• clinical studies

Clinical study of transcranial ac stimulation in the treatment of migraine without aura

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【 Abstract 】 Objective To investigate the efficacy and safety of transcranial alternating current stimulation (tACS) in the treatment of migraine without aura. Methods A prospective study was designed. A total of 40 patients without aura who visited the Vertigo Center of Neurology, the Second Affiliated Hospital of Zhengzhou University from June 2021 to June 2022 were included. They were randomly divided into real group (20 cases) and sham group (20 cases) according to simple random method. They were treated and followed up for 8 weeks (the first 4 weeks were the treatment period and the last 4 weeks were the follow-up period). The patients in the sham group were not subjected to current stimulation. In the true group, the electrodes placed in the forehead and bilateral mastoids received stimulation with an alternating current of 77.5 Hz and 15 mA (2 times /d, 40 min per time, 5 d as a course of treatment, and four courses in total). Patients' efficacy indicators and adverse reactions were assessed before treatment, at the end of treatment and at the end of follow-up. Results Compared with those before treatment, the average number of migraine attack days, visual analogue scale (VAS) score, Pittsburgh sleep quality index (PSQI), Hamilton anxiety scale (HAMA) score and Hamilton depression scale (HAMD) score in the true group at the end of treatment and the end of follow-up were all decreased significantly. The migraine-specific quality of life questionnaire (MSQ) score was significantly increased, and the differences were statistically significant (P<0.05). Compared with the sham group, the average monthly migraine attack days, VAS score, PSQI, HAMA score and HAMD score of the patients in the real group at the end of treatment and the end of follow-up were significantly decreased, and the MSQ score was significantly increased, with statistical significance (P<0.05). No adverse reactions such as epileptic seizure, hearing loss, scalp burns, dizziness, and tinnitus were observed in the patients of the two groups during the treatment and follow-up. Conclusion tACS is a safe and effective method for the treatment of migraine without aura, in that it can significantly reduce the frequency and severity of migraine and improve the quality of life of patients.

【 Keywords 】 migraine without aura; Transcranial alternating current stimulation; Efficacy; Safety fund project: Zhengzhou Science and Technology for the Benefit of the People Project (2021KJHM0023) DOI: 10.3760/CMA.J. CN 115354-20221128-00863

Transcranial alternating current stimulation in migraine without aura

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【 Abstract 】 Objective To investigate the efficacy and safety of transcranial alternating current stimulation (tACS) in treating migraine without aura.MethodsA prospective study design was used. From June 2021 to June 2022, 40 migraine without aura patients treated at Vertigo Center, Department of Neurology, Second Affiliated Hospital of Zhengzhou University were collected; they were randomly assigned to true and pseudo groups; treatment was given for 4 consecutive weeks and follow-up was given for 4 weeks. The pseudo group did not receive current stimulation, while the true group received stimulation by sending 77.5 Hz, 15 mA alternating current through electrodes placed on the forehead and bilateral mastoid. Efficacy and adverse reactions were assessed before treatme nt, and at the end of

treatment and at the end of follow-up, respectively. Results Compared with the pseudo group, the average days of migraine, visual analog scale (VAS) scores, Pittsburgh sleep quality index (PSQI), Hamilton Anxiety Scale (HAMA) scores and Hamilton Depression Scale (HAMD) scores decreased statistically in the true group (P<0.05), and the Migraine-specific Quality of Life Questionnaire (MSQ) scores increased statistically in the true group (P<0.05). In the true group, compared with those before treatment, the average days of migraine occurrence, VAS scores, PSQI, HAMA scores and HAMD scores significantly decreased, and the MSQ scores increased statistically at the end of treatment and at the end of follow-up (P<0.05). During treatment, no adverse reactions such

as seizures, hearing loss, scalp burns, dizziness, or tinnitus were noted in the two groups. Conclusion Repeated tACS treatment can significantly reduce the frequency and pain degree of migraine, improve the quality of life in migraine without aura patients; and good safety can be recorded.

【Key words】 Migraine without aura; Transcranial alternating current stimulation; Efficacy; Safety

Fund program: Zhengzhou Science and Technology Benefiting People Project (2021KJHM0023)

DOI:10.3760/cma.j.cn115354-20221128-00863

Migraine is a neurological disease characterized by recurrent moderate to severe headache on one or both sides, with the characteristics of high prevalence, long course of disease, and serious personal and social burden. Non-aura migraine is the main type of migraine. At present, the annual prevalence rate of migraine in China is about 9.3%, and the prevalence rate in women is significantly higher than that in men, ranging from 2: 1 to 4: 1 [1–3]. Traditional medication for the acute treatment and preventive treatment of migraine is mainly drugs, but except for the 5- HT receptor agonist, the rest of the medication are clinical empirical treatment. Therefore, in the situation of poor compliance with drug treatment and facing many adverse reactions after long-term use, the discovery of new treatments for migraine becomes particularly important [4]. Transcranial alternating current electrical stimulation (tACS) is a relatively new neuromodulation technology. It directly stimulates cortical neurons with sinusoidal alternating current, regulates cortical excitability and spontaneous electroencephalogram activities, improves brain network function activities, and regulates the levels of β -endorphin and monoamine substances (dopamine, 5- hydroxytryptamine, etc.) in cerebrospinal fluid, brain stem, hypothalamus and cortex to achieve the purposes of relieving pain, enhancing memory consolidation, improving body's psychological and physiological state, and regulating ganglion neural plasticity [5–6]. At present, the research on transcranial electrical stimulation of migraine in China and abroad is mostly based on DC current, and the research on tACS treatment is relatively rare. Our research group conducted a tACS treatment study for migraine without aura patients who visited the Vertigo Center of Neurology, the Second Affiliated Hospital of Zhengzhou University in recent years, and observed and evaluated its efficacy and safety, in order to provide a reference basis for the wide clinical application of tACS in the treatment of migraine. The specific contents are reported as follows.

Information and methods

I. research subjects

This study was designed as a prospective study and was selected consecutively from 2021

Patients who visited the Vertigo Center of Neurology, the Second Affiliated Hospital of Zhengzhou University from June to June 2022 for migraine without aura were included in the study. Inclusion criteria: (1) age 18–65 years old; (2) The diagnosis of migraine without aura meets the requirements of the International Headache Association Diagnostic Criteria Version 3 (ICHD-3); (3) There is no past history of head trauma and no other intracranial organic or mental diseases except migraine; (4) History of migraine ≥1 year; (5) Headache attack times ≥6 times in recent 3 months. Exclusion criteria: (1) Those who have previously received metal implantation in the head and cochlear implant, pacemaker installation, and other treatments that cannot tolerate AC current; (2) Has previously received transcranial magnetic stimulation, transcranial direct current stimulation, or other neuromodulation technology treatments.

Who; (3) Pregnant or lactating women; (4) Those who have received medication for migraine in the past three months; (5) Patients who took drugs due to intolerable pain during the study. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (approval No. 2023048). Before entering the group, all patients were informed of the purpose of the study and signed a written informed consent form for the study.

II. Research Methods and Treatment Measures

A randomized, double-blind controlled study was designed in this study. The sham therapeutic groups were set as group A and group B, respectively. The real and fake therapeutic devices were numbered as group A and group B by independent statisticians using a simple randomization method of 1: 1. The investigator, including the evaluator, tACS operator, and patient, were all unaware of the randomization, and the blindness was unblinded after completing all the studies.

1. True group: tACS devices and electrodes produced by Nexalin, the US, were used for the treatment. Three professional electrodes were placed in the prefrontal cortex and bilateral mastoids, respectively. Current intensity was 15 mA, and stimulation frequency was 77.5 Hz. The stimulation was performed twice a day, 40 min each time. Treatment lasted for 5 d as one course of treatment, and resumed after a rest of 2 d, totally 4 courses.

2. Sham group: The sham therapeutic apparatus that did not generate current and had the same appearance as the real therapeutic apparatus was used, and the electrode placement and treatment arrangement were identical to the real therapeutic apparatus.

The patients in both groups entered the follow-up period of consecutive 4 weeks after completing 4 weeks of treatment, and did not receive any treatment during the follow-up period.

III. Observation indicators

The efficacy indicators and adverse reactions were assessed before treatment, at the end of treatment and at the end of follow-up.

1. Mean number of migraine attack days and severity of headache per month: The patients were required to complete a headache diary every day from 4 weeks before treatment to the end of follow-up period, mainly covering the start and end time, location, nature, severity and accompanying symptoms of headache, and the professional neurologist should judge whether it was a migraine attack. The numb of migraine attack days is define as any number of migraine attack days recorded in that diary for the patient. 1 month is defined as 28 d(4 weeks). The visual analogue scale (VAS) was used for the assessment of the degree of headache, with the score ranging from 0 to 10 points, of which 0 was classified as painless and 10 as severe pain. The higher the score was, the more obvious the pain would be [7].

2. Migraine-specific quality of life questionnaire: migraine-specific quality of life questionnaire (MSQ) is the core tool for migraine research in the world (msq version 2.1 was used in this study). it consists of three groups of items: work

The ability-to-limit item assessed how migraine restricted people's daily social and work-related activities, the dysfunction item assessed how migraine prevented those activities, and the affect item assessed the emotions associated with migraine. The items in the three groups consisted of 14 small items, each of which was graded as 1–6 points, and the basic scores of each group were converted into 0–100 points according to the conversion formula. The higher total score represented the better quality of life [8].

3. Pittsburgh sleep quality index: Pittsburgh sleep quality index (PSQI) is a common tool for evaluating sleep quality of patients, and it includes seven subscales: subjective sleep quality, sleep latency, sleep time, sleep efficiency, sleep disorders, sleep medication use and daytime dysfunction, with a total score of 0–21 points; a score of > 5 indicates the existence of clinically significant sleep problems, and a higher score means the poorer sleep health [9].

4. Hamilton Anxiety Scale: Hamilton Anxiety Scale (HAMA) is often used in clinic to diagnose anxiety and the basis for its degree classification (HAMA-14 edition was used in this study). Among the scores, less than 7 points indicated no anxiety, ≥14 points indicated certain anxiety, ≥21 points indicated obvious anxiety, and ≥29 points indicated serious anxiety [10].

5. Hamilton Depression Scale: Hamilton depression rating scale (HAMD) is currently the most basic tool for evaluating the efficacy of antidepressant treatment (HAMD-17 edition is used in this study). Among them, < 7 points mean no depression, ≥17 points mean mild to moderate depression, and ≥24 points mean severe depression [10].

6. Adverse reactions: All adverse reactions including epileptic seizure, dizziness, scalp burn, and tinnitus during the treatment and follow-up of the patients in the two groups were recorded.

IV. Statistical analysis

SPSS 26.0 statistical software was used to process the data. The count data were expressed as the number of cases (percentage) [n(%)], and the comparison between the two groups was examined by χ^2 test. Measurement data subject to normal distribution and homogeneity of variance were expressed as mean standard deviation ($\bar{x}$ s), and two independent samples t test was used for comparison between the two groups. One-way analysis of variance was used for comparison among multiple groups, and LSD-t method was used for further pairwise comparison within the group. The measurement data of non-normal distribution was expressed as the median (first quartile, third quartile) [M(Q1, Q3)], and the comparison between the two groups was performed using Mann-Whitney U test. Comparisons between multiple groups were performed using the Kruskal-Wallis H test, and pairwise comparisons within groups were further performed using the All pairwise setting in multiple comparisons. The difference was statistically significant ($P<0.05$).

Bear fruit

I. baseline information

In this study, 67 consecutive patients with migraine without aura

Among them, nine cases showed no willingness to participate, 13 cases received medication for migraine within the past three months, and five cases failed to participate in the treatment due to epidemic situation. Eventually, a total of 40 patients were actually included in the study. After being randomly allocated to the authenticity group in a ratio of 1: 1, 20 patients in each group. There was no significant difference in age, gender, course of disease, body mass index or educational level between the two groups (P>0.05). Specific content is shown in table 1.

II. Mean Monthly Migraine Attack Days

Compared with those before treatment, the average monthly migraine attack days in the true group and the sham group at the end of the treatment period and the end of the follow-up period were significantly decreased, and the differences were statistically significant (P<0.05). Compared with the sham group, the average monthly migraine attack days in the true group at the end of treatment and follow-up were significantly decreased, and the difference was statistically significant (P<0.05). Specific content is shown in table 2.

III. VAS score

Compared with those before treatment, the VAS scores of the true group at the end of treatment and follow-up were significantly decreased, and the differences were statistically significant (P< 0.05). Compared with the sham group, the VAS scores of the true group at the end of treatment and follow-up were significantly decreased, and the difference was statistically significant (P< 0.05). See Table 3 for details.

IV. MSQ score

Compared with those before treatment, the MSQ scores of the true group at the end of treatment and follow-up were significantly increased, and the differences were statistically significant (P< 0.05). Compared with the sham group, the MSQ scores of the true group at the end of treatment and follow-up were significantly increased and the differences were statistically significant (P< 0.05). Specific content is shown in table 4.

V. PSQI, HAMA and HAMD scores

Compared with those before treatment, the PSQI, HAMA and HAMD scores of the patients in the true group at the end of treatment and follow-up period were significantly decreased, and the differences were statistically significant (P<0.05). Compared with those before treatment, the HAMD score of patients in the sham group at the end of treatment was decreased significantly, and the difference was statistically significant (P<0.05). Compared with the sham group, the PSQI, HAMA and HAMD scores of the patients in the true group at the end of treatment and follow-up were significantly decreased, and the differences were statistically significant (P<0.05). The specific content is shown in table 5.

Table 12 Comparison of Baseline Data in Patients with Non-aura Migraine between Groups

Tab.1 Comparison of general data between two groups of patients with migraine without aura

group	Number of cases	Age (years,-x̄ s)	Male [n(%)]	Body mass index (kg/m2)	Course of disease (month)	Education [n(%)]		
							12 years and under	Over 12 years
True group	20	33.0±5.3	6(30.0)	21.4±1.5	32.9±12.8		11(55.0)	9(45.0)
Pseudo group	20	33.7±4.8	5(25.0)	21.5±1.4	31.9±14.0		12(60.0)	8(40.0)
T/χ2 value		0.408	0.125	0.029	0.235		0.102	

VI. Adverse reaction occurrence

No adverse reactions such as epileptic seizure, hearing loss, scalp burns, dizziness, and tinnitus were observed in the patients of the two groups during the treatment and follow-up.

Discussion

Migraine has a complex etiology and many theories about related pathophysiological mechanisms, including cortical spread inhibition theory, trigeminal neurovascular theory, gene and ion channel theory, etc. It is now generally accepted that migraine

The pulsatile pain of is the result of activation of trigeminal neurovascular pathway: the brain and meningeal blood vessels innervated by the trigeminal nerve are rich in nociceptive afferent fibers, and calcitonin gene-related peptide (CGRP) released by trigeminal nerve activation can cause dilation of brain and meningeal blood vessels, which in turn stimulates large and fat cells to release inflammatory mediators, causes neurogenic inflammatory reaction, and causes the activation and sensitization of nociceptive nerve fibers. The nociceptive information is then projected onto multiple cortical regions involved in nociceptive signal processing through the ascending pathway through the brain stem, thalamus, and basal ganglia [11–12].

Table 22 Comparison of average monthly migraine attack days in patients without aura before and after treatment in the group [d, M(Q1, Q3)]

Tab. 2 Comparison of average monthly migraine days before and after treatment in the two groups of patients with migraine without aura (d, M[Q1, Q3])

group	Number of cases	Pre-treatment	End of treatment	End of visit	*H value*	*P value*
True group	20	7.0(6.0，7.8)	3.0(2.0，3.0)a	3.0(3.0，4.0)a	42.620	<0.001
Pseudo group	20	7.0(6.0，7.8)	5.0(5.0，6.0)a	5.5(5.0，6.0)a	27.073	<0.001
Z value		0.316	5.123	5.379		
P value		0.752	<0.001	<0.001		

Compared with pre-treatment, aP<0.05

Table 32 Comparison of VAS scores of patients with migraine without aura before and after treatment in the group [score, M(Q1, Q3)]

Tab.3 Comparison of visual analog scale scores before and after treatment in the two groups of patients with migraine without aura (M[Q1, Q3])

group	Number of cases	Pre-treatment	End of treatment	End of visit	*H value*	*P value*
True group	20	6.0(6.0，7.0)	4.0(4.0，4.0)a	4.0(4.0，5.0)a	41.904	<0.001
Pseudo group	20	6.0(6.0，7.0)	6.0(6.0，6.0)	6.0(6.0，7.0)	1.423	0.488
Z value		0.798	5.460	5.268		
P value		0.425	<0.001	<0.001		

Compared with pre-treatment, aP<0.05； ; VAS: visual analogue scale

Table 42 Comparison of MSQ scores of patients without āura migraine before and after treatment in the group (score, $\bar{x}$ s)

Tab.4 Comparison of Migraine-Specific Quality-of-Life Questionnaire scores at each time point before and after treatment in the two groups of patients with migraine without aura (Mean±SD)

group	Number of cases	Pre-treatment	End of treatment	End of visit	*variance ratio*	*P value*
True group	20	175.0±14.7	211.3±7.7a	198.6±14.4a	35.061	<0.001
Pseudo group	20	175.5±15.1	172.6±9.3	176.6±13.7	0.507	0.605
T value		0.106	14.368	4.946		
P value		0.916	<0.001	<0.001		

Compared with pre-treatment, aP<0.05； ; MSQ: migraine specific quality of life questionnaire

Table 52 Comparison of PSQI, HAMA and HAMD scores of patients without aura migraine before and after treatment in the group (score, $\bar{x}$ s)

Tab. 5 Comparison of Pittsburgh sleep quality index, and Hamilton Anxiety Scale and Hamilton Depression Scale scores between in the two groups of patients with migraine without aura before and after treatment (Mean±SD)

Example PSQI Group f value					HAMA score P value f value				HAMD score P value				
Number of treatment before the end of the treatment at the end of the follow-up period					Pretreatment	Treatment End of Treatment End of Visit			Pre-treatment	End of Treatment	End of Visit	F value	p value
True group 2011.71.3	6.0±1.2a	6.5±1.2a	134.627	<0.001	13.6±1.6	9.2±1.3a	9.6±1.1a	64.613	<0.001	15.3±1.5	7.7±1.1a	8.1±1.2a	226.984	<0.001
Sham group 2011.91.5 12.11.4		12.4±1.1	0.706	0.498	13.8±1.5	13.1±1.1	13.2±1.5	1.409	0.253	15.1±1.5	14.0±1.3a	14.3±1.3	3.958	0.025
T value	0.462	14.887	16.347		0.409	10.394	8.495		0.420	16.790	16.085			
P value	0.646	<0.001	<0.001		0.685	<0.001	<0.001		0.677	<0.001	<0.001			

Compared with pre-treatment, aP<0.05； ; PSQI: pittsburgh sleep quality index; HAMA: hamilton anxiety scale; HAMD: hamilton depression scale

Migraine has become a major public health problem that has not been fully recognized due to the numerous possible pathogenesis and high incidence and disability rate. Although there are many drug treatment options, they still face the challenges of more adverse reactions, the development of drug resistance and poor compliance. Previous studies have found that only 3%–22% of patients with acute migraine use triptan drugs, only 2%–14% of patients meet the conditions for the use of preventive drugs, and a considerable number of patients are dissatisfied with their own acute drug treatment [13–14]. Therefore, non-drug treatments for migraine, including acupuncture, peripheral nerve stimulation and transcranial stimulation technology [15], have gradually received clinical attention. As an emerging transcranial electrical stimulation, tACS seems to have great potential in preventing the onset of migraine. For example, Antal et al. [16] previously discovered after applying 0.4 mA/140 Hz tACS to the occipital region of patients with migraine without aura, that the proportion of patients in the treatment group who stopped the onset of migraine within 2 h of stimulation was significantly higher than that in the placebo group, indicating that low-intensity and high-frequency tACS applied to the visual cortex could stop the onset of migraine. In order to further explore the therapeutic effects of greater stimulation intensity and different stimulation locations on migraine, in this study, 15 mA/77.5 Hz tACS was applied to the forehead and bilateral temporal regions of patients, and the attack frequency, severity and quality of life of migraine were evaluated.

It was found in the present study that the average monthly migraine attack days and VAS scores at the end of treatment and follow-up period in the true group were lower than those before treatment, while the MSQ score was higher, and the difference was also statistically significant as compared with that in the sham group ($P<0.05$). This suggests that after four courses of 40 times of tACS treatment, the frequency and pain degree of headache of patients with migraine without aura are significantly decreased, the quality of life is significantly improved, and the level of treatment period is still maintained in the following four weeks. This may be related to the fact that tACS increases the levels of neurotransmitters such as β-EP and 5- HT in cerebrospinal fluid, hypothalamus and related brain regions so as to achieve analgesic effects [17]. Animal experiments showed that the level of 5- HT was decreased during the migraine attack, causing vasodilatory pain. The increase of β -endorphin can inhibit the release of P substance and thus relieve pain [18]. In addition, another study has shown that in migraine patients, repeated nociceptive stimulation can reduce the activation of these brain regions involved in endogenous pain control, such as the prefrontal cortex, the red nucleus, and the ventral medulla, which may represent insufficient pain inhibition in migraine patients [19]. Ahn et al. [20] also found that the pain in patients with chronic lumbago was significantly alleviated after they were treated with tACS at 10 Hz. Further studies have revealed that tACS reduces the pain by enhancing the endogenous electroencephalogram oscillation of neurons in the prefrontal cortex involved in pain management. In this study, the electrode stimulation in the prefrontal cortex of patients in the true group was also able to regulate the endogenous electroencephalogram oscillation by increasing the activation of the prefrontal cortex, thereby increasing the inhibition of pain by migraine patients and reducing the severity of headache.

This study also found that the true group of patients at the end of treatment, the end of the follow-up

The PSQI, HAMA and HAMD scores of the EA group were significantly lower than those before treatment, and the difference was also statistically significant as compared with the sham group (P <0.05)。 Sleep quality of migraine patients is generally poor, and insomnia is also one of the risk factors for migraine, which is related to the intensity and attack frequency of migraine [21]. Previous study on the treatment of chronic insomnia with tACS found that tACS could significantly reduce PSQI of patients with chronic insomnia and improve their sleep quality [22]. The relief of pain in our patient may also be related to the improvement in her sleep quality. Clancy et al. [23] increased the anxiety level of healthy subjects by giving them certain auditory and olfactory stimulation, and then performed phased 8–12 Hz tACS treatment. They found that tACS could significantly increase the neuronal connections between the parietal and frontal cortex in the resting state and enhance local α-frequency electroencephalogram activity, resulting in continuous improvement of anxiety symptoms and related behavioral indicators. In this study, we adopted a treatment protocol different from its stimulation frequency, but we also found that the anxiety level of migraine patients was reduced, but the specific mechanism still needs to be further explored. Previous studies showed that 77.5 Hz tACS could increase the level of 5- HT in the body, while the reduction of 5- HT level and activity was recognized as being closely related to depression [17,24]. Therefore, it was speculated that the improvement of depressive symptoms in migraine patients in this study might be related to the increase of 5- HT level induced by tACS stimulation.

In summary, tACS can significantly improve the frequency and pain severity of migraine without aura in patients with migraine, and improve the quality of life of patients. With good safety, it is expected to become an effective non-drug intervention for migraine without aura. But undeniably, this study has such defects as lack of objective evaluation indicators, insufficient sample size, and short follow-up time. In the future, large-sample, multi-center and long-term follow-up study is required to further confirm the conclusions of this study.

Conflict of interest all authors state that there is no conflict of interest

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essay

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(deadline: 2022-11-28)
(Edited by Liu Kai)