Migraine prevention with percutaneous mastoid electrical stimulator: A randomized double-blind controlled trial

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Abstract
Objective: To evaluate the effectiveness and safety of episodic migraine prevention with the percutaneous mastoid electrical stimulator (PMES).

Methods: This was a randomized, double-blind, and sham-controlled trial that involved four medical centers. Episodic patients with at least two migraine attacks every month were randomly 1:1 to PMES or sham stimulation treatment. The treatments were performed daily for 45 minutes over 3 months. The primary outcomes were change in migraine days per month and the 50% response rate.

Results: The PMES group had a significantly greater reduction of migraine days in the third month than the sham group (−71.3% vs. −14.4%, p < 0.001). The 50% response rate of migraine days in the PMES group (≥50% reduction of migraine days compared with the baseline) was significantly higher than that in the sham group (82.5% vs. 17.5%, p < 0.001). In the PMES group, 60% of the patients had a ≥75% reduction of migraine days in the third month, and 35% of the patients had no migraine attack in the third month. No patients in the sham group had a ≥75% reduction of migraine days. There were no adverse events in either group.

Conclusion: Treatment of migraine using non-invasive PMES was safe and effective.

Keywords
Migraine, percutaneous mastoid electrical stimulator, treatment

Introduction
The incidence of migraine in the Chinese population between the ages of 18 and 65 is 9.3%, of which 38% of patients require treatment due to moderate to severe headache (1). Medication is the most commonly used method for migraine prevention (2). However, not all patients respond to currently used medications, and their tolerability and adverse effects often limit their use (3–5). In recent years, many non-medication methods have been studied in migraine prevention. The efficacy of acupuncture in migraine prevention is still unclear and might be mainly from a placebo effect (6,7). Neuromodulation techniques targeting peripheral nerves or the brain itself are attractive alternatives to pharmacological treatment (8). The supraorbital transcutaneous stimulator (STS) has been demonstrated to prevent episodic migraine in one sham-controlled study; however, its efficacy is still limited (9). The efficacy of invasive vagus nerve stimulation (iVNS) and transcutaneous vagus nerve stimulation (tVNS) in migraine prevention has been suggested by several case reports and surveys including a small number of patients (10,11).

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The subcutaneous invasive occipital nerve stimulation (ONS) alone or in combination with invasive SNS is useful to highly disabled patients (8); however, it may not be accepted by less disabled patients with episodic migraine. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are both non-invasive ways to modulate the excitability of the underlying cerebral cortex, and a few studies showed their efficacy in migraine prevention (12–15), but the most appropriate brain regions as well as stimulation frequencies and intensities remain to be elucidated (8). The neuroprotective function of fastigial nucleus stimulation (FNS) was first confirmed by Reis et al. (16) in 1998. FNS can elicit long-lasting suppression of peri-infarction depolarizing waves (PIDs) and protect rats against cerebral ischemia (17). Cortical spreading depression (CSD), a process sharing characteristics with PIDs, is an important pathogenic mechanism of migraine. Therefore, we speculate that FNS may be useful in migraine prevention. The non-invasive percutaneous mastoid electrical stimulator (PMES) can simulate experimental FNS, and has been applied to clinical treatment in stroke patients (18). Several observational studies have shown that PMES treatment may prevent migraine and showed excellent safety (19–21). However, all of these studies had flaws in trial design, including short treatment duration (less than 1 month) and sham control. Therefore, we conducted a multi-center, randomized, double-blind, and sham-controlled trial to confirm the efficacy of PMES treatment in migraine prevention.

**Methods**

This study was a prospective, multi-center, randomized, double-blind, and sham-controlled trial, which was conducted in four medical centers. The study was approved by the ethics committees of all the medical centers. Informed consent was signed by all the participants.

This project was registered in the Chinese Clinical Trial Register (ChiCTR) (registration number: ChiCTR-ICR-15006273). The trial design conformed to the guidelines for clinical trials in migraine of the International Headache Society (22).

**Patient selection and grouping**

Inclusion criteria included: 1) aged 18–65 years old; 2) episodic migraine with or without aura (International Classification of Headache Disorders [ICHD]-II code 1.2.1 or 1.1) (23); 3) the first migraine attack was before 50 years old; 4) at least a 1-year history of migraine; 5) two or more migraine attacks per month in each of the 3 months before screening; 6) voluntary participation and a consent form was signed.

Exclusion criteria included: 1) use of a preventive treatment in the previous 3 months; 2) failure on three or more well-conducted preventive drug treatments; 3) chronic migraine (ICHD-II 1.51) and medication overuse headache (ICHD-II 8.2); 4) alcohol abuse and/or other drug abuse; 5) severe neurological or psychiatric disorders; 6) severe primary systemic disorders including heart, brain, liver, kidney, and hematopoietic system; 7) pregnant and lactating women.

**Treatment methods**

After the local skin was cleaned, stimulation electrodes were placed on the bilateral ear mastoid. The size of the electrodes was 42 × 24 mm and the conductive area was φ19 mm (Figure 1). The stimulus parameters were set as follows: pulse width 90 μs for both PMES and sham, frequency 1.8 kHz for PMES and 10 Hz for sham, peak current 10 mA for PMES and 0.18 mA for sham. The patients were required to choose peak current during treatment as long as they could tolerate it.

To reduce the surface sensation from the current stimulation, we modulated the low-frequency signal (13–45 Hz) to the 1.8-kHz intermediate-frequency signal and set 1.0–1.2 V as the voltage variation range of the low-frequency signal. This variation of the modulated signal within this range causes a mild squeezing sensation. The intermediate-frequency signal was the exponential decay signal with a base of “a” (0 < a < 1). This signal was a non-polar exponential waveform composed of positive and negative pulse waves with equivalent charges. The negative exponential pulse may depolarize the nerve fibers, while the positive pulse may balance the charge, so the electrostatic charge accumulation was eliminated and the adverse electrochemical reaction was minimized. We decreased the base value “a” rather than the pulse width to cut down the energy of the single pulse, thus reducing the degree of the squeezing sensation. The surface sensation during true stimulation was close to that during sham stimulation, which was a periodic point-contact sense of touch.

The PMES and sham group received treatment daily for 45 minutes, and the treatment lasted 3 months.

**Randomization and double blinding**

Patients who met the inclusion criteria received 1 month of baseline observation before being formally enrolled in the study. The patients who still met the criteria (two or more migraine attacks per month) were randomized 1:1 to PMES or the sham group (Figure 2).

The treatment allocation was concealed until the trial was completed. Based on the block randomization principle, the PMES devices (including true and sham
device) were numbered from 1 to 80 in advance by a third party (manufacturer) that did not participate in the trial. The devices were then randomly divided into 20 block groups, and each block group included two PMES devices (A) and two sham devices (B). Each block group was numbered (1–6). The block groups were numbered from low to high using random numbers that were obtained from a random number table.
Each research center selected the first five block group numbers. Finally, the random sequence of the numbered devices was obtained according to the sequence of the block group numbers. According to the time sequence of patient enrollment, the patients in each block group were randomly assigned to each study group.

The PMES and sham stimulators had the same external appearances, user manuals and electrodes. They could not be distinguished by their external appearance without a detection device. We took the following measures to guarantee double-blinding: enrolled patients were not acquainted with each other, there was no physical contact or communication (such as sensory perception) between patients during visits, and all of the patients would be told when enrolled that it was not possible to accurately judge whether they were receiving true or sham stimulation only based on the surface sensation.

Data collection

The migraine dairies were filled out by the patients and mainly included the records of the use of the PMES device (number of treatments and duration of each treatment), and the occurrence and severity of each migraine attack. Migraine severity was assessed by the visual analogue scale (VAS). In addition, the presence of aura, nausea/vomiting, photophobia/phonophobia, and the use of anti-migraine drugs were recorded. A migraine day was defined as any day with migraine or probable migraine with or without aura, according to the diagnostic criteria of ICHD-II, except for duration if treated. Migraine attacks with an interval of less than 1 day were considered to belong to the same migraine attack. Migraine-associated disability was assessed by the Migraine Disability Assessment Score (MIDAS). Two investigators who did not participate in the patient recruitment were responsible for collecting the migraine diaries. Monthly follow-up appointments were performed over a 3-month treatment period.

The primary outcomes were change in migraine days from baseline to the third month of treatment, and the 50% response rate, which was defined as the percentage of patients with a ≥50% reduction of migraine days in the third month compared with the baseline.

The secondary outcomes were change in average migraine days of the 3-month treatment compared with the baseline, and change in migraine attack frequency, headache severity per migraine days, accompanying symptoms during migraine, acute anti-migraine drug use, and MIDAS from baseline to the third month.

All the patients were required to record any discomfort (e.g., local tingling during PMES treatment) and report any adverse reactions (e.g., skin allergy to the electrode gel).

Statistical analysis

This study was a randomized, double-blind, and sham-controlled trial. The effective rates of the control group (sham group) and the treatment group (PMES treatment) were preliminarily set as 15% and 55% effective rates, respectively, based on a literature review and the pre-test results. To examine the significant difference between these two groups, the bilateral significance level was established at 5%, and the power of the test was 90%. Considering a 20% loss to follow-up, the sample size of each group was estimated at approximately 34 cases.

All statistical analyses were completed using SPSS11.5 statistical software. Values for patients who dropped out were included according to the last value carried forward method. Continuous data were expressed as mean ± SD. Categorical data were described using frequency and percentage. The Mann–Whiney U test was used for comparison of primary and secondary outcome measures between the two groups. The chi-square test was utilized to analyze the patient compliance rate, and the sign test for changes between baseline and the third month of treatment/average of the 3 months of treatment within the sham and PMES groups. \( p < 0.05 \) was considered statistically significant.

Results

The trial was conducted from May 2013 to July 2015. We screened 92 migraine patients; 12 did not meet the study inclusion standards during the baseline follow-up period (Figure 2). The other 80 patients were randomly distributed into the PMES and the sham group (40 in each group); 39 (97.5%) in the PMES group and 37 (92.5%) in the sham group completed the trial. The demographic and baseline characteristics are shown in Table 1. The demographic characteristics of the patients in these two groups, including age, gender, disease duration, and attack type, did not have significant differences.

Primary outcomes

The outcomes measures are detailed in Table 2. The migraine days decreased by 43.8% in the PMES group and 22.7% in the sham groups during the first treatment month. However, from the second treatment month, the migraine days continued to decrease in the PMES group, but not in the sham group (Figure 3). Compared with the baseline, migraine days in the third month decreased significantly both in the PMES
group (−71.3%) and the sham group (−14.4%); however, the difference in migraine days reduction between the two groups was highly significant ($p < 0.001$).

The 50% response rate was significantly higher in the PMES group than in the sham group (82.5% vs. 17.5%, $p < 0.001$). In the PMES group, 60% patients had a ≥75% reduction of migraine days in the third month; in addition, 35% had no migraine attack in the third month. However, no patients in the sham group had a ≥75% reduction of migraine days.

**Secondary outcomes**

1. **Average migraine days of the 3-month treatment period**: compared with the baseline, average migraine days of the 3-month treatment period decreased both in PMES (−58.2%) and sham groups (−15.2%). The difference in average migraine days of the 3-month treatment period reduction between the two groups was significant ($p < 0.001$).

2. **Migraine attack frequency**: compared with the baseline, migraine attacks in the third month decreased both in PMES (−65.0%) and sham groups (−14.3%). The difference in migraine attack frequency reduction between the two groups was significant ($p < 0.001$).

3. **Migraine severity**: compared with the baseline, mean headache severity per migraine day in the third month decreased (−62.8%) in the PMES group, but not in the sham group (+0.5%). The difference in migraine severity reduction between the two groups was significant ($p < 0.001$).

4. **Accompanying symptoms**: compared with the baseline, the symptoms that accompanied the migraine in the third month decreased (−88.4%) in the PMES group, but not in the sham group (−1.8%). The difference in accompanying symptoms reduction between the two groups was significant ($p < 0.001$).

5. **Acute anti-migraine drug use**: compared with the baseline, the frequency of acute anti-migraine drug use in the third month decreased (−87.6%) in the PMES group, but not in the sham group (+20.1%). The difference in acute anti-migraine drug use reduction between the two groups was significant ($p < 0.001$).

6. **MIDAS**: compared with the baseline, the MIDAS in the PMES group decreased (−81.0%), but not in the sham group (+0.4%). The difference in MIDAS reduction between the two groups was significant ($p < 0.001$).

**Adverse reactions and compliance**

There were no adverse reactions reported either in the PMES group or in the sham group during the treatment period. The mean number of applications of the device over the 3 months was 82 (91.6%) in the PMES group and 76 (84.4%) in the sham group. The difference between the two groups was not significant ($p = 0.172$).

**Discussion**

All of the primary and secondary outcome measures of this randomized, sham-controlled study showed that daily treatment with PMES was effective in migraine prevention. The effect size appeared very large in our study (Figure 4). Compared with sham stimulation, PMES treatment produced greater reduction of migraine days in the third month. The PMES treatment reduced mean migraine days by 58.2% and migraine attacks by 65%; the 50% response rate was 82.5%. The therapeutic gain for the 50% response rate and reduction of migraine days with PMES treatment were 65% and 43%, respectively. Moreover, most patients with PMES treatment had a ≥75% reduction of migraine days in the third month and more than one
third of patients had no migraine attack in the third month. Based on the results of this study, the preventive effect in migraine with PMES treatment was excellent.

We noticed that, compared with the baseline, the reduction in migraine days in the third month, average migraine days of the 3-month treatment period, and migraine frequency in the third month were also significant in the sham group. The preventive effect of the sham stimulation in this study might be non-specific.

A recent clinical meta-analysis showed that placebo treatment played a role in migraine prevention, and some types of placebo treatment had even more dramatic clinical improvements, especially sham acupuncture and sham surgery (24). The placebo effects of sham stimulation in this study might involve some aspects, such as contextual factors, the participants’ interest, and expectation in use of PMES device, and more attention than usual would be paid to avoid migraine.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>PMES (n = 40)</th>
<th>Sham (n = 40)</th>
<th>Comparison of changes between the two groups, p</th>
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</thead>
<tbody>
<tr>
<td>Migraine days</td>
<td></td>
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<tr>
<td>The baseline   5.60 ± 2.29</td>
<td>7.85 ± 4.60</td>
<td>&lt;0.001</td>
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<tr>
<td>The third month 1.61 ± 1.91</td>
<td>6.73 ± 4.50</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>p</td>
<td></td>
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<tr>
<td>The percentage of reduction in number of migraine days in the third month compared with the baseline</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>&lt;50%</td>
<td>7 (17.5%)</td>
<td>33 (82.5%)</td>
<td></td>
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<tr>
<td>50%–74%</td>
<td>9 (22.5%)</td>
<td>7 (17.5%)</td>
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<tr>
<td>75%–99%</td>
<td>10 (25.0%)</td>
<td>0</td>
<td></td>
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<tr>
<td>100%</td>
<td>14 (35.0%)</td>
<td>0</td>
<td></td>
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<tr>
<td>≥50%</td>
<td>33 (82.5%)</td>
<td>7 (17.5%)</td>
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<tr>
<td>Average migraine days of the 3-month treatment period compared with the baseline</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The baseline   5.60 ± 2.29</td>
<td>7.85 ± 4.60</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Average of the 3-month treatment period</td>
<td>2.34 ± 1.79</td>
<td>6.66 ± 4.43</td>
<td>&lt;0.001</td>
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<tr>
<td>p</td>
<td></td>
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<tr>
<td>Migraine attack frequency</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>The baseline   5.00 ± 2.21</td>
<td>6.60 ± 4.60</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>The third month 1.75 ± 1.92</td>
<td>5.65 ± 4.28</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>p</td>
<td></td>
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<tr>
<td>Headache severity of migraine</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The baseline   7.40 ± 1.61</td>
<td>6.10 ± 1.74</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>The third month 2.75 ± 2.51</td>
<td>6.13 ± 1.45</td>
<td>0.625</td>
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<tr>
<td>p</td>
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<tr>
<td>Accompanying symptoms</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>The baseline   2.15 ± 1.49</td>
<td>1.70 ± 1.49</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>The third month 0.25 ± 0.63</td>
<td>1.68 ± 1.58</td>
<td>0.453</td>
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<tr>
<td>p</td>
<td></td>
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<tr>
<td>Monthly acute anti-migraine drug use</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The baseline   3.88 ± 2.86</td>
<td>3.23 ± 3.73</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>The third month 0.48 ± 1.22</td>
<td>3.88 ± 5.74</td>
<td>0.210</td>
<td></td>
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<tr>
<td>p</td>
<td></td>
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<tr>
<td>MIDAS</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>The baseline   12.10 ± 6.04</td>
<td>11.98 ± 16.36</td>
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<tr>
<td>The third month 2.30 ± 4.76</td>
<td>12.02 ± 16.77</td>
<td></td>
<td></td>
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<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>0.508</td>
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</tbody>
</table>

PMES: percutaneous mastoid electrical stimulator; MIDAS: Migraine Disability Assessment Score.
triggers (such as fatigue, emotions, and poor sleep) during the treatment period. From every outcome measures, the preventive effect of the PMES treatment was much better than sham treatment, although the latter had positive effect. Therefore, the preventive effect of PMES treatment in migraine mainly derived from the PMES treatment itself.

In this study, we took some measures to guarantee double-blinding, including avoidance of communication between patients and narrowing the differences of surface sensation between PMES and sham stimulation. However, it is impossible to achieve the exactly same surface sensation between PMES and sham stimulation, so patients who perceive that they are receiving placebo tend to lose their initial benefit. We did not survey subjects to verify if the blinding with the sham device was successful. Partial unblinding might occur in our trial. However, in our trial the

Figure 3. Change in migraine days per month compared with baseline in percutaneous mastoid electrical stimulator (PMES) group and sham group.

Figure 4. Percentage decrease at end of trial compared with baseline for the various outcome measures in percutaneous mastoid electrical stimulator (PMES) group and sham group: 1) average migraine days of the 3-month treatment period; 2) migraine attack frequency; 3) headache severity per migraine days; 4) accompanying symptoms; 5) monthly acute anti-migraine drug use; 6) Migraine Disability Assessment Score (MIDAS); 7) percentage of responders (50–74% reduction in number of migraine days/month); 8) percentage of responders (75–99% reduction in number of migraine days/month); 9) percentage of responders (100% reduction in number of migraine days/month).
compliance rate in the sham group did not decrease significantly compared with the PMES group; in addition, the 50% responder rate in the sham group was up to 17.5%, which was higher than that in other trials with neurostimulation devices (9,25). Therefore, unbinding might have no significant influence on the results in our trial.

The non-invasive percutaneous FNS device, called the cerebrovascular function therapy (CVFT) device in China, uses biomimetic currents to simulate FNS, and has been applied in clinics for many years in China. Its safety has been confirmed in clinical studies (18). PMES can be used alone or in combination with drug treatment based on its excellent safety and preventive effect in migraine in our trial. However, the best treatment mode including current intensity and duration is unclear. Whether extension of the time interval (e.g., once or twice a week) of PMES treatment may also have preventive effect remains to be determined. In addition, as the patients recruited in this study were not highly disabled, the preventive effect of PMES treatment in patients with more frequent migraine episodes and in patients with chronic migraine needs further study.

The exact mechanism of action of PMES is unclear. As FNS can inhibit development of PIDs (17,26), CSD suppression might be associated with migraine prevention by PMES. CSD play a critical role as an initiating factor in the development of migraine. It has been shown to cause activation of the sensitivity of the trigemino-vascular system to initiate a series of neural, vascular, and inflammatory events that result in migraine attack (27–30). The presence of silent CSD in migraine without aura supported by imaging studies suggests that migraine with and without aura may share the same pathogenic mechanisms (31,32). Therefore, PMES treatment may modify cortical excitability and alter the development of CSD through non-invasive FNS to achieve migraine prevention.

Other mechanisms may also be involved in migraine prevention with PMES. Similarly to VNS and ONS, PMES might inhibit activation of several cortical and subcortical structures involved in nociception, which belongs to the “pain matrix”, reduce neural activity in trigemino-cervical complex, or activate descending pain-control systems and restore equilibrium in antinociceptive pathways (33). The majority of electrophysiological studies have demonstrated that the cortical preactivation level and the habituation of sensory cortices to repeated stimulations are reduced in episodic migraine due to thalamocortical dysrhythmia (34). Moreover, high-frequency rTMS and anodal tDCS may correct this abnormal interictal information processing in migraine and may be useful in migraine prevention (8,34). Whether the PMES has a similar mechanism needs further study.

Similarly to STS, PMES treatment is also a neuro-modulation method through the delivery of electrical stimulation (35). However, they may have different action mechanisms due to different locations of the electric stimulation. Head-to-head comparative trials are needed to compare the preventive effect of PMES treatment in migraine with STS treatment.

**Article highlights**

- Migraine is a common, disabling, and costly disorder. Patients with moderate to severe headache need preventive treatment. PMES treatment is a non-invasive method. This is a multi-center, randomized, and double-blind controlled trial. The results showed that PMES treatment was effective in migraine prevention, and its tolerance and safety were excellent.

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**Declaration of conflicting interest**

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