A study of acupuncture in Asian patients: clinical aspects and effects on cortical excitability

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ABSTRACT

Objective To determine the effect of acupuncture on the phosphene threshold, by transcranial magnetic stimulation (TMS), and the clinical effect of acupuncture on headache frequency, duration and severity.

Methods Twenty-one patients (16 women; mean age 46 years; range 23–61 years, 17 Chinese, 2 Malays, 2 Indians) underwent 10 acupuncture sessions scheduled twice a week for 5 weeks. The lowest TMS intensity to elicit phosphene perception is defined as the phosphene threshold. TMS was performed before the first and last sessions, and at 2 months’ follow-up.

Results Acupuncture resulted in reduction of headache frequency, duration and severity over the course of treatment. However, this was not accompanied by a corresponding increase in the phosphene threshold over a similar time course. The baseline threshold before acupuncture treatment had no predictive value for outcome of treatment.

Conclusions Although acupuncture was effective in treating migraine, the use of occipital cortex excitability as an adjunctive parameter to evaluate treatment response was not suitable. The relief of migraine with acupuncture may be related to separate neural pathways independent of occipital or visual processes in the human brain.

Migraine is a significant universal health problem. The prevalence of migraine ranges between 9% and 12% world wide. Although treatment with drugs is still the standard in many areas, alternative treatments, including acupuncture, are becoming increasingly more accepted in recent years. Recent trials have shown the efficacy of acupuncture for the treatment of migraine headaches.1,2

Transcranial magnetic stimulation (TMS) of the visual cortex has been used extensively to study excitability in migraine.3 In this method, a change in magnetic flux via a coil is employed to depolarise the occipital cortex. Subjects experience a brief flash of light known as a ‘phosphene’. The lowest TMS intensity to elicit phosphene perception is defined as the phosphene threshold. Thus, perception of phosphenes elicited with TMS has been employed as measure of visual cortex excitability. A reduced threshold for phosphene perception with TMS thus implies increased cortical excitability, and vice versa. It has also been shown that the stimulation threshold to obtain phosphenes at the occipital cortex is changed in patients with migraine as compared with control subjects.4 The hypothesis of this study is that if acupuncture is effective for the treatment of migraines, this will result in increased or decreased cortical excitability as measured by TMS and a corresponding clinical response as evidenced by a decrease in migraine frequency, severity and attack duration.5

The phosphene threshold, and hence occipital cortex excitability changes in migraine, has been extensively researched. Some studies have pointed to increased excitability/reduced thresholds,6 while others have suggested reduced excitability/increased thresholds.7 More recent studies even suggested unstable/variable excitability in patients with migraine.8 Previously, we had used TMS to study a subset of patients with migraine who do not perceive phosphens. This study suggested that this subgroup of patients may have more severe headache and lower interictal visual cortex excitability.9

To our knowledge, there are no published studies using acupuncture in the management of migraine for a multiracial Asian population. There are also no studies examining serial changes in phosphene thresholds, in relation to changes in the severity of migraine as a result of treatment.

The objective of this study, thus, was to determine the effect of acupuncture on the phosphene threshold, an estimate of occipital cortex excitability as measured by TMS, and the clinical effect of acupuncture on headache frequency, duration and severity.

METHODS

The study was approved by the Singapore General Hospital Ethics Committee and all patients signed consent forms.

Patients with migraine were recruited into the study from the Singapore General Hospital Outpatient Headache Clinic. These were patients who were diagnosed as having migraine with or without aura using the International Headache Society (IHS) criteria. Institutional board review approval was obtained and subjects with contra-indications to TMS, including history of seizures, cranial surgery and pacemaker implants, were excluded.

None of our patients had chronic daily headache, defined by having more than 15 headaches over the preceding 4 weeks. We excluded all subjects with a history suggesting analgesic overuse. This was defined as usage of triptans >3 days a week, simple analgesics >4 days a week or narcotic analgesics >2 days a week.

They underwent 10 acupuncture sessions, which were scheduled twice a week for 5 weeks. TMS was performed before the first session (t1), last session (t2) and 2 months after the last acupuncture treatment (t3) to see if there were any longlasting changes in cortical excitability from acupuncture treatment.
Acupuncture

Acupuncture was performed by one of the collaborators (SLC) who has 26 years’ in acupuncture practice after 5 years of training, specialising in pain relief. All patients received needle acupuncture with the insertion, lifting and rotation method on the following 14 acupuncture points on the body: GV20, GB20, LI4, KI1, CV18, BL8, LR3, ST40. All the points were needled bilaterally except GV20 and CV18. Electrical stimulation was applied for GB20 and LI4 acupoints. Only one needle was inserted for each acupoint. Insertion was continued until de qi sensation was experienced, usually corresponding to a 1 cm depth. The acupuncturist and the patients were not blinded. During each session, needles (Hwatuo brand, Suzhou, China, diameter: 0.3 mm, length: 50 mm) were inserted with the aid of a tube, retained for 25 min after insertion and followed by withdrawal of needles. Each course consisted of two sessions a week for 10 weeks.

Transcranial magnetic stimulation

Visual cortex TMS was performed with a Dantec S100 (Dantec, Skovlunde, Denmark) round coil with an outer diameter of 11 cm, powered by a Dantec Mag 2 stimulator. This outfit was capable of delivering a maximal magnetic field of 2.2 T. All patients were seated in a darkened room wearing soft, blackened eye pads and instructed to keep their eyes closed. A 5 min period was allowed for dark adaptation. For the visual cortex surface markings, the magnetic coil was centred in a vertical position on the nasion–inion line, 7 cm rostral to the inion (central position). Beginning from stimulator output intensity at 20%, the subject was tested at increments of 10% in a randomised fashion, until visual phenomena were reported, or until the 100% output level was reached. The intensity was then finely tuned to determine the most representative phosphene threshold. This was achieved by adjusting the stimulating intensity upwards and downwards, so that the mean level of the highest

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Figure 1  Graphical representation of threshold (%) of headaches over the three acupuncture sessions. Asterisk denotes statistical significance. t1, first acupuncture session; t2, last acupuncture session; t3, 2 weeks after last acupuncture session.

Figure 2  Graphical representation of frequency (number of attacks) of headaches over the three acupuncture sessions. Asterisk denotes statistical significance. t1, first acupuncture session; t2, last acupuncture session; t3, 2 weeks after last acupuncture session.

Figure 3  Graphical representation of duration (hours) of headaches over the three acupuncture sessions. Asterisk denotes statistical significance. t1, first acupuncture session; t2, last acupuncture session; t3, 2 weeks after last acupuncture session.

Figure 4  Graphical representation of pain score (visual analogue scale) of headaches over the three acupuncture sessions. Asterisk denotes statistical significance. t1, first acupuncture session; t2, last acupuncture session; t3, 2 weeks after last acupuncture session.
and lowest intensity for phosphenes production was obtained. If no visual phenomenon was reported at 100% intensity, the procedure was repeated with the coil moved by 1 cm steps in a 4 cm by 4 cm grid around the central position. This was also repeated with the coil rotated 180°. The frequency of TMS was no more than 4 pulses/min. Our method has previously been shown to be unable to induce eye movements, retinal or optic nerve activation, which may be responsible for non-cortically induced phosphenes.

If patients were unable to perceive phosphenes at the 100% intensity after undergoing this protocol, the procedure was repeated 3 days later before a record of absent phosphenes perception was recorded.

We ensured that testing was truly during the interictum. All patients were studied at least 3 days after the last migraine attack. None of the patients included had a migraine attack within 3 days after testing. This was achieved with a telephone check before the patient arrived for TMS. None of the patients studied were taking drugs that would affect cortical excitability, including antidepressants, sedatives, anticonvulsants, muscle relaxants, anticholinergics, calcium channel blockers or hormone replacement therapy. None had previously taken medication for migraine prophylaxis.

Clinical parameters
Apart from the phosphene threshold, three separate clinical parameters were studied. All recruited patients kept a headache diary. Headache frequency was defined as the number of attacks in the 4 weeks preceding the TMS study. Duration was calculated as the average, in hours, of each attack recorded in the 4 weeks preceding the TMS study. Duration was calculated as the average, in hours, of each attack recorded in the similar period of time. Each attack was rated on a scale from 0 (no pain) to 10 (most severe pain). The pain score was the average of the pain score of the recorded attacks over the 4 weeks. The person performing TMS was blinded to all clinical data. Patients kept a headache diary for 4 weeks before initiation of acupuncture and then throughout the treatment and up to 2 months after completing the last acupuncture session. The purpose of the diary was to follow changes in migraine frequency before, during and after acupuncture treatment. In addition, patients gave absolute outcome ratings of good, bad or unchanged at 2 months after the last acupuncture session.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>t1</th>
<th>t2</th>
<th>t3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>7.1 (4.8)</td>
<td>8.0 (6.9)</td>
<td>4.7 (5.1)*</td>
</tr>
<tr>
<td>Duration</td>
<td>8.1 (7.6)</td>
<td>7.3 (5.9)*</td>
<td>4.3 (4.2)**</td>
</tr>
<tr>
<td>Pain score</td>
<td>5.2 (2.1)</td>
<td>4.7 (1.6)</td>
<td>3.9 (2.4)*</td>
</tr>
<tr>
<td>Threshold</td>
<td>83.5 (14.4)</td>
<td>89.9 (12.4)*</td>
<td>89.8 (13.2)**</td>
</tr>
</tbody>
</table>

Each value denotes mean (SD). Frequency: number of attacks; duration: hours; pain score: visual analogue scale; threshold: %.

Frequency: significant difference between t2 and t3 (F (1, 20)=4.54, p=0.04)*, but not between t1 and t3 (F (1, 20)=3.64, p=0.07) or t1 and t2 (F (1, 20)=0.4, p=0.54).

Duration: significant differences between t1 and t3 (F (1, 20)=8.48, p=0.009)** and between t2 and t3 (F (1, 20)=4.64, p=0.04)**.

Pain score: significant difference between t1 and t3 (F (1, 20)=7, p=0.02)*.

Threshold: significant difference between t1 and t2 (F (1, 20)=41.3, p<0.001)* and t1 and t3 (F (1, 20)=25.5, p<0.001)**, but not between t2 and t3 (F (1, 20)=0.004, p=0.95).

The above results were analysed statistically using SPSS for Windows, version 12.1. Statistical significance was achieved when the p value was <0.05.

RESULTS
We included 21 patients (16 women; mean age 46 years; range 23–61 years, 17 Chinese, two Malays, two Indians). Of these, 17 had migraine without aura (IHS code 1.1) and four had migraine with aura (IHS code 1.2).

A one-way repeated measure analysis of variance was performed to compare the differences in threshold, frequency, duration and pain score at the three time points of the study. This showed significant increase in threshold values over the course of the study. There was also some reduction in headache frequency observed between t2 and t3. In addition, there was significant reduction in the pain score and headache duration over the whole study, though not over the treatment period. There was also a significant increase in threshold over the course of the entire study.

Using the Kruskal–Wallis test, we examined if initial (baseline) threshold would predict outcomes (improved, worse, no change). However, thresholds were not found to be significantly different for outcomes measured as frequency (p=0.26), duration (p=0.41) or pain score (p=0.68).

There were no significant correlation (Spearman’s correlation coefficient r) of baseline or subsequent threshold determinations with headache frequency (r = −0.19, p=0.14), duration (r=0.05, p=0.58) and pain score (r=0.2, p=0.12).

Figures 1–4 depicts these results graphically.
Table 1 provides raw data of threshold and pain parameters. Figure 5 shows the relationship between headache frequency and threshold for all three time points graphically.

**DISCUSSION**

In this study, we have shown that acupuncture has resulted in a reduction of headache as measured by frequency, duration and pain score over the course of treatment. However, this was not significantly correlated with a corresponding increase in threshold over a similar time course. Furthermore, the baseline threshold before acupuncture treatment had no predictive value for outcome of treatment. However, it should be noted that the relatively small sample size in this study may have limited the power of our statistical analysis (eg, Kruskal–Wallis tests). It is interesting to note that although no strict correlation was found between headache parameters and thresholds, it was observed that thresholds showed a trend towards an increase (figure 1) from baseline (t1). This suggests that relief of headache and increase in thresholds effected by acupuncture may involve independent mechanisms, both modulated by the acupuncture process.

The acupoints in our study were selected independently by the acupuncturist based on the theory of acupuncture and possible effects on pain alleviation. Here, we have shown that this treatment was effective.

What are the possible pathophysiological explanations for our findings? Early functional MRI studies had suggested that acupoint stimulation could result in brain activation, although point specific activation was not conclusively demonstrated.10 Other studies, however, have correlated occipital cortex activation with points BL60, GB37,11 BL6712 and LI4 and 11. 13 None of them were employed in this study. Previous studies employing acupoint LI4 used in this study had, in fact, resulted in motor cortex excitability changes and somatosensory cortex activation.14 15 Although not fully understood, the pain-relieving effects of acupuncture may be related to changes in the prefrontal–paralimbic–limbic pathways modulating mood affective components of nociception.15 In contrast, none of the acupoints used in our study corresponded to these previously studied acupoints which activate the occipital areas. Hence, the lack of correlation of occipital cortex excitability with clinical improvement from acupuncture may be due to these reasons. To this end, the mechanisms of migraine development have not been conclusively agreed upon, and involve a complex relationship involving vascular, neural and biochemical factors. Until these can be better understood, migraine prophylaxis remains largely empirical and focused on symptomatology, rather than addressing a specific pathway. Here, acupuncture may have a useful role.

In conclusion, we have shown that although acupuncture was effective in treating migraine, the use of occipital cortex excitability as an adjunctive parameter to evaluate treatment response was not suitable. The relief of migraine with acupuncture may be related to separate neural pathways independent of occipital or visual processes in the human brain. Further studies employing longer duration of acupoint needling and a greater number of acupuncture sessions over a prolonged period of time would be justified to explore further more protracted clinical responses of this treatment modality.

**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the Singapore General Hospital.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**REFERENCES**
