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Effect and reliability of transcranial magnetic stimulation on neuropathic pain in stroke patients: Preliminary study

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Abstract

Objective: In this paper, we aimed to evaluate the effect of repetitive Transcranial Magnetic Stimulation (rTMS) on central pain in patients with stroke.

Material and Methods: Ten patients who had a stroke history were included in this preliminary study. Patients with middle cerebral artery lesion, first-time stroke, subacute or chronic lesion and no other neurological involvement were included. Patients were examined before and after the first month of treatment with repetitive Transcranial Magnetic Stimulation (rTMS). Visual Analog Scale (VAS) was used for pain scale measurement; Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS) and Douleur Neuropathique en 4 Questions (DN4) were used for neuropathic pain level and Beck Depression Inventory (BDI) for depressive mood. All patients received the current treatments and appropriate neurorehabilitation as recommended for the treatment of ischemic stroke

Results: This prospective study included a total of 10 post-stroke patients (mean age 58.2 ± 16.1 years; range 29 to 75, 8 male; 2 female) with neuropathic pain. The mean values of VAS, LANSS, DN4 and BDI scales were significantly decreased after rTMS treatment in all patients.

Conclusion: We discussed the preliminary results of the efficacy and safety of rTMS in the treatment of uncontrolled neuropathic pain. We consider that, rTMS may have significant effect on relief of chronic pain. These clinical parameters can be utilized for the further study of rTMS application in pain control.

Key words: Transcranial magnetic stimulation, stroke, pain.

Introduction

Stroke is a major cause of death and disability. After stroke, survivors have typically neurological squeal and stroke-related complications. The duration of stroke rehabilitation depends on the severity of stroke and related complications. Pain is one of the most common complications in patients with stroke and may adversely affect patients' quality of life (1). Opioids, tricyclic antidepressants or anticonvulsants have been found to be useful for the treatment of neuropathic pain in stroke patients (2). Despite various clinical trials there is still no consensus about the best strategies for the management of neuropathic pain (3). The other safer and non-invasive way to provide analgesic neurostimulation is also Transcranial Magnetic Stimulation (TMS).

TMS was approved by the US Food and Drug Administration for the treatment of major depression in 2008, and researchers are still investigating TMS for a number of other neurological conditions, including chronic and neuropathic pain. Studies have reported that TMS techniques are effective in central pain and may provide pain relief by altering the cortical excitability (4-6).

The prevalence of central post stroke pain was reported as 7.3% after stroke (7). Quality of life (QoL) decreases by 40% compared to pre-stroke at the end of one year after stroke (8). It can play an important role on quality of life, mood and rehabilitation as it is known that pain affects recreational activities, occupational status and sleep quality.

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For most of the CPSP patients, pain is eventually associated with a hard and reduced physical function, reducing quality of life. Moreover, pain and psychological disorders are closely related, affecting their physical and psychosocial functioning. Likewise, CPSP has a significant effect on QoL and a strong relationship between pain and depression has been observed (9).

The aim of this study was to investigate the effect of TMS on neuropathic pain in a small number of subjects as a preliminary report.

Material and Methods

This prospective study included a total of 10 post-stroke patients with neuropathic pain. Age, gender, hemiplegic side and duration of stroke were investigated.

The study protocol was approved by the Gaziantep University Clinical Research Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. The inclusion criteria were as follows; middle cerebral artery lesion, first-time stroke, subacute or chronic lesion and no other neurological involvement. The exclusion criteria were as follows; multiple lesions on cranial imaging, aphasia, head trauma, acute stroke, epilepsy in their medical history. Pregnant women were also excluded. Table 1. shows an overview of patients based on demographic characteristics in this study. A written informed consent was obtained from each participant. All patients were evaluated with a full neurologic examination for sensory disorder, motor deficits, and spasticity.

Patients were evaluated at baseline and after the first month of treatment in respect to all clinical parameters.

Pain intensity was evaluated by a 10 cm Visual Analog Scala (VAS) asking for the pain experienced during the last week (10). This scale is 10 cm length. Slight pain is considered to be VAS<3.3, moderate pain 3.3-6.6, severe pain VAS 6.7-9.9 and unbearable pain VAS 10. We used two questionnaires for the diagnosis of neuropathic pain; Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS) and Douleur Neuropathique en 4 Questions (DN4). LANSS has high sensitivity and specificity for identifying neuropathic pain. The LANSS pain scale was first used by Bennett to clinically distinguish neuropathic pain from nociceptive pain. Shortness of application time and ease of evaluation are the advantages of this test. The reliability and validity of the pain scale of LANSS was performed in 2004 by Yücel A. et al. (11). LANSS contains five symptom and two clinical examination items. The first part consist five items asking the patient about the kind of pain experienced in the last week. In the second part, presence of allodynia and determination of pinprick perception threshold are explored by health care professional. Each item should be marked as present or absent, and the presence of each sign has different score. The possible scores range from 0 to 24, with a score of 12 or greater considered to be suggestive of neuropathic pain.

DN4 is a questionnaire for neuropathic pain consisting of interview questions and physical tests. A score of 1 is given to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of the 10 items, and a total score of 4 or more out of 10 suggests neuropathic pain (12).

We assessed post stroke depression by the Beck Depression Inventory (BDI), this method being used by other studies. BDI score over 30 was associated with a severe depression (13,14).

All patients received a rehabilitation program according to each participant's functional level or requirements. Range-of-motion exercises were applied passive, active-assistive, or active, strengthening exercise, flexibility, balance and coordination training also applied in all stroke patients.

In each TMS session, 30 trains of 10 Hz stimuli for a duration of 5 seconds at an inter-train interval of 25 seconds, a total of 1500 pulses, was applied. Total duration of a TMS session was 15 minutes at intensity equal to 80% of the resting motor threshold. This area was identified as the site at which single pulse TMS contra-laterally evoked a motor potential of maximal amplitude in the first dorsal interosseus muscle of the hand, ipsilateral to the painful zone. This procedure ensured stimulation over the precentral gyrus.

The patients received the TMS, while sitting in a comfortable chair or their wheelchair. A total of 10 sessions of TMS treatment was performed in 5 sessions per week. The levels of current, duration, and stimulation types were performed by the same physiotherapist. Side effects were reported by means of this physiotherapist after each stimulations.

Statistical Analysis

The analysis were performed with SPSS (Statistical Package for Social Sciences) 22.0 program. Paired sample's T test was used to compare the clinical parameters before and after treatment. Significance was evaluated as $p < 0.05$.

Results

The gender distribution was as 8 males and 2 females. The mean age was 58.2 ±16.1 years, mean disease duration was 2.5 ±1.7 years. All of the patients had chronic pain. The mean duration of pain was 2.0±0.7 years. Pain was localized at lower limbs at hemiplegic side and the other body parts. All patients had first ischemic cerebrovascular etiologies. Hemiplegia was on the right side in 6 patients (60%) and on the left side in 4 patients (40%). When comparing to mean difference of scores from baseline to following treatment, there was significant improvement in all clinical parameters. The mean scores of VAS, LANNS, DN4 and BDI scales were significantly better at first month of treatment in compared to baseline. TMS could improve either pain or depressive mood in all patients after the treatment sessions. Furthermore, no side effects were observed during TMS treatment. The characteristics of clinical parameters in stroke patients are determined in table 2.

Table 1. Demographic features in stroke patients

Duration of disease (year)	1 (min)	7 (max)	2.5±1.7 (mean ± SD)
Affected side	6 (right)	4 (left)	60/40 (ratio)
Age	29 (min)	75 (max)	58.2±16.1
Sex	8 (male)	2 (female)	80/20 (ratio)

SD: standart deviation; min: minimum; max: maximum

Table 2. Comparison of clinical parameters in stroke patients

	Before treatment (Mean±SD)	After treatment (Mean±SD)	*P*
LANSS	9.4±4.4	6.0±3.2	*<0.001**
VAS	4.8±1.4	3.7±1.4	*<0.001**
DN4	4.4±2.8	2.9±2.3	*0.001*
BDI	17.2±6.9	13.6±5.9	*<0.001**

LANSS: Leeds Assessment of Neuropathic Symptoms and Signs Scale; VAS: Visual Analog Scala; DN4: Douleur Neuropathique en 4 Questions; BDI: Beck Depression Inventory; *$p < 0.05$: statistically significant.

Discussion

Pain after stroke can significantly affect functionality and may adversely affect the physical activity of patients, however, there is a little data on this topic. The onset of pain in our cases occurred 1 to 4 months after the stroke. The presentation of the CPSP is variable. Adjectives such as lacerating, aching, burning, freezing, and squeezing are commonly used by patients, as observed in our patients (15). The neuropathic pain most commonly begins 1 to 6 months after stroke (16).

In some case central pain diagnosis is delayed due to the fact that patients are not hospitalized in rehabilitation clinics, their cognitive status is impaired and some of them are aphasic. It is also claimed that neuropathic pain exhibits a latent period which may be up to 18 months after stroke onset (17). In stroke survivors, the emotional status may be altered because of the functional and cognitive consequences of stroke and neuropathic pain. We evaluated 10 patients with a previous history of chronic pain who were resistant to other modalities followed in our rehabilitation clinic.

Neuropathic pain is sometimes resistant to current pharmacological treatments. Further, there are several side effects of analgesic drugs such as dizziness, drowsiness (18). In the last decade, the effects of TMS on excitatory and inhibitory cortical circuits have been used in patients with chronic pain.

Our current study showed that the neuropathic pain making difficult to treat could possibly minimize with applying TMS in patients with post stroke. We have also seen that, TMS can potentially offer a non-invasive treatment option for neuropathic pain in patients with stroke.

The analgesic effects of TMS in chronic pain have been investigated and it has been shown to provide analgesic effects in chronic pain in recent years (19-22).

Interestingly, we found a significant reduction in depression level, immediately after a rTMS sessions in patients with stroke.

Studies have shown that motor cortex stimulation has inhibitory effects on thalamic and spinal nociceptive neurons (23). Neuroimaging studies have shown that epidural electrical stimulation of the premotor cortex in patients with neuropathic pain increases blood flow in distant brain areas (eg, lateral and medial thalamus, anterior cingulate cortex, insula, brain stem) (24). It has been demonstrated that rTMS given to motor cortex activates the endogenous opioid system in a wide brain network associated with processing of pain (25).

It is unknown any procedure should be perform whether rTMS therapy is more effective in the acute or chronic stage after stroke. In our study, all patients had subacute or chronic lesion.

Stimulation frequency is play a major role on the analgesic efficacy of stimulation. It has emphasized a short-term effect of a single stimulation session of high-frequency rTMS directed at the motor cortex (26). The authors concluded that this method was not suggestive of a beneficial treatment effect for chronic pain patients long-term follow-up (27). In an another study, Hosomi et al. (28) reported data on neuropathic pain patients treated with rTMS to premotor cortex for 10 days. But they obtained a significant short term pain relief not lasting after the sessions. Short et al. (29) have shown a marginal analgesic effect of rTMS up to 2 weeks after the stimulation phase, using parameters similar to those of our study (10 Hz).

Studies have been reported that TMS was improved the neuropathic pain, with minimal side effects (30). Most safety issues concern the effects of magnetic fields on the human body, especially the risk of seizures during sessions. In our study no patients had side effects during the stimulation phase or at follow-up. We aimed that targeting

the premotor cortex in an induction 10 repeated sessions would provide an analgesic effect in pain with stroke patients (31).

According to our results, all patients tolerated well with high-frequency TMS (10 Hz) and demonstrated appreciable pain relief benefit without any side effects.

The current study has several limitations. This is a relatively small preliminary study that lacks a control group, we have shown significant benefits from rTMS for patients with neuropathic pain syndromes. Another study limitation is that the long-term effects of TMS treatment were not investigated and the data were not objective.

Conclusion

TMS is a non-invasive, short-lasting, painless and focal way modality that modulates cortical excitability. Although much has learned about the central pain modulatory mechanisms about TMS, very little is known about its mechanisms and efficacy in modulating neuropathic pain conditions. In literature controlled prospective studies are rare and the technique is still not largely used. The optimal timing for long-term efficacy and safety of post-stroke pain are still unknown. Further studies should be explored the effects of different parameters and long-term stability. Randomized controlled studies are required in further validating the efficacy of this treatment modality. Additional, studies are required to assess the underlying mechanisms of analgesia.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: TT, MSA, NT, ÖA: Research concept and design; data collecting, TT, MSA, NT, ÖA ŞŞ: Preparation of article, and Revisions. All authors approved the final version of the manuscript

Ethical issues: All Authors declare, originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities.

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