Randomized Controlled Trial

Short-term Effect of Repetitive Transcranial Magnetic Stimulation on Diabetic Peripheral Neuropathic Pain

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Disclaimer: The present study was supported by a National Research Foundation of Korea grant funded by the Korean government (grant no. NRF-2019M3E5D1A02068106).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-01-2021
Revised manuscript received: 11-02-2021
Accepted for publication: 11-30-2021

Free full manuscript: www.painphysicianjournal.com

Background: Approximately half of the patients with long-standing diabetes are known to have diabetic peripheral neuropathy (DPN). Pain from DPN deteriorates quality of life and hinders activities of daily living.

Objectives: This study aimed to evaluate the short-term effect of high-frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) on the left primary motor cortex (M1) for neuropathic pain in the lower extremities due to DPN.

Study Design: A randomized controlled trial.

Setting: The outpatient clinic of a single academic medical center.

Methods: In this randomized trial, 22 patients with DPN were randomly assigned to the rTMS group (10 Hz stimulation, 5 sessions) or the sham group. A numeric rating scale (NRS) was used to measure pain intensity before treatment and after one day and one week of treatment. Physical and mental health status were evaluated using the Short Form 36-Item Health Survey (SF-36), comprising 2 subscales (physical and mental component scores [PCSs and MCSs]), at one-week posttreatment. Of the 22 included patients, 20 (10 patients in each group) completed the study.

Results: In the rTMS group, the NRS score at one day and one week posttreatment was significantly lower than that at pretreatment. The SF-36 PCS and SF-36 MCS were significantly increased one week after the rTMS sessions. However, in the sham group, the NRS score, SF-36 PCS, and SF-36 MCS did not significantly change after the rTMS sessions.

Limitations: The small number of included patients and no long-term follow-up.

Conclusion: High-frequency rTMS on the left M1 may be useful for managing pain in the lower extremities due to DPN and may improve a patient's the quality of life.

Keywords: Diabetic peripheral neuropathy, diabetes, repetitive transcranial magnetic stimulation, pain, quality of life

Pain Physician 2022: 25:E203-E209

Diabetic peripheral neuropathy (DPN) in patients with diabetes is caused by long-term high blood sugar levels (1). It is one of the most common complications of diabetes (2). The symptoms of DPN are loss of sensation, paresthesia, and pain with burning, lancinating, and aching at the bilateral distal upper and lower extremities (3). Usually, pain from DPN initiates in the lower extremities. According to the

Centers for Disease Control and Prevention, DPN affects approximately half of the patients with long-standing diabetes (4). The risk factors for DPN are poor control of the blood sugar level, older age, smoking, obesity, hypertension, hyperlipidemia, and microalbuminuria (5). Pain due to DPN hinders activities of daily living and decreases sleep quality (6). Moreover, if the pain persists for a long time, it can induce psychological problems, such as depression and anxiety (7).

To control pain due to DPN, oral medications such as anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, non-steroidal anti-inflammatory drugs, opioids, and opioid-like drugs are usually used (8). However, these drugs often do not sufficiently control pain from DPN to a tolerable level. Moreover, oral medication can have various adverse effects such as drowsiness, dizziness, nausea, and constipation (9). Therefore, clinicians and researchers are attempting to develop nonpharmacological therapeutic tools to alleviate the pain caused by DPN effectively and safely.

Repetitive transcranial magnetic stimulation (rTMS) is a safe, noninvasive, and effective therapeutic intervention that uses an electromagnetic coil applied to the scalp to produce a magnetic field (10,11). rTMS induces changes in cortical excitability at the stimulation site and transsynaptically at distant areas. Cortical excitability is increased by high-frequency (≥ 5 Hz) stimulation and is decreased by low-frequency (1 Hz) stimulation (10). The application of high-frequency unilateral rTMS to the motor cortex in patients is reported to have a potential to control various types of pain, such as neuropathic pain, fibromyalgia, and musculoskeletal origin pain (myofascial pain syndrome, shoulder pain, and lower back pain) (10,12-15). However, little is known regarding the effect of rTMS on reducing pain due to DPN.

In the current study, we investigated the short-term effects of high-frequency (10 Hz) rTMS over the left primary motor cortex (M1) to control pain due to DPN in the lower extremities.

Methods

Patients

We prospectively recruited 22 consecutive patients who visited a pain clinic for neuropathic pain caused by DPN. The inclusion criteria were as follows: 1) diabetes, 2) neuropathic pain (stocking and glove distribution) on a numeric rating scale (NRS) score of ≥ 3 (where 0 indicates no pain and 10 indicates the most intense pain imaginable) in the lower extremities, (3) pain duration of ≥ 3 months, 4) age between 21 and 80 years, and 5) absence of contraindications for rTMS, such as a history of epileptic seizure, presence of metal in the skull, or presence of a cardiac pacemaker. Written informed consent was obtained from all patients. The study protocol was approved by the Institutional Review Board of a university hospital and was registered at ClinicalTrials.gov (Identifier: NCT0483366).

The sample size was calculated based on a previous study (16), in which the reduction in the NRS score after rTMS was 1.9 ± 1.5. Hence, the number of patients required for a type I error of 0.05 and a power of 80% was found to be 10 per group. Considering a dropout rate of 10%, we recruited 11 patients per group (Fig. 1).

Study Design

This study was designed and performed as a prospective, randomized controlled clinical trial. Twenty-two patients were randomly assigned to two groups: the rTMS and sham groups (n = 11/group). Randomization was performed using a randomization table. We used the numbers of the ones places in a random table for group allocation. We considered odd numbers in the ones place of the random table as the rTMS group and even numbers as the sham group. The patients were blinded to the group assignment throughout the study.

Each patient underwent five consecutive sessions (Monday to Friday for one week). A physiatrist who was blinded to the study protocol performed rTMS using a Magstim Super Rapid Magnetic Stimulator (The Magstim Company) with a 70 mm figure-of-eight air-cooled coil. rTMS was delivered on the left side of the patient's head. The coil was held with the handle pointing posteriorly and oriented sagittally. A cloth marked with one cm spacing and Cz-referenced to the intersection of the midsagittal and interaural lines was placed on the scalp. The patients were seated in a comfortable chair and were asked to wear foam earplugs during the rTMS session.

The motor threshold (MT) was defined as the minimum stimulus required to elicit a motor evoked potential with a peak-to-peak amplitude of > 50 μV in 3 out of 5 consecutive trials in the right abductor pollicis brevis muscle. If the MT was < 80%, the stimulation intensity was set to MT plus 20%. Hence, when the MT was > 80%, the stimulation intensity was set to 100% of the stimulator output. Motor evoked potentials were elicited in the right abductor pollicis brevis muscle. Each site was stimulated 5 times at one cm intervals, with at least a 10-second interval between

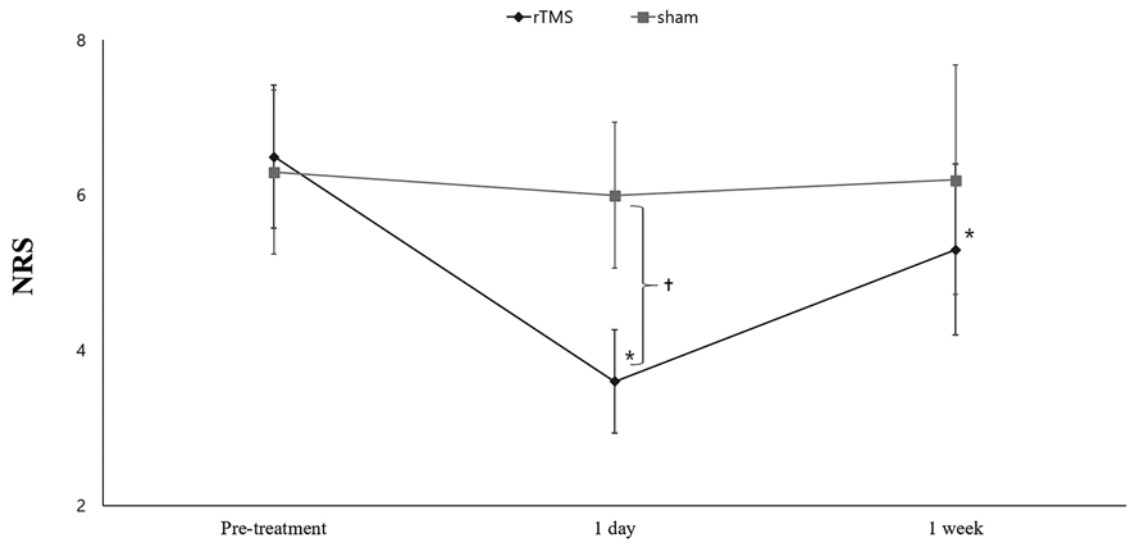

Fig. 1. *Change in the numeric rating scale (NRS) score. At one day after the repetitive transcranial magnetic stimulation (rTMS) sessions, the NRS score was significantly lower in the rTMS group than in the sham group. However, at one week after the rTMS sessions, the NRS score tended to be lower in the rTMS group than in the sham group, without statistical significance. In the intragroup comparison, in the rTMS group, NRS scores at one day and one week after the rTMS sessions were significantly lower than the NRS score before treatment; however, the NRS score did not significantly change after the rTMS sessions.*
*$P < 0.05$: Intragroup comparison between pre-treatment and post-treatment.
†$P < 0.05$: Intergroup comparison at each time point.

stimulations. We determined the optimal scalp site for rTMS, the site where the stimuli evoked motor potentials, with a maximal peak-to-peak amplitude.

Patients in the rTMS group were administered rTMS over the optimal scalp site at 10 Hz, with an intensity of 90% of the MT and a duration of 5 seconds, for a total of 20 trains separated by 55-second intertrain pauses (a total of 1,000 pulses) (17). The coil was placed tangentially to the scalp at an approximate angle of 45° tilted backward and laterally. Patients in the sham group were administered sham stimulation using the same protocol, except that the angle of the coil was 90° (i.e., perpendicular, rather than tangential) to the skull. The experimenter (GC) who delivered rTMS or sham stimulations did not participate in the outcome measurement. Oral medication dosages of all patients were not changed during the stimulation and follow-up periods.

Outcome Measures

An investigator who was blinded to the grouping of the patients and did not participate in any treatment performed the assessment of the pretreatment and follow-up data. We assessed pain intensity using the NRS score as the primary outcome (18). Average pain intensity during the 24 hours before NRS assessment was investigated. Additionally, we measured health-related quality of life using the Short Form 36-Item Health Survey (SF-36) (19). The SF-36 consists of 8 components: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. The SF-36 has 2 subscales: a physical component score (PCS) and a mental component score (MCS), reflecting overall physical and mental health status, respectively. The NRS score was assessed the day before starting the stimulation sessions (pretreatment) and one day and one week after the sessions were completed. The SF-36 PCS and SF-36 MCS were measured the day before starting the stimulation sessions and one week after the sessions were completed.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Science (SPSS, v. 24.0, IBM Corporation). De-

mographic and clinical data at each evaluation time point of the rTMS and sham groups were compared using the Mann–Whitney U test and χ^2 test. To evaluate the changes in NRS scores within groups across time, the assessment outcomes at pretreatment, and at one day and one week posttreatment were compared using a generalized linear model. Multiple comparisons were performed using Bonferroni correction as a contrast. To evaluate the changes in the SF-36 PCS and SF-36 MCS across time in each group, the assessment outcomes at one week posttreatment were compared with those at pretreatment using Wilcoxon's signed rank test. To evaluate the changes in the SF-36 PCS and SF-36 MCS within groups across time, the difference in the pretreatment and one week posttreatment scores was calculated and compared to outcomes using the Mann–Whitney U test. The level of statistical significance was set at $P < 0.05$.

Results

Two patients (one patient in each group) of the 22 included patients dropped out because of their busy schedules. Hence, 10 patients in each group completed the sessions and follow-up evaluations. No adverse side effects were reported during the rTMS sessions. In addition, no significant intergroup differences in demographic data were noted ($P > 0.05$) (Table 1).

Table 1. *Demographic characteristics and clinical outcomes of the rTMS and sham group patients.*

	rTMS group	Sham group	*P* value
Number, n	10	10	
Age, years	60.0 ± 5.0	60.8 ± 5.0	0.631
Men:Women	6:4	5:5	0.653
NRS, pretreatment	6.5 ± 0.9	6.3 ± 1.1	0.631
NRS, one day posttreatment	3.6 ± 0.7	6.0 ± 0.9	< 0.001
NRS, one week posttreatment	5.3 ± 1.1	6.2 ± 1.5	0.123
SF-36, pretreatment			
PCS	32.4 ± 2.9	32.3 ± 3.1	0.796
MCS	37.6 ± 2.9	35.4 ± 2.8	0.165
SF-36 one week posttreatment			
PCS	34.5 ± 2.7	32.4 ± 3.0	0.075
MCS	39.1 ± 3.2	35.2 ± 2.7	0.019

Abbreviations: MCS, mental component score; NRS, numeric rating scale; PCS, physical component score; rTMS, repetitive transcranial magnetic stimulation; SF-36, Short Form 36-Item Health Survey. Bolds indicate *P* value < 0.05.

The average NRS score in the rTMS group decreased from 6.5 ± 0.9 at pretreatment to 3.6 ± 0.7 at one day posttreatment and 5.3 ± 1.1 at oneweek posttreatment (Fig. 1). In the sham group, the average NRS scores at pretreatment, one day posttreatment, and one week posttreatment were 6.3 ± 1.1, 6.0 ± 0.9, and 6.2 ± 1.5, respectively. In addition, in the rTMS group, the average SF-36 PCS increased from 32.4 ± 2.9 at pretreatment to 34.5 ± 2.7 at one week post-treatment (Fig. 2A). In the sham group, the SF-36 PCS at pretreatment was 32.3 ± 3.1 and at one week posttreatment was 32.4 ± 3.0. Further, the average SF-36 MCS increased from 37.6 ± 2.9 at pretreatment to 39.1 ± 3.2 at one week posttreatment in the rTMS group (Fig. 2B). In the sham group, the SF-36 MCS score at pretreatment was 35.4 ± 2.8 and at one week posttreatment was 35.2 ± 2.7.

The NRS score, SF-36 PCS, and SF-36 MCS on the day before starting the stimulation sessions (pretreatment) were not significantly different between the rTMS and sham groups ($P > 0.05$) (Table 1). However, at one day posttreatment, the NRS score was significantly lower in the rTMS group than in the sham group ($P < 0.001$, Z = -3.752) (Fig. 1). At one week posttreatment, the NRS score tended to be lower in the rTMS group than in the sham group, without statistical significance ($P = 0.123$, Z = -1.586). In addition, the SF-36 PCS at one week posttreatment tended to be higher in the rTMS group than in the sham group, without statistical significance ($P = 0.075$, Z = -1.829) (Fig. 2A). The SF-36 MCS at one week posttreatment was significantly higher in the rTMS group than in the sham group ($P = 0.019$, Z = -2.386) (Fig. 2B).

Regarding serial changes in the clinical data, in the rTMS group, the NRS score was significantly lower at one day and one week posttreatment than at pretreatment (NRS score: $P = 0.004$, Z = -2.913 for one day posttreatment and $P = 0.006$, Z = -2.762 for one week posttreatment) (Fig. 1). The SF-36 PCS and SF-36 MCS were significantly increased at one week posttreatment (SF-36 PCS one week posttreatment: $P = 0.007$, Z = -2.687; SF-36 MCS one week posttreatment: $P = 0.004$, Z = -2.877) (Figs. 2A and 2B). However, in the sham group, the NRS score, SF-36 PCS, and SF-36 MCS did not significantly change posttreatment (NRS score: one day posttreatment: $P = 0.083$, Z = -1.732, one week posttreatment: $P = 0.655$, Z = -0.447; SF-36 PCS one week posttreatment: $P = 0.705$, Z = -0.378; SF-36 MCS one week posttreatment: $P = 0.414$, Z = -0.816) (Figs. 1, 2A, and 2B).

Discussion

In the current study, we evaluated the effective-

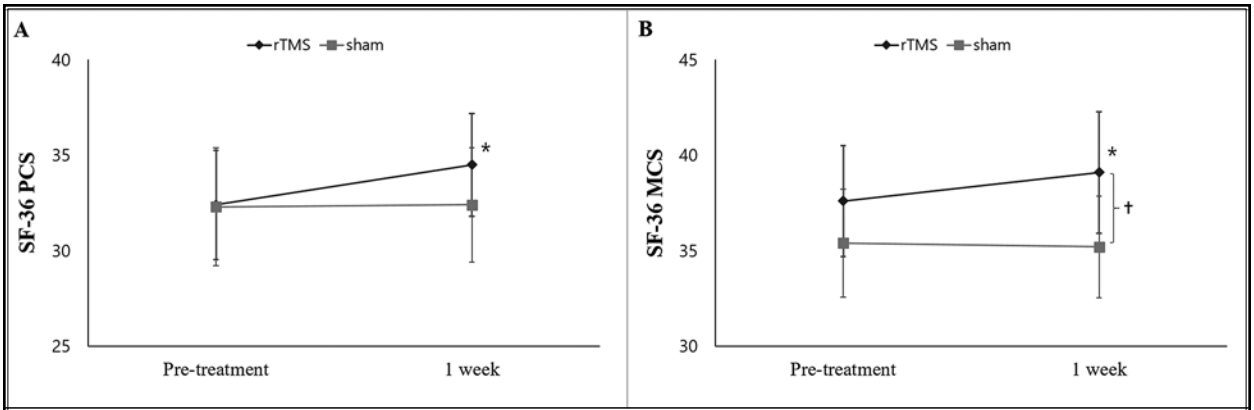

Fig. 2. *Change in the Short Form 36-Item Health Survey (SF-36) physical component score (PCS) and mental component score (MCS). (A) The SF-36 PCS at one week after the repetitive transcranial magnetic stimulation (rTMS) sessions tended to be higher in the rTMS group than in the sham group, without statistical significance. (B) The SF-36 MCS and SF-36 PCS at one week after the rTMS sessions were significantly higher in the rTMS group than in the sham group. The SF-36 PCS and SF-36 MCS were significantly increased in the rTMS group at one week after the rTMS sessions; however, they did not significantly change in the sham group.*
*$P < 0.05$: Intragroup comparison between pre-treatment and post-treatment
†$P < 0.05$: Intergroup comparison at each time point

ness of high-frequency (10 Hz) rTMS for managing neuropathic pain in the lower extremities due to DPN. Our results revealed that at both one day and one week posttreatment with rTMS, neuropathic pain in the lower extremities was significantly reduced and the SF-36 PCS and SF-36 MCS were significantly increased. However, no changes were observed after sham stimulation. Higher SF-36 PCS and SF-36 MCS are indicative of higher physical and mental quality of life, respectively (19). Therefore, our results indicate that rTMS treatment can provide better physical and mental quality of life as well as control neuropathic pain in patients with DPN. However, the pain level of the patients in the rTMS group increased from 3.6 at one day posttreatment to 5.3 at one week posttreatment. This indicates that additional rTMS sessions are needed to reinforce the analgesic effect of rTMS.

Regarding the most effective target site of rTMS for pain reduction, Hirayama et al (20) evaluated the effect of high-frequency rTMS on the M1, premotor area, supplementary motor area, and postcentral gyrus in patients with intractable neuropathic pain. In their study, only stimulation of the M1 effectively reduced pain. In previous studies, the most frequently stimulated site for pain reduction was M1, especially in the left hemisphere (21). Therefore, in our study, we targeted the left M1 for rTMS treatment.

Although the mechanism of pain reduction by rTMS has not been clearly demonstrated, some possible mechanisms have been suggested. Previous functional magnetic resonance imaging studies revealed that rTMS on the M1 resulted in changes in several cortical and subcortical structures associated with pain modulation and processing, such as the orbitofrontal cortex, anterior cingulate gyrus, medial thalamus, and periaqueductal gray matter (22,23). This indicated that rTMS can modify abnormal excitation of pain-related brain structures and thus trigger cascades of analgesic synaptic events in several pain-related brain structures. Moreover, rTMS on the M1 has been reported to reduce neuropathic pain by triggering the descending pain-inhibitory pathways (24). In addition, the pain-reducing effect of rTMS is suggested to be related to the increase in blood flow in pain-related brain structures (25). In patients with chronic pain, cerebral blood flow was reported to be reduced; however, an increase in cerebral blood flow was observed on positron emission tomography after the application of rTMS on the M1 (25,26). Additionally, in an animal study, cortical stimulation was found to have antinociceptive effects by changing neuronal activities in the periaqueductal gray matter, which is responsible for pain processing (27).

To date, the pain-reducing effect of high-frequency rTMS has been evaluated in various peripheral nerve disorders such as phantom limb pain after amputation, radiculopathy, and brachial plexopathy (28-30). Overall, previous studies have demonstrated that high-frequency rTMS has a significant short-term pain-

reducing effect, and the quality of life has been found to be improved after rTMS sessions (21). Although rTMS does not have a long-term effect, many studies have demonstrated that the effect of rTMS is maintained beyond one week posttreatment (31-33). Similarly, the degree of pain reduction after rTMS treatment was not as high as that at one day posttreatment with rTMS; however, the pain-reducing effect was significantly sustained even at one week posttreatment with rTMS. Only 2 studies have reported the effect of rTMS on pain relief in patients with DPN (16,31). In 2013, Onesti et al (16) recruited 23 patients, of which 11 were allocated to the rTMS group and 12 to the sham group. They applied deep TMS using a unique coil design (H-coil), which is larger than the conventionally used coil and can directly activate deep neuronal populations. After 5 sessions of 20 Hz rTMS using the H-coil, pain was significantly reduced and disappeared approximately 3 weeks after the treatment. However, Onesti et al (16) used a specially designed coil to directly apply rTMS to deeply located neurons. In 2019, Abdelkader et al (31) conducted 10 Hz rTMS on M1 (5 sessions) with a 70 mm diameter figure-of-eight coil in 10 insulin-dependent and 10 non-insulin-dependent patients. At the 3-week follow-up after completion of the rTMS sessions, the pain severity measured by the visual analog scale was significantly reduced compared to that at pretreatment. However, Abdelkader et al's study (31) is limited, as a control or placebo group was not included. Therefore, our study is the first randomized controlled trial to evaluate the effect of rTMS using a conventionally used coil.

A limitation of our study is that we recruited a small number of patients and did not perform long-term follow-up. The analgesic effects induced by a single session of rTMS have been reported to last up to one week, but when repeated rTMS sessions are conducted, its effect can be reinforced and sustained for up to one month (34). Therefore, a follow-up period of at least one week is recommended for the evaluation of the analgesic effect of rMTS. In addition, we did not evaluate the included patients' severity of diabetes and diabetic neuropathy. Lastly, the sham stimulation mimicked only the sound of the coil discharge and could not mimic cutaneous sensations or twitches of scalp muscles during rTMS sessions. Studies that compensate for these limitations are warranted in the future.

Conclusions

In the current study, we found that pain in the lower extremities due to DPN was significantly reduced at one day and one week posttreatment with rTMS (5 sessions). We applied high-frequency (10 Hz) rTMS to the left M1. In addition, the physical and mental quality of life of the patients improved after rTMS treatment. Therefore, we believe that rTMS is a useful therapeutic option for patients with pain caused by DPN.

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