) is a minimally invasive procedure using implanted epidural electrodes to stimulate the spinal dorsal columns at 40–70 Hz. Pain relief results from inducing paresthesia which overlaps the painful area (6). The ability to trial stimulation prior to permanent implantation and the fully reversible nature of the procedure are major advantages. Two randomized, controlled studies support the efficacy of SCS treatment in patients with persistent neuropathic lower limb pain secondary to failed back surgery syndrome (FBSS) (7,8). However, the therapy has limited utility in the treatment of axial low back pain, partially due to the technical difficulties in achieving paresthesia in the lower back (6).

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The 10 kHz SCS (HF10 therapy) does not produce paresthesia and the leads are placed anatomically without stimulation mapping. Patients with predominantly axial back pain recruited in a European multicenter cohort study treated with HF10 therapy demonstrated relief of their back pain at two years follow up, and a multicenter randomized controlled trial has confirmed the efficacy of HF10 therapy and showed its superiority to traditional low frequency stimulation (9–11). Sub-group analyses suggested that HF10 therapy could produce consistent axial back pain relief in subjects without previous spine surgery.

We designed a preliminary, single center, prospective, proof-of-concept study to explore safety, and efficacy of HF10 therapy in a cohort of surgically-naïve patients suffering from chronic, medically refractory, predominantly axial, low back pain unsuitable for surgical intervention. This is the first prospective study to report one-year HF10 therapy outcomes specifically in subjects with predominant back pain who are not candidates for spinal surgery.

METHODS

This was a preliminary, single center, prospective, proof-of-concept study designed to explore safety and efficacy of HF10 therapy in a cohort of subjects with no previous history of spine surgery, who were suffering with chronic, axial, low back pain refractory to conventional treatments, and were not suitable for evidence-based surgical treatment. The study was sponsored by Nevro Corp (Menlo Park) and was conducted in accordance with local regulations, good clinical practice guidelines (ISO 14155) and the declaration of Helsinki. Ethical committee approval was granted (NRES Committee North East—Northern & Yorkshire, REC reference 11/NE/0047, April 2011), and the study is registered on an internationally recognized clinical trials database (ISRCTN96424062). Written informed consent was obtained from all the study subjects.

Device Status

The device is FDA-approved by a corresponding national agency for this indication.

Study Participants

Between April 2012 and October 2013 all chronic lower back pain patients with no previous spine surgery history referred to the Pain Management and Neuromodulation Centre of Guy's & St Thomas NHS Foundation Trust were screened for study eligibility.

Inclusion criteria were: 1) aged between 18 and 65 years; 2) symptoms of axial low back pain for at least 6 months, with a minimum intensity of 5/10 on a Visual Analogue Scale (VAS); 3) predominant low back pain (VAS back scores being 2 cm greater than leg pain if present); 4) failure to respond to conventional medical management including where appropriate intensive physical rehabilitation program and facet joints or medial branches local anesthetic infiltrations; 5) no history of previous spinal surgery; 6) cleared of any spinal pathology that would lead to recommendation for any evidence-based surgical intervention; 7) degenerative disc disease confirmed by MRI and/or by discography; 8) on stable dose (six months or longer) of analgesic medications, including opioids and anti-neuropathic drugs. The study's key exclusion criteria are listed in Table 1.

To confirm eligibility, subjects fulfilling inclusion/exclusion criteria were reviewed by 1) a team of experienced spinal surgeons, to rule out mechanical spine instability according to clinical criteria and with the aid of flexion/extension lumbar radiography, in order to exclude any spinal pathology amendable to evidence-based spinal interventions; and 2) a multidisciplinary pain team to assess medical and psychological appropriateness for SCS technology (12).

Table 1. Key Exclusion Criteria.

Description	No. of patients
Not Able to comply with study-related requirements, procedures and visits	16
Low back pain for less than six months or not having tried conservative treatment (e.g., physical therapy, multiple facet joint injections)	15
Low back pain not predominant (VAS back pain two points or more > than leg pain VAS)	9
Active alcohol, marijuana, recreational or prescription drug abuse or dependence or unwilling to stop/reduce excessive inappropriate medication	7
Had previous spinal fusion surgery	7
A medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints	6
Evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance of intervention and/or ability to evaluate treatment outcome	4
Age less than 18 years, greater than 65 years old	3
Low back pain intensity <5 out of 10 cm on the VAS at enrolment.	2
Mechanical spine instability detected by a spinal surgeon (Validation by flexion/extension films of lumbar spine within the past six months showing 4 mm or more translational movement or excessive angular movement manifested by >5 degrees segmental angular movement)	3
A current diagnosis of a progressive neurologic disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, rapidly progressive diabetic peripheral neuropathy, brain or spinal cord tumor, or severe/critical central or foraminal spinal stenosis	1
Immunocompromised and at an increased risk for infection	1
Metastatic malignant disease or active local malignant disease	1
Pregnant (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile or be at least two years post-menopausal)	1
An existing drug pump, SCS system, and/or another active implantable device	1

Study Intervention

All the recruited subjects received a trial of HF10 therapy for 7–14 days to assess efficacy and tolerability to the treatment. A pain physician with extensive experience in neuromodulation performed the epidural leads placement under fluoroscopic guidance (Fig. 1). More details on the 10 kHz SCS technique used can be found elsewhere (9,10) and online (Supporting Information Digital Content). As HF10 therapy is a paresthesia-free system, intra-operative paresthesia testing was not performed and the leads were positioned anatomically, with the distal tip of one lead placed at T8 while a second lead tip was placed at T9, both near anatomic midline.

Bipolar stimulation program (10 kHz, 30 ms, 1–5 mA) were provided to initially target the dorsal columns in the area corresponding to T9–T10 vertebral level; stimulation intensity and location was subsequently optimized in a stepwise manner to obtain optimal analgesic response during the trial phase. For every subject we initially activated a single bipole corresponding to the vertebral area of T9–T10, titrating up the HF10 SCS amplitude (1–5 mA range) during the first two to three days of the trial. If significant relief was not obtained (50%, but usually >70%), we activated a new bipole below the tested one for the following two to three days and, if again not successful, we moved to a new bipole higher than the one initially tested. These three steps were often enough to establish whether the subject was responding to the therapy or not. All the subjects were asked to keep the stimulation on 24 hours a day.

At the end of the trial period, only those subjects reporting at least 50% or greater back pain VAS reduction from baseline were permanently implanted (Senza™ system, Nevro Corp., Menlo Park).

Data Collection

As this was a preliminary and proof-of-concept study, no single primary end-point was defined. However, a range of clinical outcome measures was prospectively collected. Baseline measures

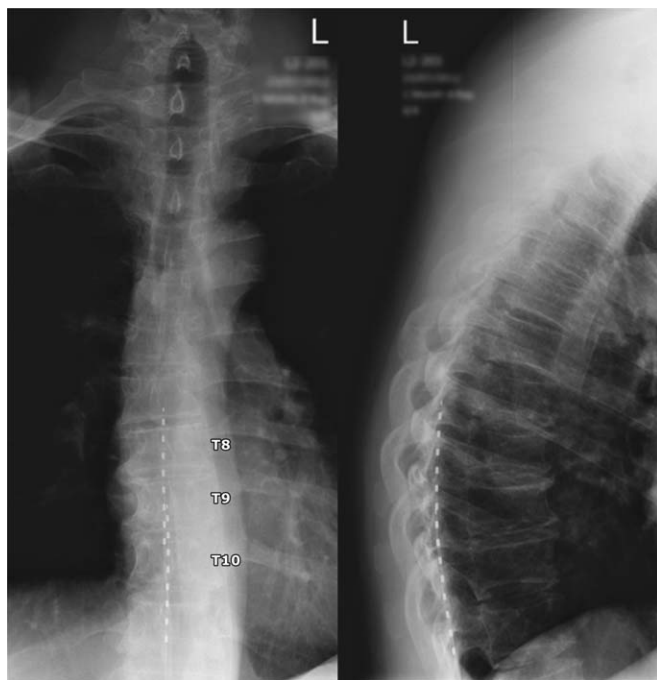


Figure 1. Antero-posterior and lateral X-ray view of two 8-contacts SCS HF10 leads. Please note the leads position within the posterior epidural space, placed to provide stimulation at approximately T9–T10 vertebral level.

Table 2. Baseline Characteristics of the Included Patients.

Age, years (mean ± SD)	43.1 ± 9.6
Female (%)	9 (42.9%)
Back VAS score (mean ± SD)	7.9 ± 1.3
Leg VAS score (mean ± SD)	3.3 ± 2.1
Oswestry disability index (mean ± SD)	53 ± 13
EQ-5D TTO (mean ± SD)	0.17 ± 0.28
SF-36 PCS (mean ± SD)	30.3 ± 8.1
SF-36 MSC (mean ± SD)	42.7 ± 11.2
Time since onset of chronic pain, years (mean ± SD)	7.0 ± 5.8
MRI findings	
Facet joint arthropathy/hypertrophy	5 (25%)
Lateral recess stenosis	8 (40%)
Foraminal stenosis	4 (20%)
Nerve impingement	3 (15%)
HIZ	10 (50%)
Modic changes	12 (60%)
Pfirrmann grade 4 or 5	18 (90%)
Schizas grade > B	6 (30%)

(Table 2) were collected at least one week prior to the SCS trial, at the end of the trial, and one, three, six, and twelve months after permanent SCS implantation.

Patients were able to visit the clinic for re-programming as required in addition to the scheduled visits.

Pain intensity for both low back and leg pain was measured using a visual analogue scale (VAS) of 0–10 cm. Functional disability was captured through the Oswestry Disability Index (ODI), including scores ranging from 0 to 100, with higher scores associated with increased disability (13). The EuroQol 5 Dimensional Questionnaire utility index was used as a measure of health-related quality of life, providing a single index value for health status (14). MOS 36 Item Short Form Health Survey v2 (SF-36) was used to acquire a patient-based assessment of general, physical, and mental health, not specifically related to the back (15); scores can range from 0 to 100 with higher scores indicating better function. Data on patients' experience (global impression of change, satisfaction, recommendation to others), opioids use, sleep quality (average sleep hours per night, average pain-induced sleep disturbances per night) and work status was also collected.

Adverse Events (AEs) were recorded as a measure of treatment safety and tolerability: specifically, data regarding lead failure (migration, fracture, and disconnection), early- and late-onset infections, painful IPG pocket and any new neurologic symptoms were systematically collected and reported.

MR Analysis

Baseline magnetic resonance (MRI) images of the lumbar spine were evaluated for all but one patient by a single experienced radiologist according to international guidelines for classification of lumbar-disk pathology (16). MRI evidence of intervertebral disc degeneration at each vertebral level was defined as the presence of at least one of the following: Pfirrmann grade 4 or 5, presence of Modic changes, presence of HIZ (Fig. 2) (further details available online as Supporting Information Digital Content).

Statistical Analysis

This was a preliminary proof-of-concept study and as such, sample size was not determined around a target effect size. Continuous

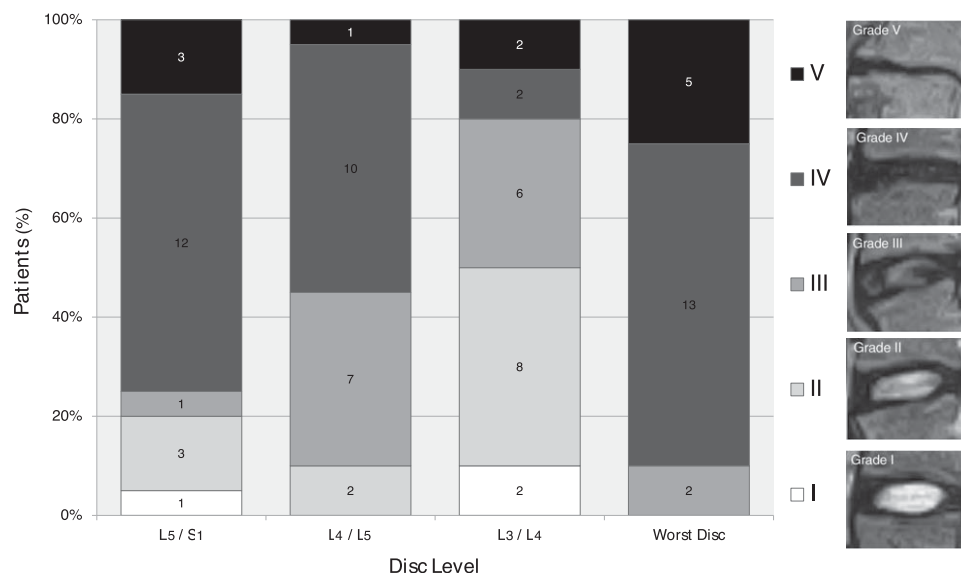


Figure 2. Pfirmann classification of lumbar disc degeneration in the included study population. The first three bars of this graph show the proportion of patients stratified according to Pfirmann grade and per disc level; the last one shows the distribution of the worse Pfirmann grade (regardless of the disc level) within the study subjects.

data were expressed as mean \pm standard deviation (SD) (standard error [SE] is used for graphs), and frequency and percentage are reported for ordinal and categorical variables. Descriptive statistics were reported as counts and percentages, mean and standard deviation or median, and range. AEs were reported descriptively. Statistical analysis were conducted using SAS v9.1 (SAS Institute Inc., The United States), and statistical significance was accepted at the $p < 0.05$ level. An analysis of variance including the period (follow-up visit) as repeated factor was applied to each of the analyzed variables; pairwise comparisons of periods were also performed within the same model. The probability value and 95% confidence limits for difference between arithmetic means were adjusted by the Dunnett method. If the analyzed variable was not homogeneous (Levene test) or variances relative to periods were not equal, the variable was \log_e -transformed. Quality-adjusted life year (QALY) gain was estimated following the multiplicative model, by subtracting from each three-month utility value the baseline value.

RESULTS

Ninety-eight potential patients were screened between April 2012 and October 2013. Of the 77 screen-failed patients, the most common reasons for exclusion were: subjects were not able to comply with study requirements (21%), had not received adequate conservative treatments (19%), reported predominant lower limb pain (12%), were unwilling to stop or reduce excessive medications dose (9%), or had some form of surgical spine intervention in the past (9%). 21 patients were included in the study and their baseline characteristics are summarized in Table 2. Baseline MRI images were available for review in 20 subjects (95%). MRI imaging of these patients revealed evidence of disc degeneration in at least one of the three lumbar levels examined in all subjects, with multiple levels of degeneration observed in 50% of the subjects (Fig. 2).

All but one of the enrolled subjects had a successful trial of HF10 therapy and proceeded to the full system implantation (95% trial success rate). All were followed up for one year, with none lost to follow up.

Back Pain Reduction

Average back pain scores decreased significantly after the SCS trial compared with preoperative data, and the pain relief was well maintained throughout the study, with statistically significant average pain scores reduction at each scheduled follow-up visit (Fig. 3) ($p < 0.0001$). An average reduction of 4.69 ± 2.78 (-59.9% vs. baseline) and of 5.59 ± 1.80 (-72.6% vs. baseline) were seen at 6 and 12 months, respectively. The 75% and 90% of the implanted patients were classified as responders (VAS reduction $>50\%$) at 6 and 12 months follow-up, respectively.

Leg Pain Reduction

Baseline leg pain scores were low. Even so these reduced with HF10 therapy. The leg pain reduction was statistically significant at month 1, 3, and 12 ($p < 0.05$), but not at months 6 and 9 (Fig. 3).

Functional Improvement

ODI scores were significantly lower at all treatment time points compared with baseline (Fig. 3) ($p < 0.0001$). An average reduction of 18.40 ± 20.15 points (-33.2% vs. baseline) and of 26.00 ± 19.05 points (-47.6% vs. baseline) was observed at 6 and 12 months, respectively. At 12 months nine patients (45%) were in the "minimal disability" category, a 20% improvement compared with the baseline, when only five patients (25%) were classified as minimally disabled.

Medication Intake

Subjects reported a reduction in the average daily opioid intake by 64% at 12 month (from 112 ± 87 to 40 ± 13 morphine milligram equivalent), and three patients completely stopped their use of opioids ($p = 0.0833$).

Overall Patient's Impression and Satisfaction

Patient satisfaction was high, with 90% of the implanted patients reporting positive (Satisfied: 5/20) or excellent (Very Satisfied: 13/20) satisfaction scores at the end of the 12 months study period. 80% of the implanted patients rated their condition as "much improved" or

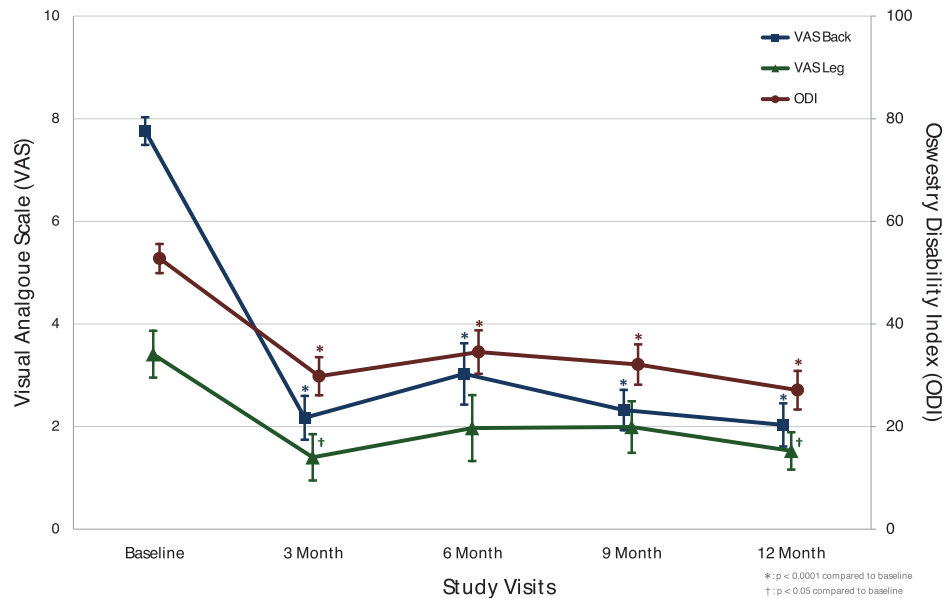


Figure 3. Pain (VAS scores for both back and leg) and physical disability (ODI score) at baseline and after 3, 6, and 12 months of HF10 SCS therapy.

“very much improved.” All enrolled subjects would recommend this treatment to others suffering from a similar condition, with 70% of the subjects choosing to “highly” recommend the treatment.

Sleep Quality

The number of sleep disturbances significantly decreased at each time point, with an average reduction, compared with baseline values, of 37% and 54% for 6 and 12 months respectively ($p < 0.05$). This is confirmed by a trend in improved sleep duration time, with an average increase of 1 ± 1.45 hours per night (+22% vs. baseline, $p = 0.074$) at 6 months and 1.15 ± 1.42 hours per night (+24%, $p = 0.062$) at 12 months.

Health, Employment, and Quality of Life Status

Data from SF-36 and EQ-5D questionnaires showed statistically significant improvements in the self-reported scores at all time-points (Fig. 4). The increase in the Time Trade-off (EQ-5D TTO) demonstrates substantial improvement, and the QALY gain estimated more than the 12-month study period is approximately 0.47.

At the end of the study, 15 out of 19 patients within working age were working, 4 more than at baseline (two part-time and two full-time) ($p = 0.0833$).

Adverse Events

No serious AE occurred. Two patients reported pain/tenderness over the IPG site, one of which required surgical revision; three subjects experienced lead migration requiring reprogramming, none required surgical revision.

DISCUSSION

This is the first study to specifically explore the role of HF10 therapy in subjects with chronic, severe, low back pain who had not undergone and were not candidates for spinal surgery. Beyond individual suffering, chronic low back pain has the largest economic impact of any chronic disease in developed countries (17).

Pain Reduction and Functional Improvement

HF10 therapy treatment was associated with a significant reduction in pain scores (>70% vs. baseline) at each observation point with 90% of patients reporting more than 50% pain relief at 12 months. Average ODI scores were almost halved at the end of the study, and four previously “disabled” or “crippled” subjects (20%) reverted to the “minimally disabled” category. At 12 months, 19 out of 20 patients exceeded both a 30% reduction in pain intensity and a 12.8 points reduction in ODI, values considered as the minimally clinically important difference in chronic low back pain studies (18). Our results compare favorably with currently recommended approaches for non-surgical, refractory back pain, including multidisciplinary biopsychosocial functional restoration programs (19), which reportedly produce only minimal reduction in pain scores (20,21).

Quality of Life Gains

Quality of life (measured by EQ5D TTO scores) improved from 0.16 to 0.47: this is a clinically significant finding after just 12 months of HF10 therapy (22), and may have relevance to cost effectiveness (23,24). The observation that four of the eight patients who were not working at baseline returned to full or part time employment also reflect an important QoL improvement.

Additional Outcomes

We observed a 64% reduction in daily opioid use, corresponding to a substantial dose reduction of 72 mg/day of morphine equivalents. This is an important finding given that high dose long-term opioids for chronic pain are associated with significant negative health impacts and societal costs (25,26). The observed trend in improved sleep could indirectly corroborate the common knowledge of a bidirectional relationship between sleep and chronic pain conditions, such that pain disturbs sleep continuity and quality, and poor sleep further exacerbates pain (27).

HF10 Therapy Mechanism of Action

While a detailed discussion of the hypothetical mechanisms of action for any SCS strategy (including paresthesia-based low

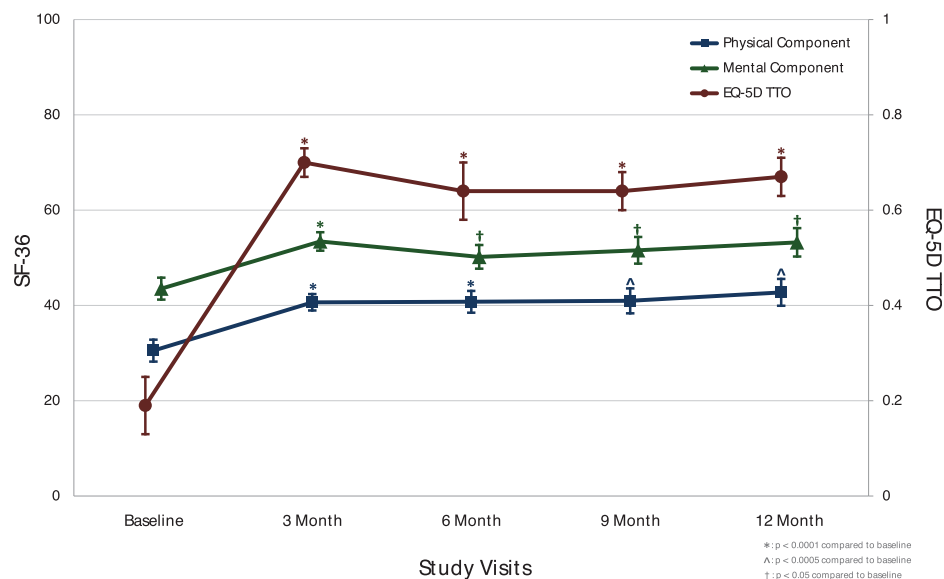


Figure 4. Quality of life measurements (EQ-5D and SF-36) at baseline and at each scheduled follow-up visit.

frequency stimulation) is beyond the scope of this clinical submission, some observations may be noted. Early preclinical studies suggested that depolarization block may be responsible for HF10 therapy effects, but clinical observations (e.g., no effect of HF10 therapy on patient sensorium) do not appear to support this mechanism (28). Current working hypotheses involve electric field modulation of spinal structures including dorsal horn neurons, and alteration of neural signaling, such as desynchronization of interneuron populations (29). It is likely that wide dynamic range neurons in the dorsal horn are the ultimate targets of HF10 therapy, as in low frequency parasthesia based SCS (30). Preclinical and clinical work is presently ongoing to elucidate the mechanisms of HF10 therapy.

Our outcomes and safety data are consistent with data from both the HF10 treatment cohort from the initial European trial and also the randomized trial comparing HF10 to conventional spinal cord stimulation for chronic back and leg pain (9–11,24,31,32).

Study Weaknesses

Our study has a few key limitations. It was a single site, small proof-of-concept study with no control group. Subjects have been followed up for one year only, as compared with the usual three to five years in the spine surgery literature, and cost-effectiveness analysis has not been included. As there is on-going controversy surrounding evidence-based surgical treatments for chronic lower back pain (33,34), we cannot exclude that some of the included subjects could have been considered for spine surgery by other criteria or surgical opinion. It is the authors' opinion that HF10 therapy should not be considered as an alternative to conventional spine surgery when there is a clear and unequivocal correlation between clinical symptoms and radiological findings. The potential role of HF10 therapy should be relegated to the subset of chronic back pain patients who present with nonspecific degenerative changes at multiple vertebral levels and complain of severe back pain with clinical characteristics of predominant central sensitization rather than mechanical nociception.

CONCLUSION

This preliminary study suggests that HF10 therapy may significantly reduce chronic low back pain and associated disability in non-surgical medically refractory subjects with no past history of surgery, increasing their physical function and quality of life up to one year from the SCS implant. The orthodoxy that considers SCS for chronic lower back pain as a treatment option only in cases of FBSS should be revisited if these results are confirmed through an appropriately designed randomized controlled trial.

Acknowledgments

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Authorship Statements

Drs. Al-Kaisy, Pang, Palmisani, and Smith designed and conducted the study, including patient recruitment, data collection, and data analysis. Dr. Al-Kaisy prepared the manuscript draft with important intellectual input from Drs. Pang, Palmisani, and Smith. All authors approved the final manuscript. Nevro Corp. provided funding for this study, statistical support in analyzing the data with input from Drs. Al-Kaisy and Palmisani. Drs. Al-Kaisy, Pang, Palmisani, and Smith had complete access to the study data. Drs. Lucas, Burgoyne, and Lam were involved in patient recruitment. Dr. Houghton provided diagnostic imaging for the duration of the study. Emma Hudson provided logistical and administrative support throughout the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENTS

This well documented single center case series reports very promising 1 year results for 10 kHz (HF10) spinal cord stimulation (SCS) in patients with predominantly axial low back pain attributed to degenerative disc disease, in whom there had been no prior surgery and in whom no surgery was indicated. The authors modestly opine “that HF10 therapy should not be considered as an alternative to conventional spine surgery when there is a clear and unequivocal correlation between clinical symptoms and radiological findings,” but this does not follow from the data presented, and the literature suggests the authors might be more optimistic.

Patients with a potentially disabling neurologic deficit attributable to surgically remediable nerve compression and those with a significant, progressive spinal deformity require corrective surgery and not just pain relief; but these are a minority. Pain is the primary reason for surgery in the great majority of cases, and it is widely accepted that if it can be relieved in such cases by non-operative treatments, up to and including minimally invasive procedures such as lumbar epidural injection and radiofrequency facet denervation, then surgery can be deferred. As a minimally invasive, reversible procedure, SCS likewise deserves to be considered before surgery, whether primary or repeated surgery.

Our 2005 randomized, controlled trial, which showed superiority of SCS to repeated low back surgery, enrolled only patients with “clear and unequivocal correlation between clinical symptoms and radiological findings,” meeting standard indications for surgery [1]. Unlike patients in the present study, in whom low back pain predominated, ours had radicular pain equaling or exceeding low back pain, and of course our study antedated the availability of 10 kHz SCS; but it established that SCS can avoid the need for repeated surgery. Further study might well show this to be the case for initial surgery and for primary axial LBP as well.

“Failed back surgery syndrome” is better avoided than treated after the fact [2]. The authors are to be congratulated and encouraged to expand this research to include (1) patients in whom surgery is indicated and

feasible but not required, (2) other centers, and (3) appropriate controls, including (a) surgical alternatives as well as (b) other waveforms (among them placebo, which can be administered in double-blind fashion with paresthesia-free stimulation). Further research might well establish a role for SCS as an alternative to initial lumbosacral spine surgery in many cases.

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This is an extremely important manuscript, providing information about the benefit of high-frequency stimulation for lower back pain in patients who are not candidates for spinal surgery and those who have not undergone prior surgery (FBSS). One of the main achievements in my opinion was to find an agreement between spine surgeons and pain specialists to proceed with high-frequency SCS. The results are impressive, although as the authors mention the follow-up is too short. I can only affirm the authors' suggestion to continue their follow-up. It would be very interesting to have more detailed information about the patients who did not comply with the study (N=16). The next step, which is certainly already in the authors' mind, is a randomized study in a cross-over design.

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The authors reported the effectiveness of 10kHz high frequency spinal cord stimulation in the treatment of chronic low back pain in patients who had not been treated by spinal surgery. At 12 months post-implant, low back pain evaluated using the visual analogue scale was significantly reduced. This 10kHz high frequency stimulation does not induce paresthesia, which appears to be an epoch-making achievement in spinal cord stimulation.

To date, we have tried for a long time to develop a technique to induce paresthesia over a painful area in each patient by spinal cord stimulation. However, 10kHz high frequency stimulation can reduce pain without inducing paresthesia. The authors introduced the current working hypothesis, which involves electric field modulation of spinal structures including dorsal horn neurons, and alteration of neural signaling, such as desynchronization of interneuron populations.

However, the mechanism of pain reduction without inducing paresthesia is unclear. Further study of the mechanism of pain reduction by 10kHz high frequency stimulation is necessary, and the applicability of this stimulation method to the treatment of intractable pain besides low back pain should be examined.

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Comments not included in the Early View version of this paper.