A sham-controlled trial of acupuncture as an adjunct in migraine prophylaxis

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ABSTRACT

Background Migraine is one of the most common types of headache, with significant socioeconomic effects. Prophylactic drugs are used to prevent migraine headaches but are unpromising.

Objective To assess the effects of adding acupuncture to conventional migraine prophylaxis.

Methods One hundred patients with migraine (41 male, 59 female), in whom prophylactic drugs had not produced a fall of at least 50% in the number of attacks, entered the study. The patients were randomised into two groups, sham and true acupuncture. The patients in both groups continued their prophylactic treatment and received 12 sessions of either true or sham acupuncture. Each session was 30 min and was repeated three times a week. The number of headaches in the two groups was compared at baseline, and at the end of four successive months.

Results There was no significant difference in the frequency of attacks between the two groups before intervention. After 1 month, the frequency of attacks each month decreased from 5.1 (0.8) to 3.4 (1.2) in the true acupuncture group, and from 5.0 (0.8) to 4.4 (1.1) in the sham acupuncture group (a significant difference, p<0.001). The frequency continued to decrease in month 2 but increased in months 3 and 4; however, it was still significantly lower than baseline, and the difference remained significant after month 4.

Conclusions Acupuncture is applicable as an adjunct to prophylactic drugs in migraineurs in whom the number of attacks does not fall with prophylactic medication.

INTRODUCTION

Migraine is a common type of headache which is characterised by recurrent attacks lasting between 8 and 72 h. The attacks are severe and interfere with normal daily activities. In America it is estimated that treatment and lost working days because of migraine cost 13 billion US dollars each year.1

Migraine treatment may be either prophylactic (preventive) or abortive (rescue). Treatment of attacks includes use of common oral analgesics (aspirin, acetaminophen), oral, nasal or subcutaneous triptans and intravenous analgesics (dihydropregotamine, sumatriptan). But ideally, attacks should be prevented. Migraine is a complex condition in which the triggers differ between individuals. Preventive methods should target the cascade leading to the attack, and include drug treatment and a change of lifestyle, meditation or exercise.

Indications for prophylactic treatment for migraine include the number and duration of attacks that interfere with normal daily tasks; the presence of severe and longlasting neurological signs with attacks; no response to symptomatic treatment of attacks; and occurrence of more than one attack a week or more than four attacks in a month. Several pharmacological agents are used for migraine prophylaxis, of which the following three groups are the most effective and have the fewest side effects: anticonvulsants such as sodium valproate, cyclic antidepressants such as amitriptyline and β blockers such as propranolol.2

Several clinical trials have compared the effect of acupuncture with anti-migraine drugs both for prophylaxis and treatment of migraine attacks. Most have shown that acupuncture is more effective than, or at least as effective as, conventional anti-migraine drugs.1–5

Sham-controlled trials of acupuncture for migraine prophylaxis have shown
varied results. One study assessed the efficacy of acupuncture at migraine-specific acupuncture points in comparison with other acupuncture points and sham acupuncture, and concluded that acupuncture appeared to have a clinically minor effect on migraine prophylaxis compared with sham acupuncture.6 Another sham-controlled study with 6 months’ follow-up after treatment reported that the real acupuncture group showed a significantly greater number of responders with at least 50% reduction in migraine attack frequency.7 In contrast, another study showed that acupuncture prophylaxis of migraine is no better than sham acupuncture for decreasing the frequency of headaches.8

A Cochrane review included 22 trials of acupuncture for migraine, aiming to investigate whether acupuncture is more effective than no prophylactic treatment; more effective than sham acupuncture; and as effective as other interventions in reducing the frequency of headaches in patients with migraine. It concluded that acupuncture provides additional benefit in the treatment of acute migraine attacks only or in routine care. There was no evidence for an effect of ‘true’ acupuncture over sham interventions, though the evidence is difficult to interpret. The authors suggested that acupuncture is possibly more effective than prophylactic drug treatment, and has fewer adverse effects.9

In view of the uncertainty and controversy about the efficacy of acupuncture for migraine prophylaxis, we decided to compare the effect of acupuncture and sham acupuncture.

METHODS
This clinical trial included 100 patients with migraine without aura who were referred to Qaem Hospital neurology clinic and in whom the number of attacks did not drop by 50% after receiving prophylactic drugs for 3 months.

The inclusion criteria were a diagnosis of migraine, more than three migraine attacks in a month, inadequate response to 3 months’ conventional prophylaxis treatment and patient consent. The exclusion criteria were absence of a diagnosis of migraine, lack of patient consent, migraine headaches which were responsive to medication and patients who had received acupuncture treatment in the past 6 months. Patients who did not complete their study treatment sessions were withdrawn and replaced by new recruits.

To calculate the sample size, we applied the formula used in a previous clinical trial by the Italian Center for Non Conventional Medicines.3 We thus estimated that 47 analysable patients would be needed in each group, and rounded the sample size up to 50.

After attending the neurologist, patients were randomly allocated into A or B parallel groups according to randomised codes in sealed envelopes. Both the neurologist and patients were blind to randomisation, and only the acupuncturist was aware of the treatment type. Patients were referred to the acupuncturist in Imam Reza Hospital Chinese Medicine and Acupuncture clinic. All patients in both groups continued their prophylactic treatment and, additionally, received 12 sessions of either true or sham acupuncture. Patients in the true acupuncture group received acupuncture according to their involved meridians (Shaoyang, Yangming, Taiyang or Jueyin) and their Chinese medicine syndrome differentiation, thus adding individualised acupuncture to the semstandarised protocol based on meridian diagnosis, while patients in the sham acupuncture group were needled superficially, not in real acupuncture points. The traditional Chinese medicine diagnosis was made by the acupuncturist in the same way for both groups. Each treatment session was 30 min and was repeated three times a week. Manual acupuncture was used without any electrical stimulation, moxa, cupping or any other intervention. Needles on the extremities were stimulated by hand until de qi was obtained. Two sizes of Hanyi disposable needles were used: 0.25 mm diameter ×40 mm length and 0.18 mm diameter ×25 mm length.

The primary outcome was the number of headache attacks per month, comparing the groups at baseline, and at the end of the first month of treatment. Follow-up results were obtained at the end of the second, third and fourth months from baseline. During the first month of treatment, patients, who attended three times a week, were asked whether they had a headache. At the end of the first month of acupuncture or sham treatment, they were asked to keep a diary of their headaches for the following 3 months and were asked by telephone about the monthly frequency of headaches at the end of months 2, 3 and 4.

The two study groups received the same information, usual care treatments and dietary instructions. In view of the effects of diet on migraine headaches, patients were advised to avoid cheese, hot dogs, salami, chocolate and other types of highly seasoned preserved food.

The study started in March 2011 and ended in January 2012. All patients signed an informed consent for their participation in the study. The study was conducted according to the declaration of Helsinki.

Data were analysed with the Statistical Package for Social Sciences (SPSS V11.5) by an independent university statistician who was blind to the study groups. Data were tested with Kolmogorov–Smirnov test and analysed with \( \chi^2 \) test, two-tailed t test or non-parametric tests. A Bonferroni correction was made for the response variable and \( p<0.01 \) was considered to be significant.

The research proposal was approved by the Research Council of Mashhad University of Medical Sciences.
and its ethics committee at 26 February 2011 (research code: 89590). The full trial protocol can be seen in the Deputy for Research of Mashhad University of Medical Sciences, also in Iranian Registry of Clinical Trials, Irtc ID: IRCT201108097265N1.

RESULTS
Some patients did not complete the treatment and were replaced; we do not have a record of the numbers or reasons for dropout. All 100 patients analysed completed the course of 12 acupuncture or sham treatments, and all provided data at all follow-up points.

The patients were aged 16–65 (mean 36.5) years, and 50 were included in each group. The baseline characteristics of two groups are given in table 1, and shows that the groups were well matched.

As shown in table 2, the number of reported headache attacks was significantly lower in the group receiving true acupuncture than in the sham acupuncture group after 1 month treatment and during months 2, 3 and 4.

Few complications were reported in either group apart from bruising, peri orbital ecchymosis in one patient, and pain on needle insertion.

DISCUSSION
This clinical trial showed a significant reduction in the number of migraine headache attacks after adding true acupuncture to conventional prophylactic drugs compared with addition of sham acupuncture. At the end of the first month, compared with the baseline, there was a significant reduction in the number of attacks in both groups. Similar results were seen during the second month. At the end of the third month, there was an increase in the number of attacks in both groups compared with the second month, which indicates decreased effect of acupuncture over time. At the end of the fourth month, there was still a significant difference from baseline in the number of attacks in both groups but this difference was minimal.

In considering the control group receiving sham acupuncture, we note that the therapeutic effects of acupuncture are not simply the result of needle insertion.

According to the Society of Acupuncture Research board of directors, acupuncture treatment has the following components: (1) needling components (ie, needle size, retention time, depth, stimulation, location, frequency); (2) specific (acupuncture theory-related) non-needling components that are traditionally considered to have therapeutic value—for example, in Chinese medicine the physical components such as palpation; and (3) generic, non-specific, non-needling components that are not unique to acupuncture, such as belief and expectations of the practitioner and patient, therapeutic setting, time and attention. In studies designed and conducted for the effects of acupuncture on chronic pain, when acupuncture is compared with conventional treatment (such as analgesics or physiotherapy), acupuncture is often found to be significantly more effective. By contrast, in studies comparing acupuncture with sham acupuncture the difference is often less significant. To improve the validity of investigating the effect of the needles, we used sham acupuncture as control in this study.

We combined two protocols for point selection—namely, a semistandardised protocol of acupuncture based on the headache site (involved meridian), and an individualised protocol based on Chinese medicine syndrome diagnosis of each migraineur. This means that besides the fixed points, we used some acupuncture points according to each patient’s identified pattern. Individualised classic acupuncture is traditionally valued and believed to influence the success of treatment. Syndrome differentiation for each patient in Chinese medicine is claimed to be the strength of this integrative type of medicine, rooted in the idea that every human body is different from others, and needs its own treatment.

Our study had a number of limitations. First, it was challenging to find patients meeting our inclusion criteria, and some did not complete the treatment course. In Iran, acupuncture is still a little bit of mystery among the general population and not accepted by all healthcare professionals. Second, the follow-up of patients after treatment was difficult because some were not local. Finally, the number of

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>True acupuncture (n=50)</th>
<th>Sham acupuncture (n=50)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>35.8 (10.9)</td>
<td>37.2 (11.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>29 (58)</td>
<td>30 (60)</td>
<td></td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>21 (42)</td>
<td>20 (40)</td>
<td></td>
</tr>
<tr>
<td>Number of headache attacks per month, mean (SD)</td>
<td>5.1 (0.8)</td>
<td>5.0 (0.8)</td>
<td>0.64</td>
</tr>
</tbody>
</table>
patients in the study was restricted by cost, as was assessment of the severity and duration of each migraine attack.

A relatively similar study was performed in 2012 in China by Li and colleagues.6 As in our study, they selected acupuncture points according to the requirements of the patient rather than using similar acupuncture points for all patients. They randomised the patients into four groups; Shaoyang-specific acupuncture, Shaoyang-non-specific acupuncture, Yangming-specific acupuncture or sham acupuncture, and found that the true acupuncture group had fewer attacks than the control group, although the difference was not significant.6 The sample size was greater than in our study with a shorter follow-up and more frequent treatment sessions. Our results did not confirm this study, since we found a significant difference between true and sham acupuncture even at the fourth month of follow-up. The better responses in our study might be due to the individualised classic acupuncture we performed. Although Li et al gave acupuncture according to the involved meridian (Shaoyang or Yangming), they did not differentiate each patient’s Chinese medicine syndrome. Moreover, the frequency of treatment in their study was more intensive than the traditional acupuncture method, which comprises three sessions a week. Additionally, they used electrostimulation, which in our experience provokes headache in some migraineurs. The intense stimulation employed in the study by Li might have provoked more symptoms in the true acupuncture group.

Our study is also in contrast with the study by Diener in 2013, which found that acupuncture prophylaxis of migraine is no better than sham acupuncture for decreasing the frequency of headaches.8 However, it is consistent with a randomised sham controlled study from Spain with 6 months’ follow-up after treatment, with a smaller sample size but longer treatment protocol (16 acupuncture sessions vs 12 sessions in our study) and longer follow-up than our study. The significant differences between real and sham groups disappeared in the third (last) treatment month in that study while it remained significantly different in our study until month four, although we also detected a decrease in the differences over time.7

The underlying mechanism of acupuncture for migraine require further investigation. One study evaluated the effect of acupuncture on cerebrovascular response in migraineurs by transcranial Doppler ultrasound, and showed that prophylactic treatment of migraine by standardised acupuncture might positively influence the dysfunction of the cerebrovascular response to autonomic stimuli, but not the cerebral vasotonus during rest.12 Conventional prophylactic drugs such as amitriptyline may cause dry mouth, drowsiness and orthostatic hypotension. Considering the side effects of drugs reported by most patients even with minimal therapeutic dosage and considering the minimal complications or side effects of acupuncture, acupuncture is recommended as an adjunct to conventional prophylactic drugs.

We suggest that future studies using the same method but with a greater number of patients might shed light on the effects of acupuncture in migraineurs, especially those who do not respond to conventional treatments. Such studies should consider other parameters such as severity and duration of attacks, not just the number of attacks.

CONCLUSION

We conclude that there was a reduction in the number of attacks by both true and sham acupuncture, but this reduction was significantly greater in the true acupuncture group.

The efficacy of acupuncture treatment gradually decreased over time so that the difference between the numbers of attacks was minimal at the end of the fourth month. In view of this decrease we suggest that research should investigate the effect of tapering treatment followed by booster treatment sessions with 1–2 month intervals.

Summary points

- Patients with migraine unresponsive to medication were recruited.
- Acupuncture was superior to sham acupuncture.
- The clinically useful effect declined after 2 months.

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