นิพนธ์ต้นฉบับ • Original Article

การศึกษานำร่องของการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกในการป้องกันอาการปวดศีรษะไมเกรน

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กลุ่มวิจัย Noninvasive Brain Stimulation

Transcranial Direct Current Stimulation on Prophylactic Treatment in Migraine Patients, an Open-Label Pilot Study

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หลักการและวัตถุประสงค์: ไมเกรนเป็นกลุ่มอาการปวดศีรษะเป็นๆ หายๆ ที่มีความชุกทั่วโลกประมาณร้อยละ 3-12 ในเพศชาย และ 6-29 ในเพศหญิง การป้องกันเป็นสิ่งจำเป็นในการเพิ่มคุณภาพชีวิต แต่ผู้ป่วยไมเกรนบางรายมีข้อห้ามหรือมีอาการข้างเคียงจากยาป้องกันไมเกรน ดังนั้นการป้องกันโดยวิธีไม่ใช้ยาจึงเป็นสิ่งจำเป็น ในการศึกษาที่ผ่านมาแสดงให้เห็นว่าการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกบริเวณเปลือกสมองส่วนมอเตอร์ด้านซ้ายสามารถลดอาการปวดเรื้อรังในอาการปวดจากระบบประสาทได้ ดังนั้นการศึกษานี้จึงมีวัตถุประสงค์เพื่อที่จะประเมินว่าการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกบริเวณเปลือกสมองส่วนมอเตอร์ต่อเนื่องกัน 20 วัน จะสามารถป้องกันอาการปวดในไมเกรนได้หรือไม่

Background and Objective: Migraine is a common episodic headache syndrome with estimated prevalence ranging 3-12% in men and 6-29% in women. Prophylaxis is necessary to improve the quality of life but some patients with migraine have contraindication or suffer from side effects of medications, and therefore, establishing non-medical, neuromodulatory approaches is necessary. Past evidence has shown that stimulation of motor cortex (M1) with anodal transcranial direct current stimulation (tDCS) is effective to relieve central pain. This study aims to determine whether 20 consecutive days of the left M1 can be an effective prophylactic treatment for migraine.
Method: Thirteen migraine patients with/without aura were identified according to the International Headache Society.

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วิธีการศึกษา: ผู้ป่วยไมเกรนที่มีและไม่มีออร่า (aura) จำนวน 13 รายตามนิยามของสมาคมปวดศีรษะนานาชาติ ถูกคัดเลือกตามเกณฑ์คัดเข้าคือ 1) อายุระหว่าง 18-65 ปี 2) ได้รับการวินิจฉัยโดยแพทย์มาแล้วอย่างต่ำ 1 ปี 3) มีอาการเกิดขึ้นมากกว่าหรือเท่ากับ 3 ครั้งใน 4 สัปดาห์ โดยอย่างน้อย 3 เดือนที่แล้ว ผู้ป่วยจะต้องมีอาการเกิดขึ้นด้วย 4) ไม่เคยได้รับยาป้องกัน หรือเคยได้รับยาป้องกันแต่ล้มเหลวอย่างต่ำ 3 เดือนก่อนจะมาเข้าการศึกษา 5) ยอมรับที่จะไม่รับการรักษาด้วยวิธีป้องกันอื่นทั้งแบบการใช้ยาและไม่ใช้ยาตลอดการวิจัย 6) ยอมรับการติดตามผลการรักษาเป็นเวลา 3 เดือน ผู้ป่วยจะได้รับการกระตุ้นด้วยไฟฟ้ากระแสตรงอย่างอ่อนขนาด 1 มิลลิแอมแปร์ เป็นเวลา 20 นาทีทุกวันต่อเนื่องกัน 20 วัน และได้รับการติดตามผลการรักษาเป็นเวลา 12 สัปดาห์ โดยติดตามทุกๆ 4 สัปดาห์ ความแตกต่างระหว่างก่อนและหลังการรักษาใช้สถิติ repeated measures ANOVA.

ผลการศึกษา: ผู้ป่วยไมเกรนที่สามารถเข้าร่วมโครงการศึกษาจนสิ้นสุดโครงการมีจำนวน 11 ราย ผลการศึกษาแสดงการลดลงอย่างมีนัยสำคัญของความถี่ของการเกิดอาการในสัปดาห์ที่ 4 หลังรักษา (0.86, 95%CI: 0.84 to 1.01, p =0.02) และสัปดาห์ที่ 8 หลังรักษา (0.68, 95%CI: 0.62 to 0.84, p =0.03) ในขณะที่ไม่มีการลดลงอย่างมีนัยสำคัญทางสถิติในสัปดาห์ที่ 12 หลังรักษา (-0.25, 95%CI: -0.32 to 0.18, p =0.41) ผู้ป่วยทุกรายทนต่อการกระตุ้นด้วยไฟฟ้ากระแสตรงได้เป็นอย่างดีโดยไม่มีอาการไม่พึงประสงค์ที่ร้ายแรง

สรุป: ผลการศึกษานำร่องนี้แสดงให้เห็นว่าการกระตุ้นด้วยไฟฟ้ากระแสตรงอย่างอ่อนบริเวณเปลือกสมองส่วนมอเตอร์อาจจะเป็นประโยชน์และปลอดภัยในการป้องกันอาการปวดศีรษะในไมเกรนโดยกลไกการเพิ่มการยับยั้งและปรับเปลี่ยนการรับความรู้สึกเจ็บปวดในสมอง แต่อย่างไรก็ดีควรมีการศึกษาเพิ่มเติม โดยการสุ่มและมีกลุ่มควบคุมเปรียบเทียบ

คำสำคัญ : ไมเกรน การป้องกันไมเกรน การกระตุ้นสมองแบบไม่รุกราน การกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลก

Inclusion criteria were 1) ages between 18 and 65 years; 2) diagnosed by a physician and present for at least one year before enrollment; 3) three or more migraine episodes per 4 weeks during at least the previous 3 months; 4) had never received any prophylactic treatment, failure of the previous prophylactic treatment, or discontinuation of treatment due to adverse events for at least 3 months prior to the start of the stimulation; 5) agreement not to take any concurrent prophylactic treatment for headaches both by pharmacological and non-pharmacological treatments; and 6) agreement to be available for a follow-up period at least 3 months. Patients received 1mA, 20 m anodal tDCS for 20 consecutive days and followed up for 12 weeks. The differences between before and after study were determined using repeated measures ANOVA.

Results: Only 11 patients could participate up to the final analyses. The results showed statistically significant reduction in the attack frequency at week 4 (0.86, 95%CI: 0.84 to 1.01, p =0.02) and week 8 (0.68, 95%CI: 0.62 to 0.84, p =0.03) while there was no statistically significant reduction in the attack frequency at week 12 (-0.25, 95%CI: -0.32 to 0.18, p =0.41). All patients could tolerate the tDCS well without any serious adverse events.

Conclusion: Our pilot study suggests that anodal motor cortex tDCS may be a safe and useful clinical tool in migraine prophylaxis. Increased cortical inhibition and modulated pain perception through corticothalamic loop may underlie these effects. However, further study with a randomized controlled trial is suggested.

Keywords: Migraine, Migraine prophylaxis, Noninvasive brain stimulation, Transcranial direct current stimulation

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Introduction

Migraine is a common episodic headache with the estimated prevalence ranging 3-12% in men and 6-29% in women[1]. Patients diagnosed with migraine have low quality of life, when compared with non-migraine patients[2, 3]. Besides the acute attack treatment, the prophylaxis is also important to improve the quality of life[4]. Beta-blockers and tricyclic antidepressants have often been used as the first-line drugs. Other preventive drugs include pizotifen, flunarizine, and methysergide[4]. However, some small proportions of migraine patients have contraindication or suffered from side effects[4], and therefore, establishing non-medical, neuromodulatory approaches are promising. Presently, the pathophysiology

of migraine is still incompletely understood[5]. Neurophysiological techniques provide an important contribution to understand the possible mechanisms of cortical dysfunctions in migraine[5]. Transcranial magnetic stimulation (TMS) is a noninvasive technique and capable of easily inducing painless cerebral stimulation through application of a magnetic field on the scalp. Repeated magnetic pulses (repetitive TMS, rTMS) are able to induce long-lasting plastic effects that also last after the end of the train and differ depending on the stimulation frequency employed. Low frequencies (≤1 Hz) reduce, while high frequencies (>1 Hz) increase cortical excitability. Transcranial direct current stimulation (tDCS) is transcranially administered through electrodes placed on the scalp, and is presumed to modulate cortical excitability by changing the potential of cell membranes depended on anodal (facilitatory effect) or cathodal stimulation (inhibitory effect). Owing to these properties, rTMS and tDCS have been used to study cortical plasticity and to explore potential therapeutic application in several neuropsychiatric disorders[5]. The mechanism of cortical dysfunction in migraine is still unclear[6-8]. The effect of noninvasive brain stimulation studied by several research centers is still controversy. Currently, there are at least three different hypotheses regarding migraine. The first shows impaired inhibitory processes of cortical circuitry[8-12], the second reveal cortical hypoexcitation[7, 13-14], and finally, the third presents neither increased cortical excitability nor reduced intracortical inhibition in migraine patients[15]. With regard to the evidence of cortical inhibition impairment, many noninvasive brain stimulation studies have shown that migraine patients have lower phosphene threshold than normal controls[16,17]. Additionally, both the intracortical and cerebellar inhibition levels were also found to be significantly lower in migraine patients, when compared to those in the controls[18]. Owing to the fact that pathophysiologic mechanism of migraine is still controversy, clinical trials using noninvasive brain stimulation technique have searched for cortical excitability status in migraine.

Currently, there are only a few clinical studies that investigated about migraine prophylaxis using noninvasive brain stimulation. Brighina et al.[19] delivered high-frequency rTMS on alternate days on the left dorsolateral prefrontal cortex for 12 sessions. They found that headache attacks, headache index, and number of abortive medications were significantly reduced. In addition, the effect of treatment was stable for a month. However, to draw stronger definite conclusions, the effects of noninvasive brain stimulation technique should be determined on a larger sample size, increasing the amount of stimulation sessions and longer follow-up periods[19].

Teepker et al.[20] applied two trains of 1-Hz TMS 500 monophasic pulses separated by a 1-min interval over the vertex on five consecutive days. A total of 27 migraine patients were randomly treated with either rTMS (n=14) or sham treatment (n=13). Measurements of attack frequency, migraine days, migraine hours, mean pain intensity, and use of analgesics were recorded before and eight weeks post-treatment. It was found that migraine attack frequency, migraine days, and migraine hours were significantly reduced in the active group. Furthermore, the migraine days were also significantly reduced in the sham group; there was no significant difference in all the outcomes between the two groups. They hypothesized that one of the pathophysiological factors involved in migraine might be owing to the reduction in cortical preactivation, rather than cortical hypoexcitability. However, the authors reported that the limitation of their study might be the feature difference between active and sham coil leading to subjects bias.

Recently, Antal et al.[21] published the first study using tDCS as a prophylactic treatment in migraine. They applied a constant current of 1 mA of tDCS to migraine patients over the visual cortex (V1) for 15 min, three days a week for six weeks. A total of 26 patients participated in the final analyses (cathodal: n = 13, sham: n = 13). The attack frequency, duration, intensity of pain, and number of migraine-related days were assessed at two months before and after treatment. The results showed a significant reduction in the intensity of pain between active and sham groups (p = 0.05), but no significant difference was observed between these two groups in other aspects.

Noninvasive brain stimulation may play an important role in the modulation of the cortical function in migraine patients. In our study, we suspect that anodal tDCS provides advantage similar to high-frequency TMS.

Furthermore, tDCS is more feasible, less expensive and easy to conduct placebo stimulation [22, 23].

Our study was designed to stimulate as long as 20 sessions[24], for awareness of the psychiatric adverse events, we did not stimulate on the left DLPFC. As well as to avoid the visual disturbance, we did not stimulate on occipital cortex. The stimulation site (primary motor cortex, M1) was chosen according to Fregni experiment[22]. They applied 2 mA of anodal tDCS over the primary motor cortex in patients who had central pain from spinal cord injury. They revealed that the mean pain score significantly reduces in the active group, when compared with the sham group. Therefore the aim of this study is to determine whether 20 consecutive days of anodal tDCS on the left primary motor cortex (M1) can be an effective prophylactic treatment of migraine.

Materials and Methods

Subjects were defined according to the International Headache Society and recruited by advertisement in Srinagarind Hospital, Faculty of Medicine and Physical therapist clinic, Faculty of Associated Medical Science, Khon Kaen University, Khon Kaen, Thailand. The volunteers received an information letter and a headache diary. They were instructed to record every migraine attack in a set of 4-week period prior to the eligibility assessment. On the enrollment visit, the diagnosis was confirmed, and neurological examination was thoroughly performed. Inclusion criteria were as follows: 1) ages between 18 and 65 years; 2) migraine with or without aura; 3) migraine present for at least 1 year before participating in the study; 4) frequency of attacks of three or more per four weeks during at least the previous three months; 5) had never received any prophylactic treatment, failure of the previous prophylactic treatment, or discontinuation of treatment due to adverse events for at least three months prior to the start of the experiment; 6) the patients agreed to take no concurrent prophylactic treatment for headaches by both pharmacological and non-pharmacological treatments; and 7) the patients were willing to be available for a follow-up period of at least three months. Exclusion criteria were psychiatric conditions, pregnancy, lactations, skull defect, and other serious neurological diseases.

All patients gave their written informed consent. The study conformed to the declaration of Helsinki and was approved by the Ethics Committee of Khon Kaen University (Identifier number is HE 521331).

Experimental design

The study contained the following three phases: 1) Baseline evaluation consisted of a 4-week period of observation to assess the baseline of attack frequency, pain intensity, and number of abortive medications; 2) A 20-day daily treatment sessions with tDCS for 20 consecutive days; and 3) a 4-week period of observation for 12 weeks follow-up period.

All the patients were informed about all possible adverse events, including headache attacks with the attendant symptoms and the number of abortive medication. We told the participants to continue their routine abortive medication regimen. All changes in dosages were recorded in the patient's medication diary. Herbal remedies and other alternative therapies such as massage were not allowed.

Direct current stimulation

Direct current was transferred using a saline-soaked pair of surface sponge electrodes (35 cm^2) and delivered through battery-driven power supply. Constant current stimulator with a maximum output of 2 mA was developed by Pattawit Electronic, JP advance LTD, Thailand. The anodal electrode was placed at the M1 and the cathodal electrode was placed over the contralateral supraorbital area. We identified M1 as the half way between C3 and F3 of the electroencephalography (EEG) 10/20 system.

Frequency of attacks

Frequency of attacks, the primary outcome, was recorded by patients four weeks before the treatment to assess the baseline. They were also requested to record their attack every four weeks after treatment. The self-recording terminated at week 12.

Pain measurement

Pain intensity, the secondary outcome, in a form of visual analog scale (VAS) was evaluated by the

patients. This self-evaluation scale ranges from 0 to 10 as visually described in centimeter units: 0 cm indicates no pain and 10 cm denotes the most possible pain. The self-recording of pain intensity was performed as frequency of attacks.

Abortive and analgesic medications

Abortive medications were recorded as the total number of tablets intake per four weeks. The diary recording was defined in pain intensity. For the abortive and analgesic medications, we prescribed 1000 mg of acetaminophen every six h in cases of mild attack; 200 mg of ibuprofen, two tablets every four h in cases of moderate attack; one mg of ergotamine with 100 mg of caffeine, two tablets at the onset, and then one tablet every half an hour until the symptom relief (maximum six tablets per day, or ten tablets per week) in cases of moderate attack; and 50-100 mg of sumatriptan at the onset and repeated after two h (maximum 200 mg per day) in severe cases. The medications were given to the patients as in medical practice.[25]

Statistical analysis

Analyses were done with Stata software, version 10.0 (StataCorp, College Station, TX). Dropouts indicated treatment failure or no improvement that discouraged them to continue in this trial. Therefore, we analyzed the endpoints using the intention-to-treat principle. We used the last evaluation carried out to the session before the missed session, assuming no further improvement after the dropout.

A repeated measure ANOVA was used to analyze the difference between baseline and every time point of post treatments period. The level for establishing significant differences was set at $p < 0.05$.

Results

A total of 13 patients were included in this study between March 2010 and July 2010. The patients were assessed for four weeks, and one did not meet the inclusion criteria. One patient in this study dropped out at the treatment period, which was excluded from this study. Eleven patients participated in follow up period and one subject dropped-out at the week 8 because her child was ill and she could not record her symptom. We considered the analysis of all the available participants (10/11) who completed the study as an intention-to-treat analysis. Table 1 shows the demographic profile of the included patients.

Table 1 Demographic data and baseline characteristics

No. of subjects	11
Sex (female/male)	7/4
Age (mean ± SD)	23.42 ± 7.68
Diagnosis	
Migraine with aura	2
Migraine without aura	9
Family history	6
Baseline pain intensity (VAS score) (mean ± SD)	4.64±1.03
Migraine attack frequency/ 4 weeks (mean ± SD)	3.79 ± 0.68
Mean age at onset of migraine (mean ± SD)	22.24 ± 5.39
Number of abortive medication/ 4 weeks (tablets) (mean ± SD)	18.96 ± 2.52
Abortive medications	
Ergotamine	9*
Ibuprofen	2
Acetaminophen	1*
History of prophylactic medications	
Failed tricyclic antidepressant	2**
Failed beta-blockers	1**
Never take prophylactic medications	9

*One patient took both ergotamine and acetaminophen
**One patient failed both tricyclic antidepressant and beta-blockers

Frequency of attacks

Compared to the baseline, there was statistically significant reduction in the attack frequency at week 4 (0.86, 95%CI: 0.84 to 1.01, p =0.02) and week 8 (0.68, 95%CI: 0.62 to 0.84, p =0.03) while there was no statistically significant reduction in the attack frequency at week 12 (-0.25, 95%CI: -0.32 to 0.18, p =0.41). (Figure 1)

Pain intensity

On comparing between before and after treatments, there was statistically significant reduction in the pain intensity at week 4 (1.10, 95% CI: 0.98 to1.12, p =0.02)

and week 8 (0.99, 95% CI: 0.91 to 1.06, p=0.03) but no statistically significant reduction observed at week 12 (-0.11, 95% CI: -2.82 to 1.06, p=0.18). (Figure 1)

Abortive medications

All patients had abortive medications until the symptom disappeared. There were three patients who took overdose of ergotamine 8-10 tablets/day. Furthermore, one patient took both ergotamine and acetaminophen for relieving her pain. However, all other patients used the medication as the dose recommended.

On comparing between before and after treatment, the reduction at week 4 was 4.16, 95% CI: 3.22 to 5.18, p= 0.01, week 8 was 1.94, 95% CI: 1.88 to 2.18, p=0.03, and week 12 was 1.01, 95% CI: 0.95 to 1.99, p = 0.05. (Figure 1)

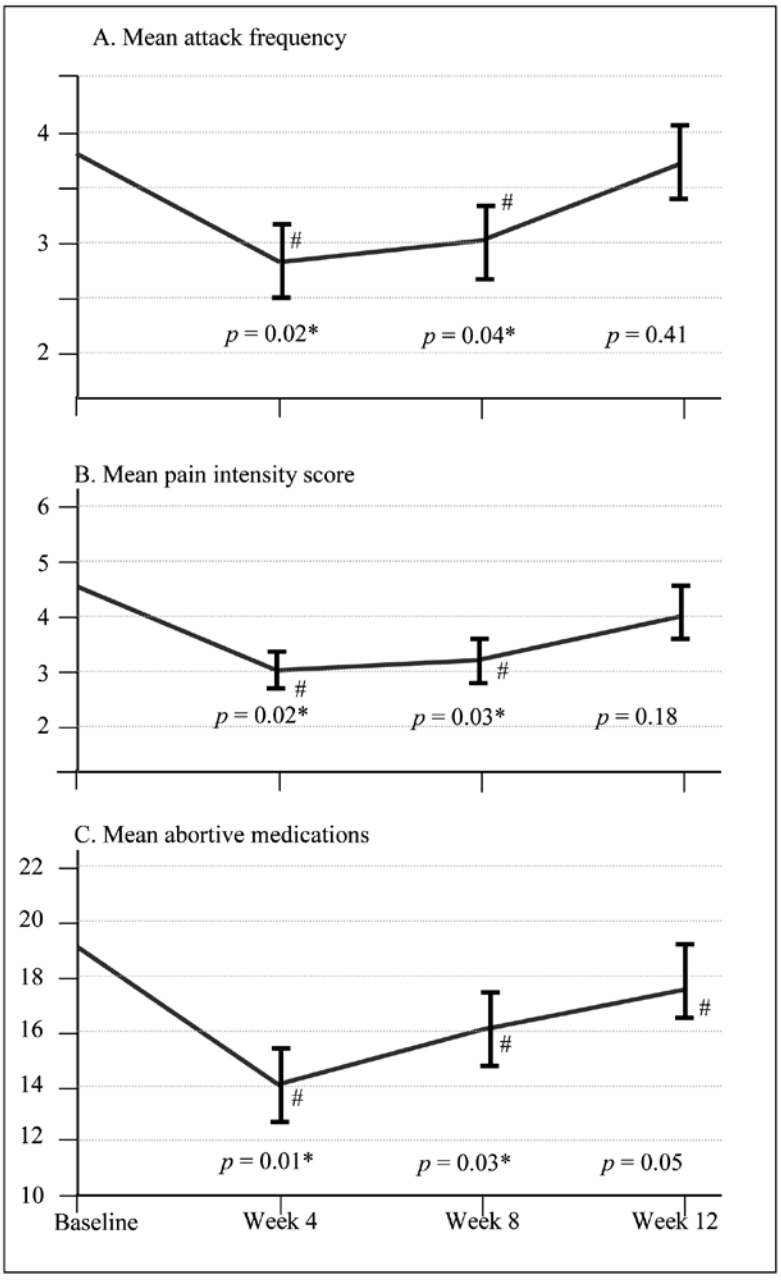

Figure 1 Means and 95% confidence intervals (vertical line) of baseline, 4, 8 and 12 weeks after treatment. #Mean value was significantly different to that at baseline (p<0.05)

Adverse events

All patients tolerated the tDCS well without any serious adverse events. There were two patients exhibited adverse events: one had transient mild first degree burn that completely healed within five days, one had rash under electrode, which disappeared in two hours.

Discussion

This is a pilot open-label study with subjects who had 3-5 episodes attack frequency per month. They had never undergone or failed prophylactic treatment. Robbins headache clinic 2000[26] analyzed 1012 migraine patients with and without aura, they found that 34.4% had failed 1-2 trials, 14.6% had failed 3-4 trials, and 12.9% had tried five or more drugs. Therefore, the purpose of this study was to assess the prophylactic effect of anodal tDCS in migraine patients. The method of this study was the consecutive 20 days of stimulation or about 1/10 of the duration of the conventional medical prophylactic therapy, which generally takes 4-6 months. We also followed-up for 12 weeks, which is supposed to be adequate to understand the long-lasting effect of 20 days of stimulation.

The primary outcome of this study was the frequency of migraine attack. We found that the frequency of attack was lower than that in the baseline at week 4 and 8 after treatments, but did not last long up to week 12. Our outcomes support the results of the study by Brighina et al.[19]; In the aspect of pain reduction, our results support the study of Antal et al.[21], they showed a significant reduction in the intensity of pain (two months post-treatment) between the active and sham groups. Moreover, there were other studies that had showed the TMS effect in pain abortion. Clarke[27] used two stimulus pulses over the area of perceived pain or over the area of the brain, generating the aura at the beginning of the attack. Lipton[28] employed hand-held devices operated by patients. The stimulator was placed over the visual area and administered three attacks over three months while experiencing aura.

Till date, the mechanism of migraine is still unclear. Many evidences have shown impaired cortical inhibition in migraine patients[8-12]. According to noninvasive brain stimulation studies, high-frequency rTMS[19] or anodal tDCS had positive effects in migraine prophylaxis. Based on these studies, it has been proposed that an increase in the local excitability of the cortex might be associated with pain control or modulation[22].

According to the neurophysiologic knowledge, anodal tDCS might have a role in corticothalamic loop by acting on the neuronal membranes leading to increased firing rates driven by postsynaptic membrane depolarization accompanied by enhanced presynaptic input, resulting in NMDA receptor-mediated augmentation of synaptic strength, presumably via the increase in the intracellular calcium levels[29]. Similar to the induction of long-term neuroplasticity, a combination of glutamatergic and membrane mechanisms is necessary to induce the after-effects of anodal tDCS, which occur in both reticular neuron and relay cell of thalamus[30]; thus, increased cortical inhibition might modulate pain perception through this loop. However, the supposed mechanism is assumed from neurophysiologic studies in Parkinson disease and central pain. The direct effects of tDCS on corticothalamic modulation in migraine patients need further study.

This study has some limitations. First, our sample size might not be large enough to detect a positive effect until 12 week-post treatment. Second, we performed an open-label which might lead to subjects' evaluation bias. Third, we could not conduct the neuro-imaging change between before and after study so the mechanism of tDCS action on migraine was not established.

In summary, we conclude that this pilot open-label study of anodal tDCS on M1 for 20 sessions can significantly decrease the frequency of attack, pain intensity, and abortive medications for eight weeks. For reducing the subjects' bias, the randomized controlled trial should be further investigated.

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Conflict of interest

The authors have no financial or personal conflicts of interest.

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