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The SENZA-RCT Randomized Controlled Trial

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ABSTRACT

Background: Current treatments for chronic pain have limited effectiveness and commonly known side effects. Given the prevalence and burden of intractable pain, additional therapeutic approaches are desired. Spinal cord stimulation (SCS) delivered at 10 kHz (as in HF10 therapy) may provide pain relief without the paresthesias typical of traditional low-frequency SCS. The objective of this randomized, parallel-arm, noninferiority study was to compare long-term safety and efficacy of SCS therapies in patients with back and leg pain.

Methods: A total of 198 subjects with both back and leg pain were randomized in a 1:1 ratio to a treatment group across 10 comprehensive pain treatment centers. Of these, 171 passed a temporary trial and were implanted with an SCS system. Responders (the primary outcome) were defined as having 50% or greater back pain reduction with no stimulation-related neurological deficit.

Results: At 3 months, 84.5% of implanted HF10 therapy subjects were responders for back pain and 83.1% for leg pain, and 43.8% of traditional SCS subjects were responders for back pain and 55.5% for leg pain ($P < 0.001$ for both back and leg pain comparisons). The relative ratio for responders was 1.9 (95% CI, 1.4 to 2.5) for back pain and 1.5 (95% CI, 1.2 to 1.9) for leg pain. The superiority of HF10 therapy over traditional SCS for leg and back pain was sustained through 12 months ($P < 0.001$). HF10 therapy subjects did not experience paresthesias.

Conclusion: HF10 therapy promises to substantially impact the management of back and leg pain with broad applicability to patients, physicians, and payers. **(Anesthesiology 2015; 123:00-00)**

We present a multicenter, randomized, controlled trial evaluating the safety and efficacy of 10-kHz high-frequency (HF10) therapy, which is an innovative spinal cord stimulation (SCS) system for the management of chronic back and leg pain. This system delivers electrical stimulation pulses at high frequency (10,000 Hz) as compared with traditional low-frequency SCS systems (typically around 50 Hz). Previous work suggests that the higher-frequency system may treat back and leg pain to a greater degree. Moreover, it may be able to do so without producing paresthesias associated with low-frequency SCS, which some patients find uncomfortable.[1–3]

What We Already Know about This Topic

- Spinal cord stimulation (SCS) often relieves radicular pain but is relatively poorly effective for the treatment of back pain
- High-frequency SCS may improve the efficacy of SCS for the treatment of low back pain

What This Article Tells Us That Is New

- This randomized trial involving 198 participants demonstrated that high-frequency spinal cord stimulation (SCS) was superior to conventional SCS for the treatment of back pain and leg pain
- The effects of high-frequency stimulation relative to conventional stimulation persisted for 12 months

This article is featured in "This Month in Anesthesiology," page 1A. Full protocol available at: gliner@nevro.com. Raw data available at: gliner@nevro.com.

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There is a substantial clinical need for improved treatments for chronic pain. More than 1.5 billion people worldwide experience chronic pain,[4,5] with low back pain being the most frequent pain condition affecting 23 to 26% of the population.[6–8] Chronic pain impacts most aspects of a person's life, including emotional distress and/or psychosocial impairment.[8] Unfortunately, currently available treatments have limited effectiveness for most people with severe chronic pain.[9] Opioid analgesics are frequently prescribed despite the lack of clinical evidence supporting their long-term use to treat chronic pain.[10,11]

Spinal cord stimulation is approved to treat chronic intractable pain of the trunk and limbs. SCS delivers electrical pulses *via* spinal epidural electrode arrays (leads) at vertebral levels associated with perceived pain. Traditional SCS devices are capable of delivering pulse frequencies in the range 2 to 1,200 Hz, with typical application of approximately 40 to 60 Hz. The objective of these relatively low-frequency SCS devices is to produce paresthesias (a tingling sensation) that overlap the pain distribution, with the intent of masking pain perception. Intraoperative paresthesia mapping is thus required, wherein patient feedback is solicited while adjusting stimulation location, pulse frequency, pulse width, and amplitude. Thus, traditional SCS success depends on adequacy and durability of paresthesia coverage as well as patient tolerance of the induced sensations.

Evaluating an approach that does not rely on paresthesias is novel to SCS and has the potential to improve the treatment of chronic back and leg pain. Over the last 40 yr, the primary focus of innovation for SCS for chronic pain has been to improve the reliability of overlapping paresthesias with distribution of pain. Achieving adequate and stable paresthesia coverage in the axial back region specifically is known to be challenging, making back pain more difficult to treat and limiting application mostly to patients with predominant leg pain.[12–14]

HF10 therapy involves application of short-duration (30 μs), high-frequency (10 kHz), low-amplitude (1 to 5 mA) pulses to the spinal epidural space in such a manner as to not produce paresthesia, thus obviating the requirement of paresthesia mapping. Previous prospective but nonrandomized studies have indicated that HF10 therapy is able to treat patients with chronic back pain and that the results are sustained for 2 yr.[1,2]

As such, a pragmatic study was designed to compare HF10 therapy to traditional SCS as widely applied in current clinical practice. Specifically, this multicenter, randomized, controlled, pivotal trial (the SENZA-RCT study) compared the safety and efficacy of HF10 therapy to traditional SCS in patients with back and leg pain (ClinicalTrials.gov identifier: NCT01609972). The Food and Drug Administration defines a pivotal study as "a definitive study in which evidence is gathered to support the safety and effectiveness evaluation of the medical device for its intended use"—*Food and Drug Administration Guidance Document: Design Considerations for Pivotal Clinical Investigations for Medical Devices*. The study was powered according to the primary objective of demonstrating noninferiority; if noninferiority was demonstrated, superiority could then be assessed secondarily.

Materials and Methods

Study Design and Population

This prospective, randomized, controlled trial was designed to assess primarily noninferiority and secondarily superiority of HF10 therapy as compared with traditional low-frequency SCS in subjects with chronic intractable back and leg pain. The study was conducted in compliance with the U.S. Code of Federal Regulations and recommendations guiding physicians in biomedical research by the 18th World Medical Assembly, Helsinki, Finland. The study protocol and informed consent forms were approved by each study site's institutional review board (Western Institutional Review Board, Puyallup, Washington; Forsyth Medical Center Institutional Review Board, Winston-Salem, North Carolina).

Consenting patients already under the care of the study investigators were assessed for eligibility based on inclusion and exclusion criteria and randomized across 10 comprehensive pain treatment centers in the United States. Key inclusion criteria were chronic, intractable pain of the trunk and/or limbs, refractory to conservative therapy for a minimum of 3 months (previous conservative treatments included pain medications, physical therapy, spinal injections, pharmacological, and behavioral treatment); average back pain intensity of 5 or greater out of 10 cm on the visual analog scale (VAS); average leg pain intensity of 5 or greater out of 10 cm on the VAS; an Oswestry Disability Index (ODI) version 2.1a score of 41 to 80 out of 100[15]; and an appropriate candidate for the surgical procedures required in this study. Key exclusion criteria were active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, inability to comply with the intervention or evaluate treatment outcomes, mechanical spine instability based on flexion/extension films of lumbar spine, or prior experience with SCS.

Randomization and Masking

After completion of the baseline assessments, subjects were randomized in a 1:1 ratio to receive stimulation with an investigational HF10 therapy system (Senza® System; Nevro Corp., USA) or a commercially available SCS system (Precision Plus System; Boston Scientific, USA). Both SCS systems consisted of two 8-contact leads and a rechargeable implantable pulse generator (IPG). Randomization was stratified by gender and primary area of pain (either back or leg) and administered centrally with each study site assigned randomly chosen alternating blocks of sizes 2, 4, and 6 with frequencies 0.25, 0.50, and 0.25, respectively. Due to practical considerations (see Limitations section), study subjects and investigators were not masked to the assigned treatment group.

Interventions

Consistent with standard clinical practice, subjects first underwent a trial SCS phase lasting up to 14 days with an external stimulator to determine short-term response. Subjects with 40% or greater back pain reduction from baseline were eligible to proceed to permanent implantation. Although lower than the primary endpoint requirement of 50% reduction, this approach allowed subjects with a clinically meaningful response[16] during short-term exposure to the therapies to progress to the permanent implant phase and evaluation at later observation points.

For traditional SCS subjects, stimulation parameters were adjusted to optimally overlap paresthesia with the region of the subject's back and leg pain (average and SD of the minimum, maximum programmed parameters: frequency 39.2 ± 15.0, 77.3 ± 133.5 Hz; amplitude 3.6 ± 2.8, 8.5 ± 4.0 mA; pulse width 347 ± 148, 591 ± 214 μs). Paresthesia testing and associated device programming were performed intraoperatively for control subjects, then as needed based on patient feedback in standard clinic visits. Subjects with HF10 therapy received 30 μs pulses delivered at 10,000 Hz with amplitude adjusted to optimal analgesic response (average minimum, maximum: 1.6 ± 1.1, 3.8 ± 3.4 mA). Intraoperative testing and programming were not needed for HF10 therapy subjects; programming occurred postoperatively and as needed based on patient feedback in standard clinic visits.

Oral analgesics were stabilized from 28 days before enrollment until activation of the implanted SCS system, excluding allowances for perioperative analgesics. Adjustments were then allowed under the guidance of a study investigator as medically necessary.

Implant Procedures

To compare the stimulation parameters, the same type of lead was used for both SCS systems. Two percutaneous leads were placed in the posterior spinal epidural space under radiographic imaging and attached to either an external stimulator (during the trial phase) or a subcutaneously implanted IPG. For HF10 therapy, the distal tip of one lead was placed at T8, whereas a second lead tip was placed at T9, both near anatomical midline. Lead position for HF10 therapy was based on extensive empirical observation that most patients respond to stimulation application near T9/T10, while allowing for patient variation by covering T8 to T11.[1,2] For traditional SCS, leads were placed at vertebral levels based on intraoperative paresthesia mapping involving patient feedback, typically resulting in parallel lead tips placement at T7 to T8.

A subcutaneous pocket was created using standard surgical technique for placement of the IPG. The leads, anchored to the supraspinous ligaments, were tunneled to the pocket site and connected to the IPG. Intraoperative impedance testing ensured electrical integrity.

Lead migration was defined as loss of efficacy or (in the case of the traditional SCS also loss of paresthesia coverage) that could not be remedied by programming. Clinically relevant lead migration was then documented radiographically and required surgical revision.

Outcomes Assessments

Key outcome measures include VAS for back and leg pain, ODI, Global Assessment of Functioning,[17] and subject satisfaction. In addition to reporting of adverse event (AE), a standardized neurological assessment (including motor, sensory, and reflex functions) was performed at scheduled visits (baseline; 1, 3, 6, 9, and 12 months). Subjects were also asked at 3 and 12 months whether they experienced paresthesias with their SCS system, and if so did they generally consider the paresthesia to be uncomfortable and did they experience uncomfortable stimulation related to changes in posture.

Statistical Analysis

Primary endpoint analyses were performed on intention-to-treat (subjects receiving a randomization assignment), per protocol (subjects completing a primary endpoint assessment), and permanent implant (subjects receiving a permanent SCS implant) populations. The primary endpoint of the study was a composite of safety and efficacy: the percentage of subjects who respond to SCS therapy for back pain (≥50% reduction in VAS score) without a stimulation-related neurological deficit. For subjects who had a successful trial phase and received an IPG implant, the primary efficacy assessment occurred at 3 months postdevice activation. Subjects who did not have a successful trial phase were considered nonresponders for the intention-to-treat and per protocol analyses.

Sample size for efficacy was based on a noninferiority comparison of the primary endpoint between treatment groups. Using an exact binomial test for noninferiority with a 10% noninferiority margin, 80% statistical power, and 0.05 one-sided significant level, a minimum of 77 randomized subjects per treatment group were required. If noninferiority was statistically demonstrated, then the results were tested for superiority.

In addition to classifying the subjects as responders or nonresponders, subjects were classified remitters or nonremitters. By expert consensus before the availability of results, we defined a pain remitter as having a VAS pain score of 2.5 or less.

Secondary endpoints were successively evaluated for tests of noninferiority (hierarchical closed-test approach) with one-sided 0.05 significance levels until statistical significance was not achieved. For each endpoint tested, if noninferiority was demonstrated, then superiority was subsequently assessed *post hoc* with a two-sided 0.05 significance level and Bonferroni correction for multiple comparisons within each family of outcomes at each time point. A conservative two-sided P value of 0.002 or less (0.05/24) was required for individual *post hoc* tests of superiority for primary and secondary

endpoints in the different analysis populations to be considered evidence of statistical significance. Secondary endpoints included percentage changes from baseline in back pain, leg pain, and ODI. AE data were collected at all scheduled visits. Proportions were compared between treatment groups using Fisher exact tests with a two-sided α level of 5%. Longitudinal results were assessed using repeated-measures ANOVA.

Study execution was overseen by an independent Data and Safety Monitoring Board, comprising an anesthesiologist, neurologist, neurosurgeon, and biostatistician.

Results

Study Subjects

From June 2012 to December 2012, 241 patients were enrolled with 198 proceeding through baseline evaluations and randomized to a treatment group (101 HF10 therapy and 97 traditional SCS). Of these, 171 subjects were implanted with an SCS system (90 HF10 therapy and 81 traditional SCS) (fig. 1). Follow-up continued through 12 months, which concluded in February 2014.

Randomized subjects averaged 13.6 yr since diagnosis, mean age was 54.9 yr, 86.6% had previous back surgery, and 88.3% were taking opioid analgesics (table 1). Although 86.6% of subjects had previous back surgery, 77.1% were diagnosed by a study investigator with failed back surgery syndrome perhaps indicating some degree of improvement from the surgery in the remaining surgical subjects. Mean baseline back pain VAS was 7.6 ± 1.2, whereas mean baseline leg pain was 7.3 ± 1.4, with all included patients having pain scores of 5.0 or more at the time of enrollment. At baseline, 56.4% of test subjects and 52.6% of control subjects had predominant back pain. Baseline pain scores were higher by a small amount for subjects randomized to traditional SCS. However, statistical analyses of the impact of baseline back and leg pain scores on treatment outcome (correlating baseline pain scores to percent decrease in pain and assessing outcome for subjects whose baseline pain scores were less than the population median *vs.* at or above the median) demonstrates that these differences do not impact the conclusions drawn from the study.

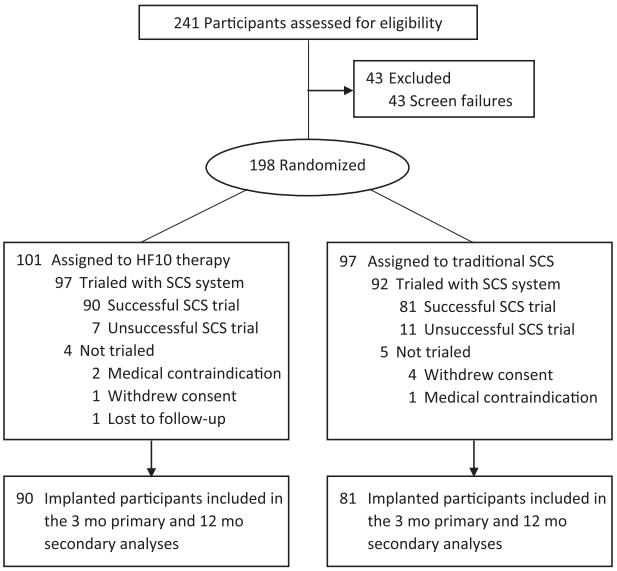

Fig. 1. Study subject flow. HF10 = 10-kHz high-frequency; SCS = spinal cord stimulation.

Trial Phase Results

Of the 97 subjects who completed a trial of HF10 therapy, 90 (92.8%) had significant back pain relief and were eligible for implant of an SCS system. In comparison, 81 of 92 subjects (88.0%) were successfully trialed with traditional SCS ($P = 0.33$).

Three-month Primary Endpoint

Because there were no stimulation-related neurological deficits in either treatment group (see Study-related AEs), the safety component of the primary outcome had no impact on the results. The differences in treatment group responder rates for back pain are presented in figure 2. For all three analysis populations, the upper bound of the 95% CI is far less than the 10% noninferiority margin (indicating noninferiority) as well as zero (indicating superiority).

For permanently implanted subjects, 84.5% were back pain responders with HF10 therapy compared with 43.8% with traditional SCS (table 2; $P < 0.001$ for both noninferiority and superiority). Similarly, 83.1% of HF10 therapy subjects were leg pain responders compared with 55.5% for traditional SCS ($P < 0.001$ for both noninferiority and superiority).

Upon successive evaluation, all secondary endpoints met noninferiority criteria and were subsequently evaluated for superiority as follows.

Back and Leg Pain Responders and Remitters through 12-month Follow-up

Both back and leg pain responder rates were sustained through 12 months for both treatment groups (table 2). However, the responder rates were significantly higher for HF10 therapy at all endpoints ($P < 0.001$). Back pain responder rate was approximately 80% throughout the 12-month follow-up period for HF10 therapy compared with approximately 50% for traditional SCS. Leg pain responder rates show a similar advantage for HF10 therapy (approximately 80% responder rate for HF10 therapy and 50 to 55% for traditional SCS).

Notably, approximately 67% of subjects receiving HF10 therapy were back and leg pain remitters over the 12-month follow-up period. In comparison, for subjects receiving traditional SCS, approximately 35% were remitters for back pain and 40% for leg pain.

Longitudinal Back and Leg Pain

HF10 therapy proved superior to traditional SCS in reducing back and leg pain over the 12-month follow-up period

Table 1. Baseline Demographics and Clinical Characteristics

	HF10 Therapy Treatment Group (N = 92)	Traditional SCS Treatment Group (N = 87)	Standard Difference*
Age, mean (SD), yr	54.6 (12.4)	55.2 (13.4)	0.05
Female (%)	62.0	58.6	0.07
Years since diagnosis, mean (SD)	13.0 (10.4)	14.2 (12.2)	0.11
Pain diagnoses (%)†			
Failed back surgery syndrome	79.3	74.7	
Radiculopathy	66.3	60.9	
Degenerative disc disease	66.3	57.5	
Spondylosis	41.3	36.8	
Mild/moderate spinal stenosis	22.8	19.5	
Sacroiliac dysfunction	20.7	16.1	
Other neuropathic pain	20.7	12.6	
Other chronic pain	19.6	20.7	
Lumbar facet-mediated pain	15.2	16.1	
Spondylolisthesis	8.7	2.3	
Previous back surgery (%)	87.0	86.2	0.02
Taking opioid analgesics (%)‡	90.2	86.2	0.12
Morphine equivalent units, mean (SD), mg/day	115.7 (89.5)	131.3 (149.3)	0.13
Back pain VAS, mean (SD)	7.4 (1.2)	7.8 (1.2)	0.33
Leg pain VAS, mean (SD)	7.1 (1.5)	7.6 (1.4)	0.34

* Standardized difference = difference in means or proportions divided by SD. Guideline for interpretation: 0.2 = small, 0.5 = medium, and 0.8 = large.[18] † Subjects may have more than one pain diagnosis. Because these characteristics are not independent, standard differences are not reported. ‡ Opioid use was defined as prescribed opioid analgesics in any amount on a regular basis.

HF10 = 10-kHz high-frequency; SCS = spinal cord stimulation; VAS = visual analog scale.

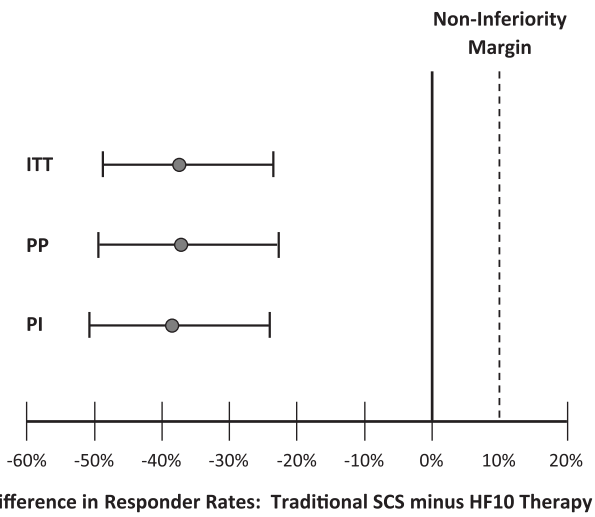

Fig. 2. Differences in treatment group responder rates for back pain and 95% CIs by analysis population. HF10 = 10-kHz high-frequency; ITT = intention-to-treat; PI = permanent implant; PP = per protocol; SCS = spinal cord stimulation.

($P < 0.001$; fig. 3). Mean back pain VAS decreased from 7.4 ± 1.2 at baseline to approximately 2.5 (a 67% decrease) over 12 months with HF10 therapy compared with a decrease from 7.8 ± 1.2 to approximately 4.3 (a 44% decrease) for traditional SCS. Mean leg pain VAS decreased from 7.1 ± 1.5 at baseline to approximately 2.1 (a 70% decrease) over 12 months with HF10 therapy and from 7.6 ± 1.4 to approximately 3.8 (a 49% decrease) with traditional SCS.

Opioid Analgesics, Functional Capacity, and Subject Satisfaction

Although the emphasis of this study was on pain relief and not on reduction in pain medication, 35.5% of HF10 therapy subjects decreased or eliminated opioid analgesic usage at 12 months compared with 26.4% of traditional SCS subjects ($P = 0.41$). Average morphine equivalent dosage decreased from 112.7 ± 91.0 mg/day at baseline to 87.9 ± 85.2 mg/day (an 18.8% average decrease) over 12 months with HF10 therapy and from 125.3 ± 150.0 to 118.0 ± 113.2 mg/day (a 1% average decrease, $P = 0.014$ between groups) with traditional SCS.

Subject's level of disability as measured by ODI improved for both treatment groups (by an average of 16.5 for HF 10 therapy and 13.0 for traditional SCS). At 12 months, 62.9% of HF10 therapy subjects had minimal or moderate disability compared with 45.7% of traditional SCS subjects ($P = 0.03$). Functionally, 70.8% of subjects receiving HF10 therapy had no symptoms to transient symptoms on the Global Assessment of Functioning at 12 months compared with 59.3% of traditional SCS subjects ($P = 0.15$).

Subjects receiving HF10 therapy did not experience induced paresthesias and did not report stimulation-related discomfort. In comparison, 46.5% of traditional SCS subjects reported uncomfortable stimulation.

Subject satisfaction was high for both treatment groups. However, more subjects were very satisfied with HF10 therapy (55.4%) than with traditional SCS (32.3%, $P = 0.002$, table 3).

Table 2. Back and Leg Pain Responder and Remitter Rates for the Permanent Implant Population

	Month 3	Month 6	Month 12
Back pain responders			
HF10 therapy, %	**84.3**	76.4	78.7
Traditional SCS, %	**43.8**	51.9	51.3
Relative ratio (95% CI)	**1.9 (1.4–2.5)**	1.5 (1.2–1.9)	1.5 (1.2–1.9)
Back pain remitters			
HF10 therapy, %	65.2	59.6	68.5
Traditional SCS, %	31.3	36.7	36.3
Relative ratio (95% CI)	2.1 (1.4–3.0)	1.6 (1.1–2.3)	1.9 (1.3–2.7)
Leg pain responders			
HF10 therapy	83.1	80.9	78.7
Traditional SCS, %	55.0	54.4	51.3
Relative ratio (95% CI)	1.5 (1.2–1.9)	1.5 (1.2–1.9)	1.5 (1.2–2.0)
Leg pain remitters			
HF10 therapy, %	76.4	68.6	67.4
Traditional SCS, %	37.5	44.3	42.5
Relative ratio (95% CI)	2.0 (1.5–2.8)	1.5 (1.2–2.0)	1.6 (1.2–2.1)

Responder: ≥50% reduction in pain from baseline. Remitter: pain score of ≤2.5. Relative ratio (95% CI): ratio of responder or remitter rates for HF10 therapy to traditional SCS with 95% CIs. Rates in bold represent the primary endpoint comparison. 10% noninferiority *P* value <0.001 at all endpoints. Between-group *P* value <0.001 at all endpoints.

HF10 = 10-kHz high-frequency; SCS = spinal cord stimulation.

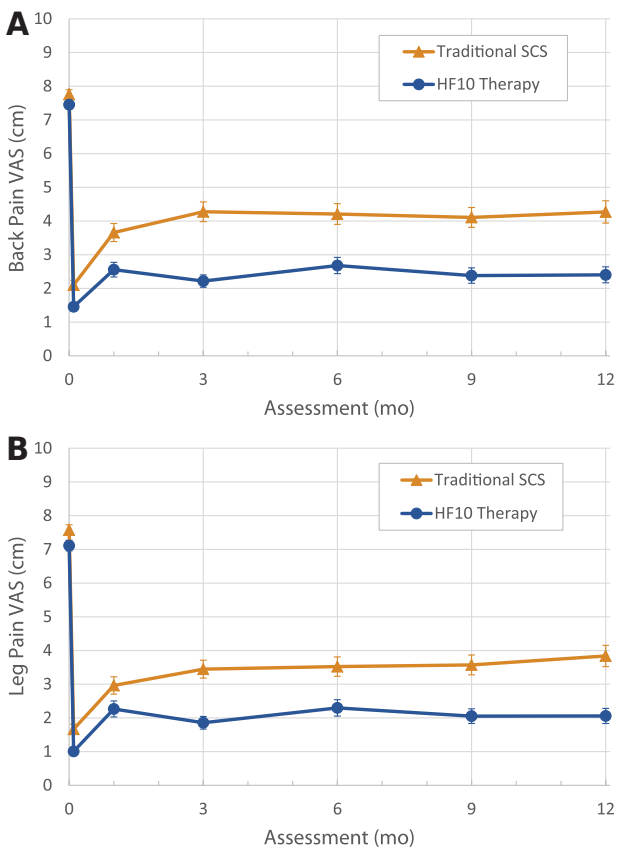

Fig. 3. Longitudinal back and leg pain visual analog scale (VAS) scores. Values at time 0 represent baselines scores, whereas values at time 0.1 represent results at the end of trial phase. (*A*) Back pain VAS, mean (SEM). (*B*) Leg pain VAS, mean (SEM). HF10 = 10-kHz high-frequency; SCS = spinal cord stimulation.

Study-related AEs

Importantly, neurological assessment revealed no stimulation-related neurological deficits in either treatment group. Only 4.0% of HF10 therapy subjects had a study-related serious AE (SAE) compared with 7.2% of traditional SCS subjects (P = 0.37). There was one death during the study period, resulting from a myocardial infarction of a subject randomized to traditional SCS. None of the SAEs were unanticipated, and none were classified as stimulation-related in either treatment group.

Nonserious study-related AEs were reported in 28 (27.7%) HF10 therapy and 32 (33.0%) traditional SCS subjects (P = 0.44). The most common study-related AEs were implant site pain (in 11.9% of HF10 therapy subjects and 10.3% of traditional SCS subjects) and uncomfortable paresthesia (in 0.0% of HF10 therapy subjects and 11.3% of traditional SCS subjects). Lead migration resulting in surgical revision occurred in 3.0% of HF10 therapy subjects and 5.2% of traditional SCS subjects (P = 0.49).

Discussion

Safety and Efficacy

The SENZA-RCT study provides the first scientifically rigorous, randomized, controlled trial demonstrating the superiority of HF10 therapy over traditional SCS in the long-term treatment of both back and leg pain. With an average of 13 yr since their pain diagnosis, 87% of subjects had previous back surgery for their pain condition and 88% relied on opioid pain medications. In spite of this extent of intractable pain, both traditional SCS and HF10 therapy demonstrated favorable safety and efficacy.

Table 3. Functional Capacity and Participant Satisfaction

	HF10 Therapy Treatment Group				Traditional SCS Treatment Group			
	Baseline	Month 3	Month 6	Month 12	Baseline	Month 3	Month 6	Month 12
ODI categorization (%)								
Minimal	0.0	16.9	16.9	16.9	0.0	6.2	11.1	8.6
Moderate	8.9	51.7	46.1	46.1	1.2	45.7	33.3	37.0
Severe	71.1	28.1	31.5	34.8	76.5	45.7	50.6	44.4
Crippled	20.0	3.4	5.6	2.2	22.2	2.5	4.9	9.9
GAF categorization (%)								
No symptoms	0.0	6.7	14.6	19.1	0.0	4.9	7.4	13.6
Minimal symptoms	6.7	27.0	28.1	24.7	9.9	23.5	27.2	22.2
Transient symptoms	17.8	27.0	23.6	27.0	19.8	22.2	25.9	23.5
Mild symptoms	37.8	29.2	24.7	18.0	35.8	29.6	24.7	23.5
Moderate symptoms	26.7	7.9	6.7	7.9	27.2	16.0	12.3	13.6
Serious symptoms	11.1	1.1	2.2	3.4	6.2	3.7	2.5	3.7
Some impairment	0.0	1.1	0.0	0.0	1.2	0.0	0.0	0.0
Participant satisfaction (%)								
Very satisfied		54.1		55.4		33.8		32.3
Satisfied		29.4		27.7		43.2		46.2
Not sure		14.1		15.7		17.6		16.9
Dissatisfied		1.2		1.2		2.7		3.1
Very dissatisfied		1.2		0.0		2.7		1.5

ODI and GAF categories with only 0% not shown.

GAF = Global Assessment of Functionality; HF10 = 10-kHz high-frequency; ODI = Oswestry Disability Index; SCS = spinal cord stimulation.

In terms of safety, the incidence of study-related SAEs over 12 months was low (4.0 to 7.2%) with no stimulation-related neurological deficits in either treatment group. Historically, lead migration has been the most frequently reported complication of SCS with rates ranging from 2.1 to 23%.[19–21] In the SENZA-RCT study, lead migration rates were comparatively low (3.0 to 5.2%), likely due to better device technology, implantation techniques, and patient selection in recent years.

Regarding effectiveness, traditional SCS results were consistent with the historical mantra of 50% of patients attaining 50% pain relief. Comparatively, the success of HF10 therapy was nearly twice that of traditional SCS, results that were statistically superior for both back and leg pain. Remarkably, two thirds of subjects receiving HF10 therapy achieved remitter status for back and leg pain, and over one third decreased or eliminated opioid analgesic usage at 12 months. The extent of these results is expected to dramatically improve subject's activity of daily living and quality of life.

Limitations

As with any clinical trial, limitations exist that deserve discussion. One consideration is the interaction of pain medications with SCS therapy. Investigators were allowed to adjust subjects' pain medication usage after device activation. Changes to opioid analgesics have the potential to confound the effects of SCS. However, the study protocol instructed not to increase opioid analgesics above baseline levels. Also, more HF10 therapy subjects reduced or eliminated opioid analgesics than traditional SCS subjects; thus, opioid analgesics were not responsible for the superior effectiveness of HF10 therapy. Because the study was not designed to resolve the chemical or psychological issues related to chronic use of pain medications, the effect of HF10 therapy and of traditional SCS on chronic opioid use requires further study.

Investigators and subjects were not masked to the assigned treatment group. Subject masking was impracticable because low-frequency SCS produces paresthesias, whereas the high-frequency SCS does not; thus, the therapies themselves become immediately known to the subjects. Due to the differences in stimulator lead placement, intraoperative testing, and device programming between the treatment groups, the study investigators could not be masked. The effect of the lack of masking in this randomized study is not known; nonetheless, the protocol was based on best practices guidance for comparative efficacy trial designs.[22–24]

It should also be noted that patients receiving HF10 therapy were instructed to recharge their devices daily. Daily recharges typically lasted 30 to 45 min, depending on the specific stimulation parameters. Patients receiving traditional SCS had various recharging routines, typically with longer recharge intervals and longer charging times consistent with the previously reported average recharge frequency of 5.2 times per month and 2.3 h per charge.[25] The comparative amount of resources to program the devices was not measured as part of this study.

Our definition for pain remission (having a pain score of ≤2.5) was determined by expert consensus, as being sufficiently low as to not significantly impact patients' quality of

life and activities of daily living. We proposed this definition as it may have great potential clinical utility, but it warrants further research and understanding.

Lastly, although specific inclusion and exclusion criteria were applied, there was heterogeneity in pain diagnoses as table 1 demonstrates. However, 75 to 80% of subjects were considered by the attending investigator to have failed back surgery syndrome, and the overall heterogeneity in diagnoses reflects the diversity of patients seen by pain specialists and is therefore a clinically relevant population to study.

Comparison to Previously Published Studies

Results from the SENZA-RCT study mirror those from the previous observational study (fig. 4), adding to the credibility of this therapy.[1,2] Comparison of SENZA-RCT results for leg pain to published literature is challenging, due to different inclusion/exclusion criteria (limited to predominant leg pain patients) and reporting methods. Nevertheless, leg pain relief for traditional SCS in the SENZA-RCT is consistent with previous reports.[12–14,26,27]

In two previous randomized, controlled trials of patients with predominant leg pain, SCS was found to be more effective than reoperation[26] and conventional medical management.[27] In the reoperation study, SCS was more effective in treating persistent radicular pain after lumbosacral spine surgery and often obviated the need for reoperation. In the conventional medical management study, more subjects randomized to SCS had a significant reduction in leg pain. These results along with those of the SENZA-RCT study suggest that HF10 therapy may be even better in comparison.

Conclusions

Potential Impact of HF10 Therapy Utilization

The SENZA-RCT study provides the first scientifically rigorous, randomized, controlled trial demonstrating the superiority of HF10 therapy over traditional SCS in the long-term treatment of both back and leg pain. Given the need for improved treatment options, the superior effectiveness of HF10 therapy promises to contribute substantially to the management of back and leg pain and potentially other chronic pain conditions to be studied. In addition, the superior efficacy, high responder rate, and low-risk profile as compared with alternative treatments position HF10 therapy favorably in terms of healthcare economic benefits.

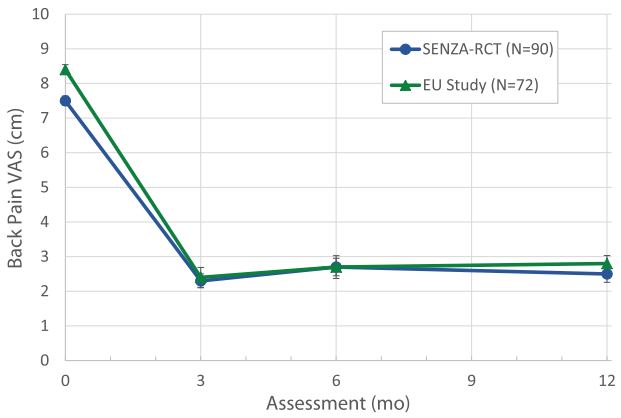

Fig. 4. Comparison of 10-kHz high-frequency (HF10) therapy results in the SENZA-RCT study to published European multicenter study (EU) results, mean (SEM). VAS = visual analog scale.

The paresthesia-free nature of HF10 therapy translates into benefits to patients and implanting physicians. Patients do not undergo the constant sensations associated with traditional low-frequency SCS, which at times is considered uncomfortable, may interrupt therapy and impact patients' quality of life. Physicians no longer need to perform intraoperative paresthesia mapping.

Furthermore, over one third of subjects receiving HF10 therapy reduced or eliminated their opioid analgesic intake, despite an average of 13 yr of chronic pain. In the context of insufficient evidence to support long-term opioid analgesic management of chronic pain and the epidemic consequences of nonmedical use, the marked pain relief experienced by responders to HF10 therapy is encouraging and may provide physicians with a therapeutic alternative in the management of chronic back and leg back.

The SENZA-RCT study is a landmark study, advancing the field of neuromodulation. The study is the first pivotal study in the history of SCS to provide comparative safety and effectiveness data between two SCS systems, providing long-term outcomes for both back and leg pain. Based on these results, HF10 therapy promises to substantially impact the management of back and leg pain with broad applicability to patients, physicians, and payers.

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Competing Interests

All authors have completed and submitted the International Committee of Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest. Dr. Kapural reported having received grants from Boston Scientific (Marlborough, Massachusetts) and personal fees from Medtronic (Minneapolis, Minnesota) and St. Jude Medical (St. Paul, Minnesota). Dr. Yu reported having received personal fees from Boston Scientific, Medtronic, and St. Jude Medical. Mr. Gliner reported having received personal fees from Nevro Corp. (Menlo Park, California). Dr. Vallejo reported having received grants from Nevro Corp. and Boston Scientific and personal fees from Nevro Corp. and Boston Scientific. Dr. Amirdelfan reported having received personal fees from Nevro Corp., Medtronic, and St. Jude Medical. Dr. Brown reported having received personal fees from Nevro Corp., Medtronic, and St. Jude Medical. Dr. Benyamin reported having received grants and personal fees from Boston Scientific. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Kapural: Carolina's Pain Institute at Brookstown, Wake Forest Baptist Health, 605 Cotton Street, Winston-Salem, North Carolina 27103. lkapural@ccrpain.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix

The SENZA-RCT Investigators and Participating Centers: Center for Clinical Research and Carolina's Pain Institute at Brookstown, Wake Forest Baptist Health, Winston-Salem, North Carolina (Leonardo Kapural, M.D., Ph.D.; Christopher A. Gilmore, M.D.; James E. North, M.D.; Richard Rauck, M.D.); Swedish Pain and Headache Center, Seattle, Washington (Cong Yu, M.D.; Thomas Yang, M.D.); The Pain Center of Arizona, Phoenix, Arizona (Matthew W. Doust, M.D.; Abram H. Burgher, M.D.; Todd W. Turley, M.D.); Millennium Pain Center, Bloomington, Illinois (Ricardo Vallejo, M.D., Ph.D.; Ramsin Benyamin, M.D.); Advanced Pain Therapy, PLLC, Hattiesburg, Mississippi (B. Todd Sitzman, M.D., M.P.H.); IPM Medical Group, Inc., Walnut Creek, California (Kasra Amirdelfan, M.D.); Pain Consultants of Oregon, Eugene, Oregon (Donna M. Morgan, M.D.; Joseph Dunn, M.D.; Peter S. Kosek, M.D.); Coastal Orthopedics and Sports Medicine, Bradenton, Florida (Lora L. Brown, M.D.; Richard Bundschu, M.D.; Gennady Gekht, M.D.); Comprehensive Pain and Rehabilitation, Pascagoula, Mississippi (Thomas L. Yearwood, M.D., Ph.D.; Matthew Barfield, M.D.; Hunt T. Hapworth, M.D.); Houston Pain Associates, Houston, Texas (Allen W. Burton, M.D.). *Data and Safety Monitoring Board:* Allen Wyler, M.D. (Chair); Sunil Panchal, M.D.; Bruce C. Stouch, Ph.D.; and James C. Watson, M.D. *Additional Contributor:* Richard G. Holcomb, Ph.D. (Independent Biostatistician) contributed substantially to the conception and design of this trial and to the analysis and interpretation of data.