International Medical Case Reports Journal

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE SERIES

Feasibility and Tolerability of Controllable Pulse Parameter Transcranial Magnetic Stimulation in Patients with Painful Diabetic Neuropathy: A Case Series Study

Jiyeon Park[1], Stevie D Foglia[2], Chloe C Drapeau[1], Perry V Mayer[3], Harsha Shanthanna[4], Aimee J Nelson[1,2]

[1]Department of Kinesiology, McMaster University, Hamilton, ON, Canada; [2]School of Biomedical Engineering, McMaster University, Hamilton, ON, Canada; [3]The Mayer Institute, Hamilton, ON, Canada; [4]Department of Anesthesia, McMaster University, Hamilton, ON, Canada

Correspondence: Aimee J Nelson, McMaster University, 1280 Main Street West, Hamilton, ON, L8S 4K1, Canada, Tel +1 905-525-9140 x28053, Fax +1 905-523-6011, Email nelsonaj@mcmaster.ca

Abstract: This case series highlights the feasibility and tolerability of using controllable pulse parameter Transcranial Magnetic Stimulation (cTMS) in individuals with painful diabetic neuropathy (pDN). cTMS delivers repetitive monophasic pulses, which allows for greater and longer lasting effects compared to traditional repetitive TMS (rTMS). All participants (N = 2) tolerated 10 sessions of cTMS over a two-week period (five days per week) with no discomfort from the stimulation. They reported no pain from the stimulation despite their heightened pain sensitivity as a result of pDN. The cTMS intervention improved their pain and quality of life as determined through questionnaires evaluating pain, depression, anxiety, and other related measures. Notably, cTMS has never been evaluated in diabetic neuropathy, and our data suggest that it is feasible and tolerable in this clinical population. It further proposes a potential therapeutic treatment option for individuals with pDN.

Keywords: pDN, cTMS, rTMS, neuropathic pain, non-invasive brain stimulation, monophasic

Introduction

Controllable pulse parameter Transcranial Magnetic Stimulation (cTMS) allows for the delivery of repetitive monophasic pulses, which appear to impact corticospinal excitability to a greater extent than traditional biphasic pulses in healthy controls.[1,2] Goetz et al[1] note greater inhibition in corticospinal excitability from monophasic pulses compared to biphasic repetitive TMS (rTMS). Further, Arai et al[2] indicate enhanced magnitude and longevity of monophasic rTMS effects when compared with biphasic rTMS. As monophasic pulses activate a more uniformly distributed population of cortical interneurons, they can produce longer and more pronounced after-effects on the motor cortex, when compared to biphasic pulses.[2] However, the sensation of cTMS may be a barrier for clinical populations as Peterchev et al[3] report that cTMS at 100% and 120% resting motor threshold (RMT) is sharp and uncomfortable in healthy participants. The feasibility of using cTMS in a clinical population remains unknown.

rTMS has been shown to alleviate pain in various chronic pain conditions including neuropathic pain, central pain and fibromyalgia.[4] However, headache and discomfort due to rTMS stimulation have been reported despite its non-invasiveness[5] and considering that rTMS protocols are delivered over several days or weeks,[4] intolerability and refusal to treatment may be a barrier. Chronic pain is associated with hyperalgesia due to central sensitization, which may increase scalp sensation leading to discomfort.[6] To date, no study has evaluated the feasibility of cTMS in a chronic pain cohort with heightened sensitivity to pain and cTMS has not been performed in a clinical population. As there is no cure for painful diabetic neuropathy (pDN), clinical management primarily relies on

Received: 12 April 2025
Accepted: 1 September 2025
Published: 26 September 2025

pharmacological therapies aimed at alleviating symptoms.[7] However, they are often limited with suboptimal efficacy and adverse side effects, underscoring the need for alternative therapeutic approaches such as cTMS. The goal of the present study was to determine the feasibility and tolerability of cTMS in two patients with pDN with heightened sensitivity.

Materials and Methods

This is a sub-study report of the full research protocol approved by the Hamilton Integrated Research Ethics Board. Here in, we reported on two individuals before and after the real stimulation component in a larger placebo-controlled, cross-over study. Feasibility was assessed in two male participants (A and B) both aged 65 years suffering from type 2 diabetes and pDN in both feet of >3 years (see Table 1). Patients with pDN suffer from neuropathic pain and present with hyperalgesia and allodynia, suggesting heightened sensitivity to pain.[7] In our study, participants were directly referred by the physician who diagnosed their pDN which included symptoms of allodynia and hyperalgesia as determined via quantitative sensory testing. Neither participant were engaged in non-pharmacological interventions such as physical therapy or exercise during the study. However, both were maintained on pharmacological treatment regimens that included medications indicated in Table 1. No changes in glycemic control were made during the duration of the study. We used an intensity of 80% RMT,[8,9] which is below the threshold suggested for inducing pain when rTMS is used.[10] In line with Tani et al,[10] the intensity used in repetitive biphasic clinical protocols (80% RMT) is the same as the threshold for pain, which was found to be 79% RMT in healthy individuals. Considering the threshold of 80%, feasibility was tested by assessing for tolerability, effectiveness and safety in patients with pDN.

cTMS protocol consisted of completing five consecutive sessions per week of cTMS for two weeks (10 session total). Both participants were blinded to the type of stimulation (real, placebo) and both received the real stimulation. Ten Hz stimulation was applied to the vertex (Cz) over the presumed leg representation of the primary motor cortex (M1).[11] The coil was positioned at a 45° angle with respect to the posterior-to-anterior (PA) axis, and this site was digitally registered using Brainsight Neuronavigation (Rogue Research, Canada). The stimulation was applied at 80% RMT obtained from the right abductor pollicis brevis (APB).[11] Each session consisted of 2004 pulses (1.2s trains, 12 pulses per train, 3s interstimulus interval) for 11.5 minutes using a figure-of-eight coil (70mm inner diameter) with an Elevate TMS device (Rogue Research, Canada) and a standard pulse width of 80 μs was used throughout the protocol as used elsewhere.[3,11] RMT was obtained in all 10 sessions. Assessment took place before (T0) and immediately after (T1) the 10-day intervention. The assessment aimed to evaluate feasibility related to adherence to the designed protocol, safety related to the reporting of any adverse events, and tolerability related to participants' enjoyment and sensation of the stimulation. If participants attended 90% of the sessions, then the protocol was considered feasible. Regarding tolerability, participants were asked to report the sensation and comfort level of the stimulation (comfortable or uncomfortable). We also explored the effectiveness of the stimulation. This included pain intensity numerical rating scale (NRS), as well as a Pain

Table 1 Participant Demographics

	A	**B**
Age (Years)	65	65
Sex	Male	Male
Diabetes Type	Type 2	Type 2
Duration of pDN (Years)	3	9
Insulin Dependent	Yes	Yes
Non-Pharmacological Treatment	None	None
Diabetes Medications	Metformin, Sitagliptin, Insulin glargine, Insulin aspart	Metformin, Insulin aspart, Empagliflozin
Pain Medications	Pregabalin, Oxycodone/acetaminophen	Pregabalin, Gabapentin

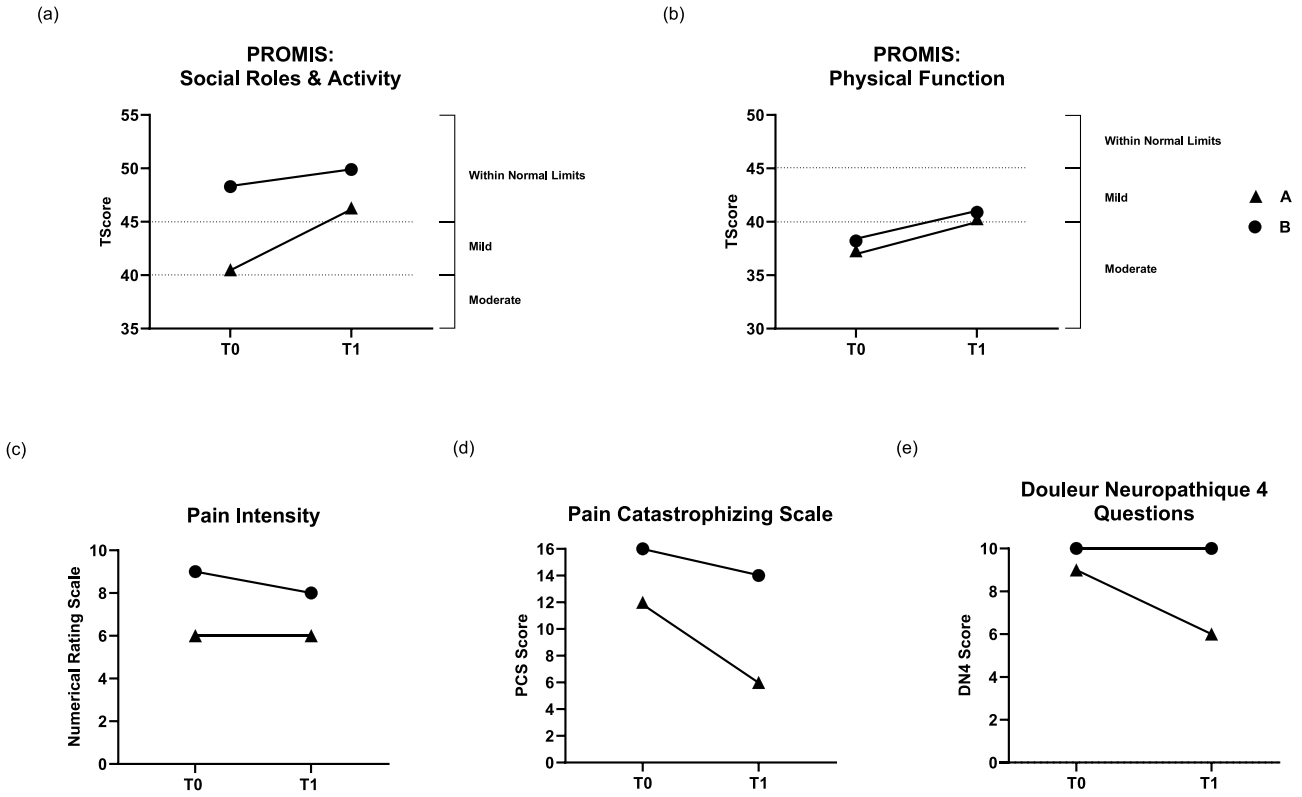

Figure 1 Changes in PROMISE-29 v2.0 (social participation (**a**) and physical function (**b**)), pain intensity (**c**), PCS (**d**), and DN4 (**e**). "A" represents Participant A and "B" represents Participant B.

Catastrophizing scale-EN-SF (PCS), Patient-Reported Outcomes Measurement Information System 29-Item Profile (PROMIS-29 v2.0) and the Douleur Neuropathique 4 Questions (DN4).

Results

Both participants completely adhered to the study protocol deeming the study feasible. No adverse events occurred before, during, or up to two months following the intervention. Both participants tolerated cTMS without any discomfort and indicated that the intervention "felt nice" and that they "enjoyed" receiving the intervention. Further, participants noted that no pain was experienced during tapping sensation. Figure 1 shows the changes in PROMIS-29 v2.0, as well as the changes in pain intensity, PCS and DN4.

Discussion

Our results indicated that cTMS delivered over 10 sessions was feasible and tolerated by two participants with pDN. Long durations of therapy and the associated time commitment (i.e., over 6 weeks) are often barriers for participants completing clinical rTMS studies.[12] However, both participants attended all sessions of cTMS at a rate of 5 sessions per week, within the time frame of two weeks. Additionally, tolerance of rTMS studies may be low in pain populations for reasons such as headache, migraine, scalp sensitivity, and discomfort.[6] In our study, both participants tolerated the protocol and neither reported discomfort such as sharpness or headache associated with cTMS. Despite the participants' hypersensitivity to pain, no adverse events were reported.

Importantly, we delivered cTMS at 80% RMT. Peterchev et al[3] reported discomfort and sharpness with cTMS at approximately 100% RMT and 120% RMT in their healthy control group. Using a stimulation intensity of 80% RMT aligns with established safety guidelines for TMS, minimizing the risk of seizures, excessive cortical activation, or other adverse events.[13] This subthreshold intensity is frequently used in clinical protocols to optimize the balance between safety and therapeutic efficacy. RMT at 80% has been shown to recruit excitatory cortical neurons while remaining below

the threshold for activating peripheral pain fibers, thereby enhancing tolerability and reducing discomfort.[4,11,14] This intensity is beneficial for use in pain populations where minimizing adverse effects is essential for maintaining compliance and retention.

Our study employed a standard pulse width of 80 μs, which may contribute to greater tolerability, as shorter pulse widths (i.e., 30 μs) used in cTMS have been associated with sharper pain and discomfort compared to wider pulses.[3] Shorter durations (<80 μs) generate more focal stimulation by limiting the duration of current delivery, which reduces the likelihood of activating deeper structures. However, this also decreases the total energy delivered, potentially leading to insufficient neuronal recruitment unless the stimulation intensity is increased. In contrast, longer pulse widths (>120 μs) can expand the spread of activation to non-target areas, increasing the risk of discomfort and off-target effects.[3,15] A pulse width of 80 μs is therefore considered a practical balance that provides adequate cortical activation while minimizing the stimulation of scalp nociceptors and reducing the likelihood of discomfort. These findings underscore the importance of parameter selection in the application of cTMS to manage chronic pain, given its tolerability and effectiveness in this patient group.

Relating to effectiveness, cTMS resulted in an improvement in the ability to participate in social roles and physical function as both participants reached normal levels and/or stayed within the normal level. Participant A showed no change in pain intensity, whereas participant B, who exhibited more severe pain at the baseline, noted a 10% reduction. While a 10–20% reduction on the NRS is generally considered the minimal clinically important difference,[16] it may still represent a meaningful improvement in quality of life, particularly in the context of refractory symptoms and limited treatment options. Both participants A and B indicated improvement in pain catastrophizing by 6 points and 2 points, respectively. However, these changes are below the 8 point difference in the pain catastrophizing scale required for a clinically meaningful change.[17] These findings align with studies using rTMS to decrease pain in diabetic neuropathy where participants received traditional rTMS stimulations for 5 days.[18,19] The DN4 data revealed no change in participant B and a 33% improvement for participant A. Importantly, it is our view that even modest symptom relief may indicate the potential effectiveness of cTMS and support its further investigation in painful diabetic neuropathy. Collectively, the data suggest variability in the responses across the various measures with some indication of improvement and other data suggesting little to no change. Importantly, no participant experienced worsening of symptoms. These preliminary findings support the acceptability of the intervention and provide valuable insights to guide outcome measure selection and study design for the larger ongoing trial.

Contextual and motivational factors may have contributed to the adherence and tolerability observed in this study. Participants were aware that they would receive both real and placebo interventions, this might have contributed to study retention and positive attitudes towards the study as a whole. Further, the physician who diagnosed and manages their pDN referred the participants to the study, which may have encouraged retention in the study. Efforts were made to ensure that the lab was accessible to participants such as close proximity to parking spaces, flexible time of testing, the use of pillows and other comfort aids during testing, all of which may contribute to the tolerability of the intervention. Last, the two participants expressed that they were refractory to other pain treatments, which may have increased motivation to adhere to the study protocol.

A limitation of this study is the absence of a placebo as this is a sub-study of the full research protocol. The full research protocol is a placebo-controlled, cross-over study where all participants will receive either a ‘real’ or ‘placebo’ cTMS condition and then receive the opposite condition after a 2-month washout period. Of note, the efficacy results of this case series study are preliminary and based on a sample size of two participants. The importance of placebo control in TMS trials for chronic pain lies in its ability to rigorously isolate true neuromodulatory effects from non-specific factors such as participant expectations and the treatment context, which are particularly pronounced in pain populations.[20] This is especially critical given that the placebo response can itself produce analgesia, approaching or exceeding the effects of real stimulation.

Conclusion

This study is the first to use cTMS in a chronic pain condition, specifically in pDN, and it suggests that cTMS is tolerable and feasible when delivered at 80% RMT for 10 sessions over a two-week intervention in this population. These case

findings provide preliminary evidence supporting the feasibility and potential therapeutic effects of cTMS in pDN. However, as this report is based on a subset of participants from an ongoing placebo-controlled, cross-over trial, definitive conclusions regarding efficacy must await completion of the full study.

Data Sharing Statement

All other data can be accessed from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The Hamilton Integrated Research Ethics Board has reviewed and approved the study protocol (16481) and registered at https://clinicaltrials.gov (NCT05937984). All participants provided written informed consent including permission for publication prior to their participation in this study. The study complied with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

We thank the Institute for Pain Research and Care (IPRC) 2023 research seed grant competition for funding.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Goetz SM, Luber B, Lisanby SH, et al. Enhancement of neuromodulation with novel pulse shapes generated by controllable pulse parameter transcranial magnetic stimulation. *Brain Stimul*. 2016;9(1):39–47. doi:10.1016/j.brs.2015.08.013
2. Arai N, Okabe S, Furubayashi T, et al. Differences in after-effect between monophasic and biphasic high-frequency rTMS of the human motor cortex. *Clin Neurophysiol*. 2007;118(10):2227–2233. doi:10.1016/j.clinph.2007.07.006
3. Peterchev AV, Luber B, Westin GG, Lisanby SH. Pulse width affects scalp sensation of transcranial magnetic stimulation. *Brain Stimul*. 2017;10(1):99–105. doi:10.1016/j.brs.2016.09.007
4. Yang S, Chang MC. Effect of repetitive transcranial magnetic stimulation on pain management: a systematic narrative review. *Front Neurol*. 2020;11:114. doi:10.3389/fneur.2020.00114
5. Overvliet GM, Jansen RAC, van Balkom AJLM, et al. Adverse events of repetitive transcranial magnetic stimulation in older adults with depression, a systematic review of the literature. *Int J Geriatr Psychiatry*. 2021;36(3):383–392. doi:10.1002/gps.5440
6. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895–926. doi:10.1016/j.jpain.2009.06.012
7. Sloan G, Shillo P, Selvarajah D, et al. A new look at painful diabetic neuropathy. *Diabetes Res Clin Pract*. 2018;144:177–191. doi:10.1016/j.diabres.2018.08.020
8. Park J, Foglia SD, Drapeau CC, Mayer P, Shanthanna H, Nelson AJ. Advanced controlled transcranial magnetic stimulation to alleviate pain in diabetic neuropathy. *Brain Stimul*. 2025;18(1):390–391. doi:10.1016/j.brs.2024.12.524
9. Drapeau C, Foglia S, Park J, Shanthanna H, Maida E, Nelson A. Investigating the effects of controlled-pulse parameter transcranial magnetic stimulation to reduce pain in fibromyalgia. *Brain Stimul*. 2025;18(1):372–373. doi:10.1016/j.brs.2024.12.475
10. Tani K, Hirata A, Tanaka S. Quantitative assessment of pain threshold induced by a single-pulse transcranial magnetic stimulation. *Front Neurosci*. 2020;14:559. doi:10.3389/fnins.2020.00559
11. Foglia SD, Rehsi RS, Turco CV, Shanthanna H, Nelson AJ. Case report: the feasibility of rTMS with intrathecal baclofen pump for the treatment of unresolved neuropathic pain following spinal cord injury. *Front Rehabil Sci*. 2022;3:893014. doi:10.3389/fresc.2022.893014
12. Zhang T, Huang Y, Jin Y, Ma X, Liu Z. Treatment for major depressive disorder by repetitive transcranial magnetic stimulation in different parameters: a randomized double-blinded controlled trial. *Front Psychiatry*. 2021;12:623765. doi:10.3389/fpsyt.2021.623765
13. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: expert guidelines. *Clin Neurophysiol*. 2021;132(1):269–306. doi:10.1016/j.clinph.2020.10.003
14. Sun X, Long H, Zhao C, et al. Analgesia-enhancing effects of repetitive transcranial magnetic stimulation on neuropathic pain after spinal cord injury: An fNIRS study. *Restor Neurol Neurosci*. 2019;37(5):497–507. doi:10.3233/RNN-190934
15. Milosevic M, Marquez-Chin C, Masani K, et al. Why brain-controlled neuroprosthetics matter: mechanisms underlying electrical stimulation of muscles and nerves in rehabilitation. *Biomed Eng Online*. 2020;19:81. doi:10.1186/s12938-020-00824-w

16. Smith SM, Dworkin RH, Turk DC, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. *Pain*. 2020;161(11):2446–2461. doi:10.1097/j.pain.0000000000001952
17. Monticone M, Portoghese I, Rocca B, Giordano A, Campagna M, Franchignoni F. Responsiveness and minimal important change of the Pain Catastrophizing Scale in people with chronic low back pain undergoing multidisciplinary rehabilitation. *Eur J Phys Rehabil Med*. 2021;58 (1):68–75. doi:10.23736/S1973-9087.21.06729-0
18. Abdelkader AA, El Gohary AM, Mourad HS, El Salmawy DA. Repetitive TMS in treatment of resistant diabetic neuropathic pain. *Egypt J Neurol Psychiatry Neurosurg*. 2019;55(1):30. doi:10.1186/s41983-019-0075-x
19. Yang S, Kwak SG, Choi GS, Chang MC. Short-term effect of repetitive transcranial magnetic stimulation on diabetic peripheral neuropathic pain. *Pain Physician*. 2022;25(2):E203–E209.
20. André-Obadia N, Magnin M, Garcia-Larrea L. On the importance of placebo timing in rTMS studies for pain relief. *Pain*. 2011;152(6):1233–1237. doi:10.1016/j.pain.2010.12.027