INPLASY PROTOCOL

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Corresponding author:
Taylor Rod

rod.taylor@glasgow.co.uk

Author Affiliation:
Commexus Ltd

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Indirect Comparison of 10 kHz Spinal Cord Stimulation (SCS) versus Traditional Low-Frequency SCS for the Treatment of Painful Diabetic Neuropathy: A Systematic Review of Randomized Controlled Trials

Hoelzer, BC[1]; Edgar, D[2]; Lu, S[3]; Taylor, R[4].

Review question / Objective: **For patients with lower limb pain due to painful diabetic neuropathy (PDN), how effective is high-frequency SCS at 10 kHz (10 kHz SCS) compared with low-frequency SCS (LF-SCS), as measured by pain intensity and responder rate outcomes?**
Condition being studied: **We are studying painful diabetic neuropathy (PDN), which typically manifests as burning pain with concurrent paresthesia. This type of neuropathic pain often results in poor health-related quality of life, depression, anxiety, and impaired sleep.**
Eligibility criteria: **Inclusion: Study reported pain-related outcomes from an RCT of SCS that enrolled PDN patients with lower limb pain symptoms. Exclusions: Study report not peer-reviewed; study has no full-text manuscript available (eg, conference proceedings); study does not report original data; data cannot be extracted for the population of interest.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 September 2022 and was last updated on 13 September 2022 (registration number INPLASY202290056).

INTRODUCTION

Review question / Objective: **For patients with lower limb pain due to painful diabetic neuropathy (PDN), how effective is high-frequency SCS at 10 kHz (10 kHz SCS) compared with low-frequency SCS (LF-SCS), as measured by pain intensity and responder rate outcomes?**

Rationale: **Until recently, data were only available from randomized controlled trials (RCTs) of LF-SCS in the PDN indication. A contemporary review will update the literature and allow an indirect comparison of 10 kHz SCS and LF-SCS treatment outcomes. The analysis may be useful to**

clinicians and patients during their evaluation of SCS modalities.

Condition being studied: We are studying painful diabetic neuropathy (PDN), which typically manifests as burning pain with concurrent paresthesia. This type of neuropathic pain often results in poor health-related quality of life, depression, anxiety, and impaired sleep.

METHODS

Search strategy: PubMed search strategy:
#1. randomized controlled trial[pt]
#2. controlled clinical trial[pt]
#3. randomized[tiab]
#4. placebo[tiab]
#5. drug therapy[sh]
#6. randomly[tiab]
#7. trial[tiab]
#8. groups[tiab]
#9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10. animals[mh] NOT humans[mh]
#11. #9 NOT #10
#12. clinical trials, phase iii[MeSH Terms]
#13. "Phase 3"[tiab] or "phase3"[tiab] or "phase III"[tiab] or P3[tiab] or "PIII"[tiab]
#14. #12 OR #13
#15. #11 OR #14
#16. "spinal cord"[tiab] OR spine[tiab] OR spinal[tiab] OR epidural[tiab] OR "dorsal column*"[tiab]
#17. stimulation[tiab] OR stimulator[tiab] OR neuromodulation[tiab] OR neurostimulator[tiab]
#18. #16 AND #17
#19. "spinal cord stimulation"[mesh] OR "electric stimulation therapy"[mesh] OR scs[tiab]
#20. #18 OR #19
#21. "Diabetic Neuropathies"[mesh]
#22. diabet*[tiab] AND (neuropath*[tiab] OR polyneuropath*[tiab])
#23. #21 OR #22
#24. #20 AND #23
#25. #15 AND #24
CENTRAL search strategy:
#1. "spinal cord":ti,ab OR spine:ti,ab OR spinal:ti,ab OR epidural:ti,ab OR "dorsal column*":ti,ab
#2. stimulation:ti,ab OR stimulator:ti,ab OR neuromodulation:ti,ab OR neurostimulator:ti,ab
#3. #1 AND #2
#4. MeSH descriptor: [Spinal Cord Stimulation] explode all trees
#5. MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#6. scs:ti,ab
#7. #4 OR #5 OR #6
#8. #3 OR #7
#9. MeSH descriptor: [Diabetic Neuropathies] explode all trees
#10. diabet*:ti,ab AND (neuropath*:ti,ab OR polyneuropath*:ti,ab)
#11. #9 OR #10
#12. #8 AND #11 in Trials.

Participant or population: Painful diabetic neuropathy patients with lower limb pain symptoms.

Intervention: Spinal cord stimulation: During LF-SCS, electrical pulses are applied to the spinal cord at a frequency between 40 Hz and 60 Hz. Paresthesia is elicited in the painful area by the electrical stimulation and masks the sensation of pain. During 10 kHz SCS, no paresthesia is felt or required for pain relief.

Comparator: The target population received either 10 kHz SCS or LF-SCS during separate RCTs. We indirectly compared the two modalities.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Inclusion: Study reported pain-related outcomes from an RCT of SCS that enrolled PDN patients with lower limb pain symptoms. Exclusions: Study report not peer-reviewed; study has no full-text manuscript available (eg, conference proceedings); study does not report original data; data cannot be extracted for the population of interest.

Information sources: PubMed and CENTRAL databases. Authors were contacted for access to individual patient data.

Main outcome(s): Two standard SCS efficacy outcomes were defined: (1) mean pain intensity reduction from baseline (2) responder rate, defined as the proportion of subjects with at least a 50% reduction in pain intensity from baseline. Six-month data were used since this was the longest follow-up period common to the RCTs. Two effect measures were also defined: (1) Mean difference (MD) with a 95% confidence interval (CI) for the pain intensity reduction from baseline outcome (2) Relative risk (RR) with a 95% CI for the responder rate outcome.

Quality assessment / Risk of bias analysis: A single reviewer assessed the risk of bias for each eligible RCT using the Cochrane Risk of Bias tool (RoB 2) tool. The assessment considered: (1) Bias arising from the randomization process(2) Bias due to deviations from intended interventions (3) Bias due to missing outcome data (4) Bias in measurement of the outcome (5) Bias in selection of the reported result.ach domain was graded as low risk, high risk, or with some concerns.

Strategy of data synthesis: The analysis indirectly compared the absolute treatment effect of 10 kHz SCS and LF-SCS using SCS treatment arm data from the included RCTs. We defined 2 populations for each study to allow the comparison of equivalent patient cohorts between the RCTs: (1) A modified intention-to-treat (mITT) population: randomized subjects who entered the SCS trial phase (2) A permanent implant population: subjects who completed the SCS trial phase and received a permanent system. We also pooled the unweighted outcomes from the LF-SCS studies for each of the 2 populations to create another comparator group. We calculated the mITT mean pain intensity reductions with 95% CI for the 10 kHz SCS cohort and each LF-SCS group and compared the 10 kHz SCS pain reduction with each LF-SCS group using the two-sample t-test. In addition, we performed a test for the assumption of equal variance, with the Satterthwaite method used to derive the pooled variance if we found the variance to be unequal. We also calculated responder rates and RRs with 95% CI for each mITT and permanent implant analysis population and compared responder rates between the 10 kHz SCS and LF-SCS groups. For this comparison, we used the Wald Chi-square statistic under the null hypothesis of RR=1, ie, no difference between groups.

Subgroup analysis: N/A.

Sensitivity analysis: N/A.

Country(ies) involved: UK & USA.

Keywords: Painful diabetic neuropathy; peripheral neuropathy; spinal cord stimulation; 10 kHz SCS; diabetes; neuropathic pain; systematic review; meta-analysis.

Contributions of each author:
Author 1 - Bryan Hoelzer - Author 1 was involved in the conceptualization of the study and reviewing /editing of the manuscript.
Author 2 - Deborah Edgar - Author 2 was involved in the conceptualization of the study and the development of the study methodology. She also prepared the original manuscript draft.
Author 3 - Shiao-ping Lu - Author 3 conducted the formal statistical analysis and was involved in reviewing/editing the manuscript.
Author 4 - Rod Taylor - Author 4 was involved in the conceptualization of the study, development of the study methodology, and reviewing/editing of the manuscript.

Conflicts of interest: Author B.H. is a paid consultant for Nevro Corp. and Vertiflex. Author D.E. received a fee from Nevro Corp. in her capacity as an independent medical writer. Author S.L. received a fee from Nevro Corp. in her capacity as an independent statistician. Author R.T. is a paid consultant for Nevro Corp., Medtronic, and Saluda Medical.