Durability of high-frequency 10 kHz spinal cord stimulation for patients with painful diabetic neuropathy refractory to conventional treatments: 12-month results from a randomized controlled trial

Short running title: 10 kHz SCS for refractory PDN

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Trial registration: ClincalTrials.gov - NCT03228420 (registered July 24, 2017). URL- https://clinicaltrials.gov/ct2/show/NCT03228420

Word count: 750

Figures: 1

Diabetic sensorimotor peripheral neuropathy is the most common complication of diabetes and results in potentially debilitating symptoms, including numbness, tingling, and frequently neuropathic pain. Approximately 20% of persons with diabetes will develop painful diabetic neuropathy (PDN) with paresthesia, burning, and shooting pain (1).

Currently, there are no disease-modifying treatments for PDN. Therapeutic goals include symptom management along with behavioral modifications to mitigate further damage (2). Neuropathic pain medications are recommended, including gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and opioids. Adherence to commonly prescribed PDN medications is poor due to inadequate pain relief or intolerable side effects.

Spinal cord stimulation (SCS) involves a surgically implanted device delivering mild electrical pulses to modulate chronic pain pathways. High-frequency (10 kHz) SCS provides superior pain relief for chronic back and leg pain, and recent data demonstrate it also results in substantial pain relief for PDN patients (3,4). This RCT evaluated the long-term impact of 10 kHz SCS for PDN patients with refractory symptoms.

Methods have been described previously (4). Participants had symptoms for at least 12 months that were refractory to medications, lower limb pain ≥5 on 10 cm visual analog scale (VAS), HbA1c ≤10%, BMI ≤45 kg/m^2. Participants were eligible to crossover at 6 months if they had <50% pain relief, were dissatisfied with treatment, and the investigator deemed it medically appropriate. Temporary trial SCS evaluated eligibility for permanent device implant (Nevro Corp., Redwood City, CA) with success defined as ≥50% pain relief. Neurologists trained investigators to perform comprehensive neurological examinations assessing lower limb motor strength, reflexes, and sensation, including pinprick and 10g monofilament. Paired t-tests assessed mean

percent change from baseline within treatment groups. Categorical variables were compared between treatment groups using Fisher's Exact test.

In total, 216 patients were randomized 1:1 to continued conventional medical management (CMM, n=103) or the addition of 10 kHz SCS to CMM (n=113). Treatment groups were well matched for baseline characteristics (4). Among participants assigned 10 kHz SCS+CMM, 104 proceeded to temporary trial SCS, and 90 received permanent device implants. In the CMM group, 95 completed 6-month follow-up and 81% (77/95) crossed to 10 kHz SCS, compared to none from the 10 kHz SCS+CMM arm ($p < .001$). Sixty-four participants received permanent device implants after crossover.

Mean lower limb pain VAS was 7.6 cm (95% CI: 7.2-7.9) for 10 kHz SCS+CMM patients at baseline, 1.7 cm (95% CI: 1.3-2.1) at 6 months and maintained at 1.7 cm (95% CI: 1.3-2.1) to 12 months, representing 77.1% mean pain relief (95% CI: 71.8-82.3, $p < .001$, Figure A). At both 6 and 12 months, 86% (72/84) were treatment responders, defined as those with at least 50% pain relief from baseline (Figure B). For the crossover group, mean baseline lower limb pain VAS was 7.2 cm (95% CI: 6.8-7.6) with no change at 6 months but improvement after crossover similar to the originally assigned 10 kHz SCS group: mean 70.3% pain relief (95% CI: 63.4-77.1, $p < .001$), lower limb pain VAS score of 2.0 cm (95% CI: 1.6-2.4, Figure A) and 84% responders (49/58, Figure B).

Investigators reported neurological improvements, particularly improved sensory function, maintained over 12 months for majority of patients with 10 kHz SCS: 68% (52/76) of participants originally assigned to SCS and 62% (32/52) of participants after crossover (Figure C). Insensate feet limit activities of daily living and may result in debilitating sequelae, including injury from falling, foot ulceration, and lower limb amputation.

There were 8 procedure-related infections (5.2%): 3 resolved with conservative treatments and patients continued in the study, while 5 (3.2%) required surgical explant of the device. There were no explants for loss of efficacy. Two participants (1.3%) had the location of the implantable pulse generator revised and 1 (0.6%) participant experienced lead migration that required a revision procedure; all 3 continued in the study.

The crossover group replicates the findings from the original implant group, providing a cumulative sample of 154 implanted patients with long-term data. In addition to a higher proportion of pain responders compared with pharmacotherapy or low-frequency SCS (5), 10 kHz SCS does not induce paresthesia, an advantage for PDN patients with uncomfortable paresthesia at baseline. Additionally, sleep disturbance due to pain, a common ailment for PDN patients, markedly improved by mean 61.7% (95% CI: 55.9-67.5) with 10 kHz SCS. This study, the largest RCT conducted for SCS treatment of PDN, demonstrates substantial, durable pain relief and potentially disease-modifying neurological improvements over 12 months, providing high-quality evidence in support of 10 kHz SCS for PDN patients with refractory symptoms.

Acknowledgements

The authors are grateful to Joe Massaro, PhD, professor of biostatistics, mathematics, and statistics at Boston University and director of biostatistics and data management at Harvard Clinical Research Institute for his independent statistical analyses for this publication. The authors are also indebted to Brian Levy, MD, for his thoughtful review and expert feedback on the manuscript. This study was funded by Nevro Corp.

Author contributions: ESB, KA, MNG, VG, RHB, CEA, CEN, RST, DLC, and NAM contributed to the conception and design of the study. EAP, TGS, JAS, JLW, SMS, KA, MNG, JX, CY, AN, DGP, KCT, MJC, VG, RHB, NDM, DS, SPL, DJD, KAS, JHG, MTB, NJH, AFI, PC, and PWW recruited subjects and acquired data. EAP, ESB, CEA, CEN, RST, DLC, and NAM were involved in the analysis and interpretation of the data along with an independent biostatistician. All authors reviewed the manuscript critically and approved of its content. EAP had full access to the study data and takes responsibility for the integrity of the data and accuracy of analysis.

Disclosures: EAP has received consulting fees from Abbott, Medtronic, Neuros Medical, Nevro, Saluda, Vertos and research support from Medtronic, Neuros Medical, Nevro, ReNeuron, Saluda. JAS has received research support from Boston Scientific, Nevro, Saluda, Vertiflex. JLW has received consulting fees from Lilly, CALIBR. SMS has received research support from Nevro. KA has received consulting fees from Nevro, Nalu, Saluda, Biotronik, Medtronic and research support from Nevro, Biotronik, Vivex, Saluda, SPR Therapeutics. MNG has received consulting fees from Nevro, Saluda, Avanos and research support from Abbott, Saluda, Neuros, Nevro, Nalu, Avanos. JX has received research support from Nevro, NIH K08 Grant CA228039. CY has received research support from Nevro. AN has received consulting fees from Flowonix, Nevro and research support from Nevro. DGP has received consulting fees from Abbott, AIS, Allergan, Amgen, CornerLoc and research support from Abbott, Biotronik, Flowonix, Nevro, Nuvectra, Vertiflex. NDM has received consulting fees from Nevro, Salix Pharma, Biodelivery Sciences, Averitas and research support from Boston Scientific, Medtronic, Nevro. DS has received consulting fees from Abbott, Boston Scientific, Nevro, Vertos, Vertiflex and research support from Abbott, Biotronic, Nevro, Vertos, Vertiflex. SPL has received consulting fees from Nevro. JHG has received consulting fees from Stratus Medical and Abbott, and research support from SPR Therapeutics and Mainstay Medical. CEA has received consulting fees from Nevro, Vertex, Lilly, Pfizer, Teva and research support from Allergan, Amgen, DSI, Lilly, Novartis, Teva. CEN has received consulting fees from Siemens Healthineers, Horizon Therapeutics, Nevro, Neurogastrx, Exelixis. RST has received consulting fees from Medtronic, Nevro, Saluda. NAM has received consulting fees from Boston Scientific, Sollis Therapeutics, Saluda Medical, Nevro, Abbott (formerly Spinal Modulation), Vertos Medical, Nuvectra, Relievant Medsystems, is a Medical Monitor for Mainstay's RESTORE clinical trial, and has received research support from Avanos "Halyard," Mallinckrodt, Mesoblast, Neuros Medical. ESB and DLC are employees of Nevro Corp. TGS, VG, KCT, MJC, RHB, DJD, KAS, MTB, NJH, AFI, PC, and PWW have no conflicts to disclose.

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Figure legend

Pain and Neurological Results Over 12 Months

A) Average lower limb pain scores over time for 10 kHz SCS+CMM participants (n=84, left) and CMM participants who crossover after 6 months (n=58, right). Participants rated pain on a 10 cm visual analog scale with 0 representing “no pain” and 10 being the “worst pain imaginable”. Left and right lower limbs were each rated separately and the scores were averaged together for each participant. Error bars: 95% CI. **B)** Proportion of pain responders, defined as those with at least 50% pain relief from baseline, at 3, 6, 9, and 12 months for 10 kHz SCS+CMM participants (n=84, left) and CMM participants who crossover after 6 months (n=58, right). **C)** Proportion of participants over time who investigators reported to have improvement on neurological examination for 10 kHz SCS+CMM participants (n=76, left) and CMM participants who crossover after 6 months (n=52, right). Assessment included motor strength and reflex testing as well as sensory testing for light touch, pinprick, and 10g monofilament. All follow-up assessments were compared to baseline and the investigator categorized motor, reflex, and sensory separately as an “improvement”, “no change”, or a “deficit”. Overall neurological improvement was defined as an improvement in motor, reflex, or sensory function without a deficit in any category.