Original Article

JHSMR Journal of Health Science and Medical Research

The Effects of Transcranial Direct Current Stimulation in Patients with Chronic Intractable Peripheral Neuropathic Pain: A Randomized Sham-Controlled Study

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Received 11 June 2025 ● Revised 23 June 2025 ● Accepted 25 June 2025 ● Published online 29 October 2025

Abstract:

Objectives: Transcranial direct current stimulation (tDCS) has demonstrated efficacy in managing neuropathic pain associated with spinal cord injury and fibromyalgia, with a low incidence of adverse effects. This study aimed to evaluate the effects of tDCS in patients with refractory peripheral neuropathic pain.

Material and Methods: In this prospective, randomized, double-blind, sham-controlled study, 12 patients with chronic intractable peripheral neuropathic pain (≥6 months) were randomly allocated to receive either active tDCS (2 mA for 20 minutes) or sham stimulation for 5 consecutive days. The primary outcome was pain reduction, measured using the Numeric Rating Scale (NRS) at baseline, daily during stimulation (days 1-5), and post-treatment (weeks 1, 2, 4, and 6). Secondary outcomes included the Neuropathic Pain Symptom Inventory (NPSI) and the EQ-5D-5L at the 4-week follow-up. Adverse events were recorded.

Results: Active tDCS resulted in a statistically significant pain reduction on days 2, 3, and 5 compared to the sham group (NRS reduction: Day 2, 5.00±2.37 vs. 1.67±1.75, p-value=0.020; day 3, 5.17±2.32 vs. 1.83±1.94, p-value=0.022; day 5, 5.50±2.07 vs. 2.67±2.25, p-value=0.047). However, no significant differences in pain reduction were observed at weeks 1, 2, 4, or 6. NPSI and EQ-5D-5L scores also showed no significant differences between the groups at the 4-week follow-up. Adverse events were mild and comparable between the groups.

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J Health Sci Med Res
doi: 10.31584/jhsmr.20251276
www.jhsmr.org

Conclusion: tDCS demonstrated significant short-term pain relief in patients with chronic intractable peripheral neuropathic pain. However, larger studies with longer follow-up periods are required to validate its long-term efficacy.

Keywords: intractable, neuralgia, transcranial direct current stimulation, pain, randomized controlled trial

Introduction

Peripheral neuropathic pain (PNP) is a chronic pain condition resulting from nerve lesion or disease, with common etiologies including painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and radiculopathy[1]. Despite the availability of pharmacological treatments, such as anticonvulsants and antidepressants, their efficacy remains limited, with a number needed to treat ranging from 3.6 to 7.7[2]. Furthermore, long-term studies indicate that only 23.7% of patients with neuropathic pain achieve clinically significant improvements in pain and function after one year of treatment[3]. The limited effectiveness of conventional pharmacotherapy, coupled with the burden of adverse effects, highlights the need for alternative treatment strategies.

Interventional therapies, including neurostimulation techniques, have been explored for managing refractory neuropathic pain. Spinal cord stimulation, deep brain stimulation, and high-frequency transcutaneous electrical nerve stimulation have demonstrated varying degrees of efficacy[4,5]. In recent years, 2 non-invasive brain stimulation techniques—repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)—have emerged as promising treatment modalities for neuropathic pain[6]. While rTMS received approval from the United States Food and Drug Administration in 2008 for major depressive disorders, and has shown potential for pain relief in fibromyalgia and neuropathic pain[7-9], the accessibility and feasibility of this technique are limited due to its high cost and equipment requirements. In contrast, tDCS is a more affordable, portable, and user-friendly alternative, making it a more viable option for broader clinical applications.

The analgesic effects of tDCS are thought to be mediated by the modulation of cortical excitability, primarily through polarity-dependent changes in neuronal resting membrane potential. Anodal stimulation generally enhances cortical excitability, whereas cathodal stimulation exerts inhibitory effects. Studies suggested that tDCS modulates pain perception through multiple mechanisms, including alterations in regional cerebral blood flow, changes in glutamatergic and GABAergic neurotransmission, and enhanced endogenous opioid release[10,11].

Previous studies have shown that tDCS provides pain relief in patients with central neuropathic pain, including those with stroke, spinal cord injury, multiple sclerosis, and trigeminal neuralgia[12-14]. Our previous review reported that 5 out of 6 prospective sham-controlled studies demonstrated significant pain relief following single or multiple sessions of tDCS in patients with spinal cord injury-related neuropathic pain[15]. A systematic review suggested that tDCS is a safe and potentially effective intervention for reducing pain intensity in fibromyalgia[16]. For peripheral neuropathic pain, a randomized controlled trial investigating tDCS for painful diabetic neuropathy demonstrated significant immediate and short-term pain relief lasting up to 4 weeks[17]. However, the evidence for tDCS in peripheral neuropathic pain remains limited and inconclusive due to the limited number of studies, with conflicting findings across the studies[18]. Given the variability in study protocols and patient populations, further research is necessary to establish the therapeutic efficacy of tDCS in different neuropathic pain conditions.

This study primarily aimed to evaluate the analgesic effects of tDCS in patients with chronic intractable peripheral neuropathic pain. The secondary objectives also included evaluating changes in neuropathic pain symptom severity, quality of life, and any adverse effects associated with the intervention. By addressing these gaps in the literature, this study sought to contribute to the growing body of evidence on the potential role of tDCS as a non-invasive neuromodulatory therapy for neuropathic pain management.

Material and Methods

Study design

This study was a prospective, randomized, double-blind, sham-controlled trial conducted at the Pain Clinic, Siriraj Hospital, Bangkok, Thailand. This trial was conducted in accordance with the principles of the Declaration of Helsinki, registered in the Thai Clinical Trials Registry (TCTR20141016001), and approved by the Siriraj Institutional Ethics Committee (COA. Si179/2014). All participants provided written informed consent before enrollment.

Participants

Participants were adults aged 18 to 65 years diagnosed with chronic peripheral neuropathic pain for at least 6 months. Inclusion criteria required a baseline Numeric Rating Scale (NRS-11) pain score of at least 4/10 and a history of refractory pain despite treatment with at least 2 neuropathic pain medications at adequate dosages for 6 months. Participants were required to meet the International Association for the Study of Pain criteria for probable or definite neuropathic pain and have no prior experience with tDCS[19,20]. Patients with clinically significant or unstable medical or psychiatric conditions, substance abuse, implanted electronic devices, central nervous system diseases, or pregnancy were excluded. Participants could withdraw from the study at any time without consequence. Although participants were permitted to take rescue medication as needed, no changes to their regular pain medication regimens were allowed throughout the study.

Randomization and blinding

Participants were randomly assigned in a 1:1 ratio to receive either active or sham tDCS using a computer-generated randomization sequence. Allocation was concealed using sequentially numbered opaque envelopes. Blinding was maintained by ensuring that treatment assessments were conducted by an assistant nurse who was not involved in the intervention. Both participants and study personnel responsible for data collection were blinded to treatment allocation.

Interventions

The direct current stimulator used (TCT Research 1CH tDCS Stimulator Model 101) is powered by a 9V alkaline battery and delivers a constant current. As for the ethical and safety issues, the protocol of tDCS's procedure followed the standard guidelines[21]. Stimulation was applied via a pair of saline-soaked surface sponge electrodes (35 cm^2). Electrode placement followed the international 10/20 electroencephalogram (EEG) system: the anodal electrode was positioned over the primary motor cortex (M1) contralateral to the pain side, while the cathodal electrode was placed over the supraorbital region ipsilateral to the pain side. Both electrodes were secured using rubber bands.

To identify M1, 20% of the auricular distance from Cz was measured along the auricular line, corresponding to the C3/C4 EEG location. In cases of asymmetrical pain, the contralateral M1 was targeted; for symmetrical pain, the dominant hemisphere (typically the left for right-handed individuals) was stimulated.

During active stimulation, the current was gradually increased over 8 seconds and maintained at 2 mA for 20 minutes daily over 5 consecutive days (Monday to Friday). In the sham stimulation, the current ramped up

and stopped after 10 seconds, with no further stimulation during the 20-minute session. However, the device screen continued to display current and impedance levels to maintain blinding[22,23].

Two minutes after stimulation began, skin under the electrodes was checked for redness or irritation, and participants were asked about their sensations. Impedance was recorded at the start and every 5 minutes. If impedance approached 7 kΩ, 0.25 mL of saline was added to each sponge to maintain conductivity. After the 20-minute session, electrodes and rubber bands were removed.

Outcome measures

The primary outcome was the reduction in pain intensity, measured using the NRS-11 scale (0=no pain, 10=worst imaginable pain)[24,25]. Pain intensities were recorded at baseline, immediately before and after each stimulation session from day 1 to day 5, and at follow-up visits conducted at weeks 1, 2, 4, and 6 after treatment. The pain reduction was defined as the difference between the immediate pain score after stimulation and the baseline.

Secondary outcomes included changes in neuropathic pain symptom severity and quality of life. Neuropathic pain symptom severity was evaluated using the Thai version of the Neuropathic Pain Symptom Inventory (NPSI-T), a self-reporting questionnaire comprising 12 items (Q1–Q12). Ten of these items assess pain intensity on a scale from 0 (no pain) to 10 (worst imaginable pain), grouped into 5 clinical domains: superficial spontaneous pain (Q1), deep spontaneous pain (Q2, Q3), paroxysmal pain (Q5, Q6), evoked pain (Q8–Q10), and paresthesia/dysesthesia (Q11, Q12). The remaining 2 items—Q4 and Q7—evaluate the duration of spontaneous pain and frequency of paroxysmal pain, respectively. The NPSI-T total score, ranging from 0 to 100, is calculated by summing the scores from the 10 intensity-rated items[26]. The Thai version of the EuroQol-Five Dimensions-Five Levels (EQ-5D-5L) questionnaire, a self-reporting tool, was used to evaluate quality of life. This instrument asks respondents to rate the severity of problems in 5 domains—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—using a 5-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to). The EQ-5D-5L also includes a utility score reflecting overall quality of life, ranging from 0 (equivalent to death) to 1 (representing full health), with possible negative values (<0) indicating health states perceived as worse than death. In Thai populations, scores have ranged from –0.42 to 0.94[27]. Additionally, participants rated their overall health on a 100 mm Visual Analog Scale, anchored by "worst imaginable health" and "best imaginable health." Adverse events, including skin irritation, discomfort, headaches, and other side effects, were documented after each session.

Baseline assessments included average pain intensity over the week prior to treatment using the NRS-11, the NPSI-T, and the Thai version of the EQ-5D-5L questionnaire. Pain intensity was recorded before and immediately after stimulation on each of the 5 treatment days (days 1–5). Follow-up assessments of average pain intensity were conducted via telephone by a blinded nurse at weeks 1, 2, and 6. At week 4, participants attended an in-person follow-up at the pain clinic, where the NRS-11, the NPSI-T, and the Thai version of the EQ-5D-5L evaluations were repeated.

Sample size calculation

The sample size was determined based on a previous study by Fregni *et. al.*, which reported a mean difference of 4 points on the Visual Analog Scale (VAS) between the active and sham tDCS groups[13]. Assuming an effect size of 2, a power of 80%, an α level of 0.05, with 10% drop-out, the required sample size was 6 participants per group.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, with continuous variables presented as mean±standard deviation and categorical variables as frequency and percentage. The primary outcome, pain intensity reduction between-group comparisons, was performed using independent t-tests for continuous variables and Fisher's exact test for categorical variables. Within-group comparisons were conducted using paired t-tests for pre- and post-treatment assessments. All statistical analyses were performed using IBM SPSS Statistics 29, and a p-value of less than 0.05 was considered statistically significant.

Results

Participant characteristics

A total of 13 patients with chronic peripheral neuropathic pain were initially enrolled in the study. One participant in the active tDCS group was lost to follow-up after the first stimulation session. The final analysis included 12 participants, with 6 in each group (active tDCS and sham tDCS) (Figure 1).

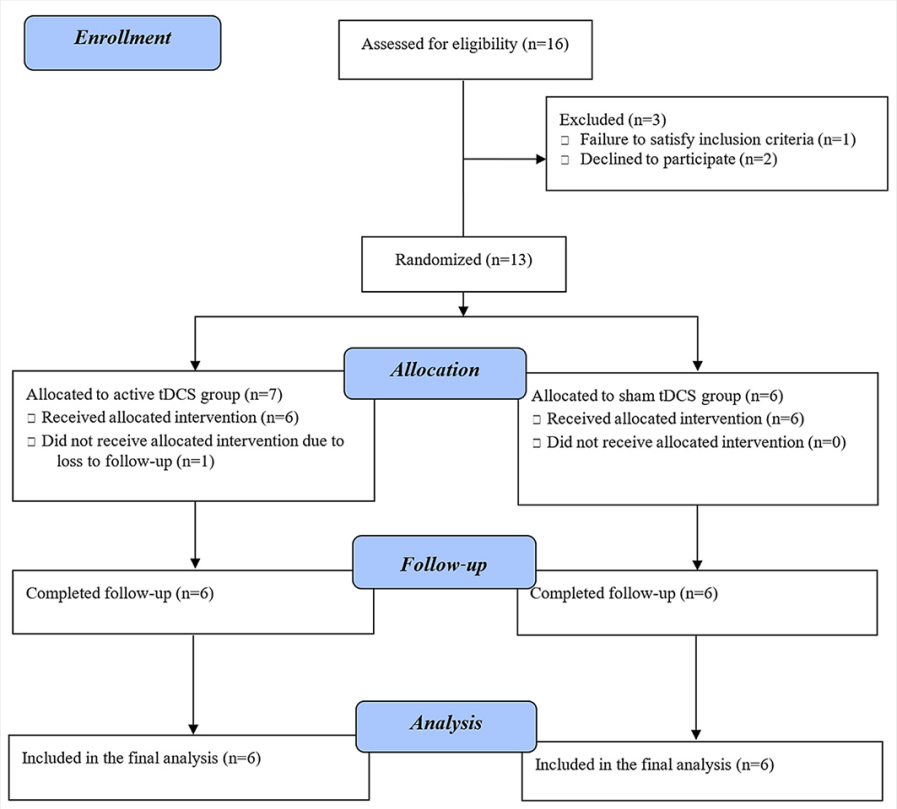

Figure 1 CONSORT flow diagram of the study protocol. A total of 16 participants were assessed for eligibility, of whom 3 were excluded because they did not meet the inclusion criteria or declined to participate. Thirteen participants were randomized into 2 groups: 7 to the active transcranial direct current stimulation (tDCS) group and 6 to the sham tDCS group. One participant in the active group was lost to follow-up and did not receive the allocated intervention. All remaining participants completed the follow-up and were included in the final analysis.

Baseline demographic and clinical characteristics were comparable between the 2 groups, with no statistically significant differences (Table 1). The mean age was 53.3±11.5 years in the active tDCS group and 51.3±14.0 years in the sham group (p-value=0.792). The mean duration of pain was 80.8±38.1 months in the active group and 84.0±61.2 months in the sham group (p-value=1.000). The predominant diagnosis was peripheral nerve injury, which accounted for 100% of cases in the active tDCS group and 83% in the sham group.

Pain reduction after tDCS stimulation

The primary outcome analysis revealed a statistically significant reduction in pain intensity, based on the NRS-11 scale, in the active tDCS group compared to the sham group. At post-stimulation days 2, 3, and 5, pain reduction was significantly greater in the active tDCS group: (Day 2: 5.00±2.37 vs. 1.67±1.75 (p-value=0.020), Day 3: 5.17±2.32 vs. 1.83±1.94 (p-value=0.022), Day 5: 5.50±2.07 vs. 2.67±2.25 (p-value=0.047), respectively). No statistically significant differences were observed on days 1 and 4 or during follow-up assessments at weeks 1, 2, 4, and 6 (Table 2).

Pain intensity was assessed daily before and after each stimulation session. Both groups demonstrated a reduction in post-stimulation pain scores; however, the difference between the active and sham groups did not reach statistical significance in immediate post-session comparisons (Figure 2).

Table 1 Clinical characteristics and demographic data of patients

Characteristics	Active tDCS (n=6)	Sham tDCS (n=6)	p-value
Sex: Male	4 (67%)	5 (83%)	1.000
Age; years	53.3±11.5	51.3±14.0	0.792
Duration of pain; months	80.8±38.1	84.0±61.2	1.000
Diagnosis			1.000
Brachial plexus injury	2 (33%)	3 (50%)	
Other peripheral nerve injury	4 (67%)	2 (33%)	
Radiculopathy	0 (0%)	1 (17%)	
Baseline Pain NRS	6.7±2.2	6.7±2.3	1.000
Baseline NPSI			
NPSI total (0-100)	40.17±12.45	26.16±22.39	0.210
Burning pain (0-10)	2.50±3.02	3.00±4.69	0.831
Squeezing pain (0-10)	6.83±2.93	2.00±3.16	***0.021***
Pressure pain (0-10)	3.83±4.49	2.33±3.01	0.512
Electrical shock (0-10)	4.83±4.12	5.00±3.95	0.944
Stabbing (0-10)	3.50±3.15	2.83±3.66	0.742
Provoked by blushing (0-10)	4.17±3.92	2.17±3.49	0.372
Provoked by pressure (0-10)	4.00±3.84	1.00±2.45	0.054
Provoked by cold stimulation (0-10)	3.67±3.27	2.17±3.71	0.138
Pins and needles (0-10)	3.67±3.83	3.50±2.88	0.934
Tingling (0-10)	3.17±3.76	2.17±2.48	0.599
EQ-5D-5L scores††			
EQ utility	0.75±0.11	0.69±0.29	0.627
EQ VAS (0-100)	67.50±10.36	64.16±22.00	0.744

Data are presented as n (%) or mean±standard deviation. A p-value<0.05 indicates a statistically significant difference, based on the Fisher's exact test and independent t-test, as appropriate. tDCS=transcranial direct current stimulation, NRS=numeric rating scale, EQ=EuroQol, EQ-5D-5L=EuroQol five-level and five-dimensional, VAS=visual analogue scale

Table 2 Mean pain reduction after active and sham tDCS stimulation at the 1st–5th day, 1st, 2nd, 4th and 6th week

Timepoint	Active tDCS (n=6)	Sham tDCS (n=6)	p-value
Day 1	3.83±2.56	2.17±2.14	0.331
Day 2	5.00±2.37	1.67±1.75	***0.020****
Day 3	5.17±2.32	1.83±1.94	***0.022****
Day 4	4.17±3.19	2.33±2.25	0.277
Day 5	5.50±2.07	2.67±2.25	***0.047****
Week 1	3.33±2.88	2.17±2.14	0.444
Week 2	4.17±2.56	2.17±2.14	0.173
Week 4	3.50±3.08	2.17±2.32	0.417
Week 6	4.00±2.53	2.00±2.68	0.214

Data are presented as mean±standard deviation. An asterisk (*) indicates statistical significance, defined by a p-value<0.05, based on the independent t-test. tDCS=transcranial direct current stimulation

To ensure that the results were not influenced by selection bias, we also evaluated the number of participants achieving at least a 30% reduction in pain in both groups. The findings were consistent with the mean reduction in the NSR-11 pain scores (Supplementary figure1).

Neuropathic pain symptom severity and quality of life

Neuropathic Pain Symptom Inventory: In both groups, the total NPSI-T score significantly decreased from baseline to week 4 (p-value=0.015 for active tDCS and p-value=0.014 for sham). However, there were no statistically significant differences between the active and sham groups in individual symptom sub-scores (burning pain, squeezing pain, pressure pain, electrical shock, stabbing, and evoked pain components) (Table 3).

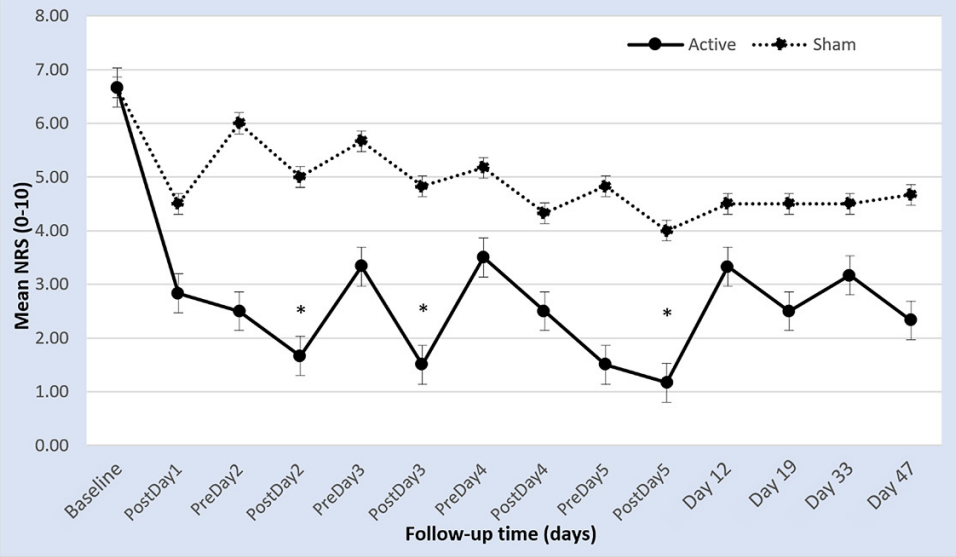

Figure 2 Mean numeric rating scale (NRS)-11 pain scores (0–10) over time in the active and sham stimulation groups. Pain intensity was assessed at baseline and at multiple time points during the follow-up period: immediately before and after stimulation on days 1 to 5, and on follow-up days 12, 19, 33, and 47. The active stimulation group demonstrated a significant reduction in mean NRS scores compared with the sham group, with the largest effects observed immediately after stimulation on days 2, 3, and 5. * indicates statistical significance (p-value<0.05) between the groups on post-stimulation.

Table 3 NPSI-T and EQ-5D-5L questionnaire at baseline and 4 weeks after the intervention

	Active tDCS		p-value	Sham tDCS		p-value	p-value*
	Baseline	4 week Post-stimulation		Baseline	4-week Post-stimulation		
NPSI-T scores**							
NPSI-T total (0-100)	40.17±12.45	25.83 ± 12.67	***0.015***	26.16±22.39	17.00±24.96	***0.014***	0.457
Burning pain (0-10)	2.50 ± 3.02	2.50±3.21	1.000	3.00 ± 4.69	1.50±3.67	0.420	0.626
Squeezing pain (0-10)	6.83±2.93	4.67±3.44	0.157	2.00±3.16	3.00±3.95	0.536	0.454
Pressure pain (0-10)	3.83 ±4.49	2.50±3.33	0.484	2.33±3.01	1.17±2.86	0.220	0.474
Electrical shock (0-10)	4.83±4.12	3.83±2.71	0.348	5.00±3.95	3.67±2.07	0.274	0.937
Stabbing (0-10)	3.50±3.15	1.50±1.97	0.182	2.83±3.66	1.33±3.27	0.137	0.917
Provoked by blushing (0-10)	4.17±3.92	3.67±2.07	0.812	2.17±3.49	2.83±3.71	0.175	0.641
Provoked by pressure (0-10)	4.00±3.84	2.50±3.02	0.203	1.00±2.45	1.00±2.00	1.000	0.334
Provoked by cold stimulation (0-10)	3.67±3.27	2.00±2.45	0.250	2.17±3.71	1.33±3.27	0.259	0.698
Pins and needles (0-10)	3.67±3.83	3.50±2.07	0.915	3.50±2.88	1.50±2.51	0.189	0.163
Tingling (0-10)	3.17±3.76	1.67±2.25	0.370	2.17±2.48	0.83±2.04	0.318	0.517
EQ-5D-5L scores***							
EQ utility	0.75±0.11	0.79±0.13	0.660	0.69±0.29	0.76±0.27	0.079	0.765
EQ VAS (0-100)	67.50±10.36	76.67±16.63	0.117	64.16±22.00	64.17±18.00	1.000	0.240

Data are presented as mean±standard deviation. A p-value<0.05 indicates a statistically significant difference using paired t-tests and post-stimulation independent t-test (*). NPSI-T scores (**), including the total score and 5 sub-scores, are rated on an 11-point numerical rating scale (0=no pain, 10=worst imaginable pain). EQ-5D-5L scores (***) include the EQ utility and EQ VAS. EQ utility=1 – sum of coefficients from each of the 5dimensions (Level 1=no problem, coefficient =0; Level 5=severe problems, coefficient calculated from http://www.hitap.net/documents/87962). EQ VAS ranges from 0 (worst health imaginable) to 100 (best health imaginable). EQ=EuroQol, EQ-5D-5L=EuroQol five-level and five-dimensional, NPSI-T=Thai neuropathic pain symptom inventory, VAS=visual analogue scale, tDCS=transcranial direct current stimulation

Quality of Life (EQ-5D-5L): There were no significant changes observed in EQ utility scores and VAS scores between the groups at baseline and week 4 post-intervention (p-value=0.765 for EQ utility and p-value=0.240 for EQ VAS).

Adverse events

All participants tolerated the tDCS sessions well, with no reports of severe adverse events. Four participants from each group reported mild skin redness, likely due to electrode pressure. Two participants in the active tDCS group reported mild discomfort or pain (NRS 1–2) under the electrodes, which was alleviated by adjusting saline-soaked sponges. Sleepiness was reported in the sham group, which may have been related to concurrent medication use.

Discussion

This study demonstrated that tDCS significantly reduced pain in patients with chronic intractable peripheral neuropathic pain after multiple stimulation sessions. The active tDCS group showed significant pain reduction at days 2, 3, and 5 post-stimulation compared to the sham group. However, no significant differences were observed at 1, 2, 4, and 6 weeks post-treatment, suggesting that the analgesic effects may be short-lived or require repeated stimulation sessions for sustained benefit.

Our findings align with previous studies that have reported tDCS as an effective short-term analgesic intervention in neuropathic pain. A study by Fregni *et al.* demonstrated a significant reduction in pain intensity following anodal tDCS in patients with spinal cord injury,

with effects lasting up to 2 weeks post-stimulation[13]. Similarly, Bae et. al. observed pain relief in post-stroke neuropathic pain patients undergoing 9 sessions of tDCS, though no long-term follow-up was conducted[28]. These studies highlight the potential of multi-session tDCS in modulating pain perception. A recent review article reported that single or multiple sessions of tDCS provided significant pain relief in patients with spinal cord injury-related neuropathic pain[15]. This supports the growing body of evidence suggesting that tDCS may be particularly beneficial in neuropathic pain conditions linked to central nervous system dysfunction. However, the variability in study protocols, patient populations, and stimulation parameters highlights the need for standardized methodologies to optimize treatment efficacy.

A recent narrative review and systematic review concluded that conventional anodal tDCS over the affected M1 alone or integrated with other therapies (e.g., mirror therapy or motor imagery) has an analgesic effect on phantom limb pain (PLP)[29,30]. Although the PLP is classified as peripheral neuropathic pain, its mechanism of producing pain involves both peripheral and central pathways, particularly cortical reorganization. The review also found that single-session treatment could modify PLP intensity for hours and multi-session treatment could modify PLP for months[30]. The results of this study suggest that anodal tDCS is beneficial only for centrally mediated pain. However, a previous randomized controlled trial demonstrated that M1 tDCS applied for 5 consecutive days significantly reduced pain in patients with painful diabetic polyneuropathy compared to the sham stimulation, with effects lasting up to 4 weeks[17]. These findings indicate that the efficacy of tDCS extends beyond centrally mediated neuropathic pain to include neuropathic pain involving peripheral mechanisms as well. Additionally, Attal *et al.* found that 3 daily consecutive sessions of rTMS were more effective than tDCS and sham stimulation in patients with lumbar radiculopathy[31]. The result also supported the short-term efficacy of tDCS in peripheral neuropathic pain, which is consistent with our study. Given these findings, future research should explore whether combining tDCS with rTMS or other neurostimulation techniques could enhance pain relief in chronic neuropathic pain conditions.

Although the results of our study did not demonstrate a significant difference between the active tDCS and sham groups beyond one week post-stimulation, pain score reductions in the active tDCS group appeared greater compared to the sham group. As previously mentioned, regarding the sustained effects of tDCS reported in earlier studies, the mechanisms underlying the cumulative effects observed with multiple-session tDCS remain to be elucidated. Specifically, pharmacological investigations have indicated that tDCS influences neurotransmitter systems implicated in pain modulation. Studies have reported increased endogenous opioid release, reduced glutamatergic activity, brain-derived neurotrophic factor (BDNF) signaling[32], and alterations in gamma-aminobutyric acid-ergic (GABAergic) transmission following tDCS. In an animal study, the authors reported that direct current stimulation regulates oxidant/antioxidant levels and reduces central neuroinflammatory mediators, including tumor necrosis factor-alpha (TNF-alpha), interleukin 1-beta (IL-1beta), IL-6, and IL-18[33]. These neuromodulatory effects underpinning the mechanisms of tDCS may explain its immediate and short-term efficacy in alleviating both the sensory and emotional dimensions of neuropathic pain. Although the mechanisms underlying the long-lasting effects of tDCS remain incompletely understood, prolonged alterations in cortical excitability and the synthesis of proteins associated with synaptic development and plasticity may contribute to maintaining the sustained therapeutic benefits of tDCS[34]. However, further studies incorporating neuroimaging and neurophysiological assessments are needed to elucidate the precise mechanisms.

Given its non-invasive nature, ease of application, and relatively low cost compared to other neuromodulation techniques, tDCS holds promise as an adjunct therapy for chronic neuropathic pain. The ability to perform tDCS in a clinical setting or at home under appropriate supervision makes it an attractive option for patients who have limited access to interventional pain treatments. However, given the short duration of pain relief observed in our study, tDCS may need to be administered in repeated sessions or combined with pharmacological or behavioral interventions to achieve sustained benefits. Moreover, the appropriate parameters of tDCS are crucial. A recent systematic review recommended that the most effective parameters of tDCS are a current intensity of 2 mA, a session duration of 20-30 min, and 5-10 sessions[35].

The safety profile of tDCS remains favorable, with mild and transient adverse effects such as skin redness and mild discomfort under the electrodes. No serious adverse events were reported in this study, reinforcing the feasibility of tDCS as a well-tolerated treatment modality for neuropathic pain. Nevertheless, this could lead to ethical and legal concerns related to potential misuse or overuse. To prevent inappropriate applications, it is essential to ensure that professionals receive thorough training and that patients are properly educated[36].

This study has several limitations that warrant consideration. The relatively small sample size limits the generalizability of our findings, and the inclusion of mainly patients with peripheral nerve injury may not reflect the full spectrum of peripheral neuropathic pain conditions. Additionally, the relatively short follow-up period precludes conclusions about the long-term efficacy of tDCS. Future studies should aim to conduct larger, multicenter trials with extended follow-up durations to evaluate the long-term effects of tDCS. Additionally, research should explore variations in stimulation parameters, such as increased current intensity, session frequency, and alternative electrode placements. The potential synergistic effects of combining tDCS with other pain management strategies—such as pharmacotherapy, physical therapy, or mindfulness-based interventions—should also be investigated. Finally, future work should incorporate neuroimaging and neurophysiological tools, including functional magnetic resonance imaging and EEG, to elucidate the cortical and subcortical mechanisms underlying the effects of tDCS.

Conclusion

tDCS demonstrated significant short-term pain relief in patients with chronic intractable peripheral neuropathic pain. However, the effects did not persist beyond the treatment period, highlighting the need for further research into optimizing stimulation protocols and exploring long-term therapeutic strategies. Despite these limitations, tDCS remains a promising non-invasive neuromodulation approach that warrants further investigation for clinical implementation.

Acknowledgement

The authors gratefully acknowledge the patients who generously participated in this study. We thank Somthawil Potranan and Phantip Phongwanichanan, pain specialist nurses, for their outstanding clinical support, as well as Chernporn Payomyam, Natsupa Wiriyakulsit, and Sunsanee Maliong for their valuable assistance with research coordination. We also extend our appreciation to Mr. Suthipol Udompunthurak from the Division of Clinical Epidemiology, Department of Research and Development, Faculty of Medicine Siriraj Hospital, for his support in statistical analysis.

Conflict of interest

All authors declare that they have no conflict of interest.

Funding sources

Routine to Research Funding (R015835005) from the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Study site

Pain Clinic, Faculty of Medicine Siriraj Hospital, Mahidol University.

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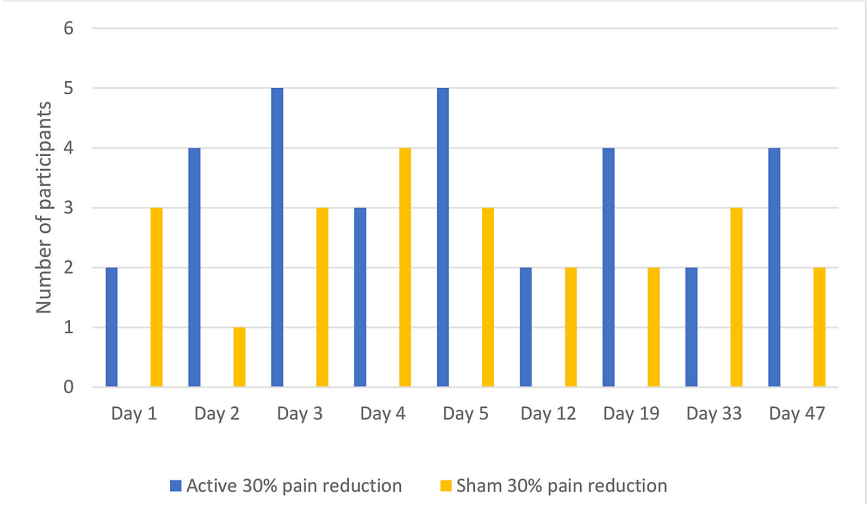

Supplementary Figure 1 The number of participants achieving at least a 30% pain reduction in the active and sham groups