Efficacy of acupuncture for migraine prophylaxis: A single-blinded, double-dummy, randomized controlled trial

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Keywords:
Migraine
Acupuncture
Prophylaxis treatment
Flunarizine

ABSTRACT

Insufficient clinical trial data were available to prove the efficacy of acupuncture for migraine prophylaxis. A multicenter, double-dummy, single-blinded, randomized controlled clinical trial was conducted at the outpatient departments of acupuncture at 5 hospitals in China to evaluate the effectiveness of acupuncture. A total of 140 patients with migraine without aura were recruited and assigned randomly to 2 different groups: the acupuncture group treated with verum acupuncture plus placebo and the control group treated with sham acupuncture plus flunarizine. Treated by acupuncture 3 times per week and drugs every night, patients from both groups were evaluated at week 0 (baseline), week 4, and week 16. The primary outcome was measured by the proportion of responders (defined as the proportion of patients with a reduction of migraine days by at least 50%). The secondary outcome measures included the number of migraine days, visual analogue scale (VAS, 0 to 10 cm) for pain, as well as the physical and mental component summary scores of the 36-item short-form health survey (SF-36). The patients in the acupuncture group had better responder rates and fewer migraine days compared with the control group (P < .05), whereas there were no significant differences between the 2 groups in VAS scores and SF-36 physical and mental component summary scores (P > .05). The results suggested that acupuncture was more effective than flunarizine in decreasing days of migraine attacks, whereas no significantly differences were found between acupuncture and flunarizine in reduction of pain intensity and improvement of the quality of life.

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1. Introduction

Migraine is a common primary headache disorder in which typically patients suffer a pulsating quality, moderate/severe pain in a unilateral location. Some typical symptoms are photophobia, phonophobia, nausea, and vomiting [19]. Affecting approximately 15% of the European population [27] and 8% to 13% of people in Asia [1,7,23,32]. Patients with migraine usually require medical management and treatment [12,22,25]. Based on the guidelines provided by the European Federation of Neurological Societies (EFNS), the fundamental strategy for migraine therapy includes acute treatment during attacks and prophylactic treatment after relief [10]. Despite some improvement in some patients undergoing this migraine therapy, regular use of analgesics or specific antimigraine treatments could cause medication overuse headache (MOH) [24,26] and an increase in headache frequency [13]. A high dropout rate in most clinical trials for this indication suggests that the drugs were not well accepted by patients [18].

As a major component of traditional Chinese medicine (TCM), acupuncture has been used to treat headache in China for thousands of years. During the past few decades, acupuncture has also been used widely as a treatment for migraine in western countries as well [21,30]. Because of the growing use of acupuncture, the US Headache Consortium has suggested that acupuncture might play an important role in managing migraine without any side effects.
Clinical studies have shown that acupuncture is effective in treating migraine, especially for the prevention of migraine. A recent systematic review reveals that acupuncture for migraine prophylaxis is similar to or probably more effective than preventive medication. However, reviews questioned the methodology design of the acupuncture clinical trials performed in China, such as inappropriate control group setting, inadequate outcome measurements, unclear classification between acute and preventive treatment, and the lack of detailed randomization and blinding information. To overcome these limitations, the present study was rigorously designed to conduct a randomized controlled trial on acupuncture for migraine prophylaxis in Chinese patients.

Moreover, studies have shown that more withdrawal was found among the patients from the drug control group, as patients tend to have higher expectations with acupuncture treatment. Chinese patients who seek acupuncture treatment usually have a better understanding and higher expectations of the acupuncture technique as well. The study by Linde et al. showed that a higher expectation was associated with better outcomes. On the other hand, Bausell et al. argued that the results from trials that have different forms of interventions between experimental groups and control groups (such as acupuncture vs medicine) cannot be used to compare and evaluate the efficacy of acupuncture. Therefore, we designed the present trial as a patient-blinding, double-dummy, randomized parallel controlled trial to evaluate the efficacy and safety of acupuncture with flunarizine.

2. Methods

2.1. Participants

One hundred and forty patients with migraine without aura were recruited between June 2007 and February 2009 from outpatient acupuncture departments in the following 5 hospitals: Beijing Traditional Chinese Medical Hospital affiliated with Capital Medical University, the Third Hospital of Peking University, Beijing Tiantan Hospital affiliated with Capital Medical University, Huguosi Hospital affiliated with the Beijing University of Chinese Medicine, and Dongzhimen Hospital affiliated with the Beijing University of Chinese Medicine. In the 2 general hospitals, patients were recruited from outpatient units of the Acupuncture Department, Neurology Department, and Pain Department; in the 3 TCM hospitals, patients were recruited from the Outpatient Unit of the Acupuncture Department. During the trial, advertisements of this clinical trial were placed in these 5 hospitals. Patients were informed that they would be randomly assigned to the experienced acupuncture formula group plus placebo drugs group and the new acupuncture formula group with equal chance.

The main inclusion criteria were: diagnosed as migraine without aura according to the diagnostic criteria specified by the International Classification of Headache Disorders; more than 2 migraine attacks within 4 weeks; age between 18 and 65 years old; history of migraine at least 1 year before study entry; no prophylactic treatment of migraine with acupuncture or drugs in the past 3 months; and written informed consent provided. The main exclusion criteria were: tension-type headache, cluster headache; history of migraine at least 1 year before study entry; no migraine attacks within 4 weeks during the baseline period. After the initial assessment and screening, patients who met the inclusion criteria were randomly assigned into the acupuncture group or the control group in a 1:1 ratio.

This study was designed and carried out cooperatively by a group of experienced acupuncture experts, acupuncture practitioners, neurologists, methodologist, and statisticians. Details of the methodological designs can be found in Zhang et al.

2.3. Researchers

All physicians and assessors were required to receive special training prior to the trial to guarantee consistent practices among the 5 investigation sites. The training program also included training on standard operation procedures, diagnoses and differential diagnoses of migraine without aura, standard inclusion and exclusion criteria, the use of randomization opaque sealed envelopes, the completion of case report forms, and locations of the acupoints and acupuncture manipulation techniques used throughout the study. Verum and sham acupuncture were both performed by acupuncturists with at least 20 years of clinical experience. Regular discussions with experts in the treatment of migraine were made to confirm the diagnosis. The study was regularly monitored by

Fig. 1. Trial flow.
clinical monitors to ensure the consistency of practice among all hospitals.

2.4. Sample size

According to previous studies and our pilot study, it was anticipated that the proportion of responders [9] (defined as the proportion of patients with a reduction number of migraine days by at least 50%) would be 65% [5,36] in the control group and 90% [31] in the acupuncture group. Calculated by EpiCalc 2000 version 1.02, 56 patients were required for each group based on 0.9 power to detect a significant difference ($\alpha = 0.05$, two-sided). Seventy patients per group were recruited to compensate for a dropout rate of 20%.

2.5. Randomization

The central randomization was performed by the Research Center of Clinical Epidemiology affiliated with Peking University. Randomization numbers with a block of 4 were sealed in a predetermined computer-made randomization opaque envelope. The patients’ screening sequence numbers were printed outside the envelope, whereas the group names were printed inside. All envelopes were numbered consecutively and connected into a strain. Researchers who selected the eligible patients after baseline screening separated the envelopes from the strain and opened them according to the patients’ screening sequence numbers, and then assigned the patients into either the acupuncture group or the control group.

2.6. Interventions

2.6.1. Acupuncture group

In the acupuncture group, verum acupuncture treatment consisted of three 30-minute sessions per week, administered over 4 weeks, and placebo medication was taken once per night (10 mg in the first 2 weeks and 5 mg in the next 2 weeks).

The acupoints, including both obligatory and additional points, were selected based on the consensus of clinical experiences of acupuncture experts. The obligatory points included DU20 (Baihui), DU24 (Shenting), GB13 (Benshen), GB8 (Shuaigu), and GB20 (Fengchi). Additional points were chosen individually depending on different syndromes: SJ5 (Waiguan) and GB34 (Yanglingquan) for Shaoyang headache (TE-GB); LI 4 (Hegu) and ST 44 (Neiting) for Yangming headache (LI-ST); BL 60 (Kunlun) and SI 3 (Houxi) for Taiyang headache (SI-BL); LR3 (Taichong) and GB40 (Qixu) for Jueyun headache (PC-LR); PC6 (Neiguan) for nausea and vomiting, and LR3 (Taichong) for dysphoria and susceptibility to rage.

Acupoints of DU20 (Baihui), DU24 (Shenting), GB13 (Benshen), and GB8 (Shuaigu) were punctured horizontally. The needle was inserted obliquely under the galea aponeurotica and then turned horizontally with twirling. The other acupoints were punctured perpendicularly with lifting, thrusting, and twirling for obtaining DeQi. The sensation of DeQi was defined as numbness, distension, soreness, and heaviness around the point felt by patients.

2.6.2. Control group

The control group was treated with flunarizine, once per night (10 mg in the first 2 weeks and 5 mg in the next 2 weeks) and three 30-minute sessions of sham acupuncture treatment per week for 4 weeks.

The sham points were chosen by the following 4 rules: (1) Acupoints that were defined as unrelated to headache based on a vast amount of TCM reference books. (2) In order to avoid possible therapeutic effects from acupuncture, 30 acupoints in the vicinity of elbow and knee joints were selected while the acupoints in the head, hands, feet, and trunk were excluded. The actual sham points were located 3 mm apart from these selected acupoints. (3) The 30 sham points in the vicinity of elbow and knee joints were randomly assigned to 5 subgroups: B, C, D, E, and F, and were recorded in predetermined computer-made randomization sealed envelopes. Each subgroup has 2 points on the arms and 3 points on the legs. The patients in the control group were assigned into 1 of these 5 subgroups. (4) The number of sham points in the control group was identical to that in the acupuncture group. All points were punctured perpendicularly with lifting, thrusting, and twirling to obtain DeQi. The details of the sham points in the control group were the same as in Zhang et al. (2009) [38]. For this study, both the flunarizine (production No. 070319716) and the placebo medication (production No. 07052934) were produced by Xi’an Janssen Pharmaceutical LTD, Xian, China, 5 mg per capsule.

2.7. Blinding

Blinding was implemented by means of double-dummy with verum acupuncture plus placebo medication in the acupuncture group and flunarizine plus sham acupuncture in the control group. The follow-up assessors and statisticians, who were uninvolved in clinical management, were blinded throughout the study. Due to the procedure of the acupuncture technique, acupuncture practitioners in this trial were unable to be blinded.

To achieve a fully blinded trial, several common approaches of acupuncture were performed for patients from both groups: bilateral points: usage of disposable, sterile steel needles (1.5-inch filiform needle, 0.32 × 40 mm); 10 to 12 needles used each time; sterilized with 75% alcohol; needles were inserted into skin for 10 to 15 mm and retained for 30 minutes; no moxibustion or electrical stimulation; DeQi obtained by 5 to 10 times of lifting, thrusting, and twirling the needles; 12 sessions of verum/sham acupuncture over 4 weeks (3 sessions per week). Additionally, the appearance of placebo medication was exactly the same as that of flunarizine.

2.8. Outcome measures

The headache diary captures the duration (hours), location (the forehead, top, temporal, and back of the head), intensity (mild, moderate, and severe), types of pain, accompanying symptoms (nausea, vomiting, photophobia, and phonophobia), triggers and medications for each migraine attack, any additional special feelings between attacks, and the dates of receiving acupuncture treatments. Patients were asked to record headache diaries from baseline (4 weeks before the beginning of treatment) to the end of the follow-up period as well as distinguish recurrence from new migraine attacks according to the International Headache Society [29]. A migraine attack that was interrupted either by sleep or treatment but relapsed within 48 hours was required to be documented as a single attack.

The outcome measures reported here are different from the protocol published in the past. Many primary outcome measures were selected in our original protocol, which might fail to clearly interpret the results because differences may be found between groups in some of the primary outcome measures, but others may not. To eliminate any influence on the result, we have decided to choose the proportion of responders as the primary outcome measure, which was defined as the proportion of patients with at least a 50% reduction in the number of migraine days, and others such as the change of migraine days, visual analogue scale (VAS, 0 to 10 cm) for pain, 36-item short-form health survey (SF-36), the number of patients with acute medication and adverse events (AE) as secondary outcome measures. All of the outcome measures
were assessed at weeks 0, 4, and 16. Adverse events were collected and recorded in case report forms after each acupuncture treatment and interview (week 4 and 16) by interviewers. Additionally, patients were required to record adverse events in their headache diaries.

Patient satisfaction was assessed as the percentage of patients who were satisfied with acupuncture treatment for migraine. At the end of the trial, patients were asked whether they were satisfied with the acupuncture treatment they received. The appraisals were classified as satisfaction, acceptable, and dissatisfaction.

2.9. Statistical analysis

Outcome parameters were analyzed by the intention-to-treat method (randomly allocate patients after baseline assessment regardless of the type of treatment received). Missing data were replaced by the data from the previous visit. An analysis of variance to reject the null hypothesis $h_0$ was that there was no difference in the success probability between the acupuncture group and the control group. The significance level used for statistical analysis with 2-tailed testing was 5%. Data values were presented by mean ± SD, 95% confidence intervals (CI), or percentage. The Student’s t-test or Wilcoxon rank sum test was used to compare the differences between groups at baseline. For the change in number of migraine days, analysis of covariance with baseline migraine days as a covariate was used to compare the differences between groups at the last 2 time points. For VAS and SF-36 scores, analysis of variance for repeated measures was used to compare the between-group and within-group differences. In the case of proportions, a chi-square test was applied. All analyses were done using the Statistical Package for the Social Sciences (SPSS) software program (version 11.5) for Windows XP.

3. Results

3.1. Dropouts

During the study, 20 patients dropped out, a rate of 14.3% (9 from the acupuncture group [12.9%] and 11 from the control group [15.7%]). Among these, 17 dropped out prematurely during the treatment period (8 from the acupuncture group, 9 from the control group) because of time restrictions, changed residence, dissatisfaction, and fear of needling. The other 3 patients were lost to follow-up due to change of contact information (1 from the acupuncture group, 2 from the control group). The reasons for the dropouts in the 2 groups are detailed in Fig. 2.

3.2. Characteristics of baseline

The demographic and baseline parameters with the intention-to-treat population were shown in Table 1, which showed that the 2 groups were comparable at baseline. The average ages in the acupuncture and control groups were 39.2 and 39.9 years, respectively.

3.3. Outcome measurements

Within-group comparisons of all outcome measures demonstrated that there are statistically significant differences from baseline to the end of treatment and follow-up ($P < .001$) (Table 2).

3.4. Proportion of responders

The responder rates in the acupuncture group and the control group were 59% vs 40% after 4 weeks ($P = .043$), and 56% vs 37% after 16 weeks ($P = .042$). Significant differences were found between the 2 groups during the trial (Table 2).

3.5. Number of migraine days

Four and 16 weeks later, the migraine days in the control group decreased to 4.3 days and 4.2 days, respectively, whereas in the acupuncture group, the migraine days reduced to 3 days and 3 days, respectively. In other words, the mean reduction of migraine days in the acupuncture group were 4.1 days, compared with 1.9 days in the control group at week 4 (Table 2), and a mean reduction of 4.1 days in the acupuncture group compared with 2.0 days in the control group at week 16 (Table 2). The differences in the number of migraine days between the acupuncture group and the control group were more than 2.0 days for both the week 4 and the week 16 ($P < .001$, Table 2).

3.6. Pain intensity

The mean VAS scores have significantly decreased in the acupuncture group from 6.9 ± 1.7 at baseline to 4.3 ± 2.7 at week 4 and to 4.6 ± 2.6 at week 16, whereas in the control group from 6.7 ± 1.9 at baseline to 5.2 ± 2.0 at week 4 and to 5.4 ± 2.3 at week 16 ($P < .001$). However, no significant differences were found between the 2 groups for the VAS scores by analysis of variance for repeated measures ($P = .143$).

3.7. Quality of life

Comparing weeks 4 and 16 with baseline, both the physical and mental components of the SF-36 scores have significantly improved in both groups. The results of repeated measurement of SF-36 scores on physical health and mental health showed that the scores significantly increased with time. However, no significant differences were observed between the 2 groups ($P > .05$, Table 2).

3.8. Acute medication

The number of patients using acute medication, such as aspirin, aminopyrine, phenacetin, or ibuprofen, has reduced significantly in the acupuncture group compared with the control group at weeks 4 and 16 ($P < .05$).

3.9. Safety and tolerability

A total of 12 patients (5 in the acupuncture group, 7 in the control group) reported mild adverse effects during the study period. In the acupuncture group, 3 patients complained of mild bleeding in a few acupoints after needle removal (without formation of subcutaneous hematoma); 1 patient reported discomfort in the scalp. These complaints were classified as a cause relevant to acupuncture. One patient in the acupuncture group complained of fatigue with unknown cause. In the control group, 5 patients complained of fatigue or faintness, and the other 2 patients documented weight gain during the treatment. All of these were considered to be related to the side effect of flunarizine. Although there was no significant difference between the 2 groups regarding the incidence of side effects, the overall pattern of the incidences were distinct. The occurrence of mild bleeding in local points in the acupuncture group was more than that in the control group. This might be associated with different locations of needle insertions between the 2 groups. The scalp and the facial area have more vascular distribution than the limbs. All of the patients with adverse effects recovered rapidly in this trial. Fifty-five patients were satisfied with acupuncture treatment in the acupuncture group, and 46 patients
in the control group (the treatment satisfaction in the acupuncture group and the control group was 78.6% vs 65.7%, respectively; \( P = .132 \)).

4. Discussion

The present trial demonstrated that the prophylactic effects of both acupuncture and flunarizine persisted from the end of the treatment through the next 3 months, and verum acupuncture was slightly better than flunarizine. The proportion of responders and migraine days of the acupuncture group significantly changed compared with the control group. Additionally, the number of patients who acquired acute medication in the acupuncture group have significantly reduced compared with the control group. However, no statistically significant differences in VAS score and the physical and mental components summary scores of SF-36 were found between the 2 groups during the trial.

The proportion of responders in the acupuncture group in our trial was significantly higher than in the control group. This result was in agreement with the findings of the trial by Diener et al. [9], which compared verum acupuncture with standard drugs after 6 weeks of treatment. In their study, the responders were significantly higher in the verum acupuncture group (52%) than in the standard drug group (39%) at week 6 (\( P = .012 \)), whereas no significant differences was detected between the 2 groups at week 26 (47% in verum group, 40% in standard group, \( P > .05 \)). They also found that the efficacy of acupuncture over 6 weeks were similar to that of 24 weeks with continuous standard drug treatment [9]. In our trial, there were no significant differences for the reduction of pain intensity between the 2 groups. However, the studies by Diener et al. and Allais et al. [3,9] have shown that acupuncture was better for pain relief than medication.

The comparison between verum acupuncture plus placebo drugs and true drugs plus sham acupuncture is seldom used in acupuncture clinical trials. The better efficacy of verum acupuncture plus placebo in our trial is different from the previous findings in most western trials, which suggested that the efficacy of verum acupuncture was not superior to that of standard drugs or sham acupuncture [3,19,28]. The contradictive finding might be due to the differences in the design and duration of the trial. In addition, the 4-week duration of flunarizine treatment is shorter than a typical acupuncture trial conducted in the past. The efficacy of flunarizine with 4 weeks of treatment might be inferior to that with 6 months. Despite guidelines recommending that it is best to undergo prophylactic therapy for several months, most Chinese migraine patients are unwilling to take medicine for such a duration. In addition, the sham acupuncture points were located on the limbs, far away from the verum Chinese acupuncture points in the head. Actually, some large-scale acupuncture trials reported that great differences between verum and sham acupuncture were observed when sham points were located far away from verum points [9,35].
Whether DeQi is a critical factor for acupuncture therapy is still controversial [34]. Owing to profound cultural background on the knowledge of DeQi in China, this sensation could be an important factor affecting the results in acupuncture clinical trials. In this study, needling sensation was required in both groups to fully blind patients by the manipulations of lifting, thrusting, and twirling the needles. Blinding patients to interventions is an important step, especially when the response criteria are subjective, such as alleviation of pain [8]. Blinding is used to rule out biases caused by expectations and subjective assessments [8]. Nevertheless, it is difficult to achieve full blinding in acupuncture clinical trials, particularly when making comparisons of acupuncture and medication [8,34]. We considered that open labels for comparing acupuncture with medicine might have some limitations during the process of the trial. Few outcome assessors and patients could avoid being influenced by subjective biases in assessments.

Moreover, Chinese migraine patients might have higher expectations for acupuncture due to their culture background, and this psychological factor may affect the actual effect of acupuncture. The drug-only controlled treatment might cause the withdrawal of enrolled patients for not being assigned into the acupuncture group, leading to a relatively high rate of dropout. The double-dummy technique was used to achieve blinding for this study to compare the efficacy of these 2 completely nonidentical therapies provided in the clinical management, as commonly used in other clinical drug trials [8]. The success of blinding or the expectations of patients were not formally examined because the manipulation of verum and sham acupuncture and the needle sensations between the 2 groups were similar. However, similar dropout rates (9 vs 11 patients) and patient satisfaction rates have demonstrated that patients were successfully blinded and the treatments of the 2 groups were equally convincing.

During the follow-up period, several patients in the acupuncture group have reported that the attacks seemed to be a prodrome of a migraine episode, such as tense paresthesias in the head, and lasted from several seconds to a few minutes. These attacks failed to develop into a typical migraine and required no medication. An analogous description also has been reported in other acupuncture literature [3]. The symptoms might demonstrate that acupuncture could reduce a migraine attack after prodrome occurs.

### Table 1
Demographics and characteristics at baseline (ITT).

<table>
<thead>
<tr>
<th></th>
<th>Acupuncture group N = 70 (ITT)</th>
<th>Control group N = 70 (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>59 (84.3)</td>
<td>60 (85.7)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>39.2 ± 10.9</td>
<td>39.9 ± 13.1</td>
</tr>
<tr>
<td>Days of migraine (mean ± SD)</td>
<td>7.1 ± 3.5</td>
<td>6.2 ± 3.4</td>
</tr>
<tr>
<td>Visual Analogue Scale (VAS) (mean ± SD)</td>
<td>6.9 ± 1.7</td>
<td>6.7 ± 1.9</td>
</tr>
<tr>
<td>SF-36 (mean ± SD)</td>
<td></td>
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<tr>
<td>Location of headache, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top of the head</td>
<td>16 (23)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>Forehead</td>
<td>19 (27)</td>
<td>18 (26)</td>
</tr>
<tr>
<td>Back of the head</td>
<td>12 (17)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Temporal area of the head</td>
<td>23 (33)</td>
<td>19 (27)</td>
</tr>
<tr>
<td>Type of pain, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsating</td>
<td>49 (70)</td>
<td>41 (59)</td>
</tr>
<tr>
<td>Stabbing</td>
<td>12 (17)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Dull</td>
<td>25 (36)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Distention</td>
<td>39 (56)</td>
<td>45 (64)</td>
</tr>
<tr>
<td>Other</td>
<td>48 (69)</td>
<td>51 (73)</td>
</tr>
<tr>
<td>Accompanying symptoms, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>64 (91)</td>
<td>59 (84)</td>
</tr>
<tr>
<td>Photophobia or phonophobia</td>
<td>62 (89)</td>
<td>57 (81)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (25)</td>
<td>18 (25)</td>
</tr>
</tbody>
</table>

Data were presented as mean ± SD, number (percentage).

In our trial, the acupoints were selected according to experts’ experience complying with the methodology of syndrome differentiation of meridians. Similarly, Facco et al. suggested that traditional acupuncture provided long-lasting effects (6 months) in decreasing both Migraine Disability Assessment index and rizatriptan intake compared with standard mock acupuncture (using 5 obligatory acupoints without syndromes differentiation) [11], indicating the importance of syndrome differentiation on theories of TCM when we select acupoints.

### Table 2
The primary and secondary outcome measures.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time point</th>
<th>Acupuncture group n = 70</th>
<th>Control group n = 70</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>95% CI</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Responder rate (ITT)</td>
<td>Week 4</td>
<td>41 (59%)</td>
<td>–</td>
<td>28 (40%)</td>
</tr>
<tr>
<td></td>
<td>Week 16</td>
<td>39 (56%)</td>
<td>–</td>
<td>26 (37%)</td>
</tr>
<tr>
<td>Difference from baseline in days of migraine (ITT)</td>
<td>Week 4</td>
<td>4.1 ± 3.5 (3.2–4.9)</td>
<td>1.9 ± 2.3 (1.4–2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Week 16</td>
<td>4.1 ± 3.5 (3.3–5.0)</td>
<td>2.0 ± 2.7 (1.4–2.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual Analogue Scale (ITT)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>6.9 ± 1.7 (6.5–7.3)</td>
<td>6.7 ± 1.9 (6.2–7.1)</td>
<td>.143</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>4.3 ± 2.7 (3.7–5.0)</td>
<td>5.2 ± 2.0 (4.7–5.7)</td>
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<tr>
<td></td>
<td>Week 16</td>
<td>4.6 ± 2.6 (3.9–5.2)</td>
<td>5.4 ± 2.3 (4.9–6.0)</td>
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<tr>
<td>SF-36 (ITT), Physical</td>
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<tr>
<td></td>
<td>Baseline</td>
<td>49.7 ± 7.3 (48.0–51.5)</td>
<td>50.6 ± 6.4 (49.1–52.1)</td>
<td>.249</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>55.9 ± 7.7 (54.1–57.7)</td>
<td>53.6 ± 7.1 (51.9–55.3)</td>
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<tr>
<td></td>
<td>Week 16</td>
<td>57.0 ± 7.5 (55.2–58.8)</td>
<td>54.8 ± 7.2 (53.0–56.5)</td>
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<tr>
<td>SF-36 (ITT), Mental</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>49.7 ± 9.0 (47.5–51.8)</td>
<td>51.0 ± 7.5 (49.2–52.8)</td>
<td>.213</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>56.0 ± 7.1 (54.3–57.7)</td>
<td>52.6 ± 7.4 (50.8–54.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 16</td>
<td>55.5 ± 6.9 (53.9–57.2)</td>
<td>53.6 ± 7.0 (52.0–55.3)</td>
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</tr>
<tr>
<td>Reduction in the number of people with acute medication, n (%) (ITT)</td>
<td>Week 4</td>
<td>20 (28%)</td>
<td>–</td>
<td>4 (14%)</td>
</tr>
<tr>
<td></td>
<td>Week 16</td>
<td>17 (25%)</td>
<td>–</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ITT, intention-to-treat; SF-36, 36-item short-form health survey.

Significant difference, P < .05. Data presented as mean ± SD, number (percentage) and 95% CI.

* P for comparison with control group.

† P values based on chi-square test.

‡ P values based on analysis of covariance analysis.

§ P values based on repeated measures.

¶ P for comparison within each group.
Although we selected nonpoints unrelated to treatment and allocated them into 5 subgroups randomly, sham acupuncture still produced nonspecific effects in the control group. It is believed that placing a needle anywhere might have a physiological effect through the mechanism of diffuse noxious inhibitory control [17]. Some researches [14,16] have shown that sham acupuncture might produce similar analgesic effects compared with verum acupuncture, but verum acupuncture induced more prominent functional magnetic resonance imaging changes in certain brain areas than that induced by sham acupuncture. In addition, our method of selecting sham points is uncommonly used in acupuncture trials. Further study on the selection of nonacupoints or irrelevant acupoints is needed for sham acupuncture.

It is worthwhile to note that our trial design was superior to other trials and compared the efficacy of acupuncture and medicine in several ways: a double-dummy, single-blinded trial, which minimized the influence of psychological factors and maintained identical conditions throughout the trial; standardized manipulation of acupuncture; combination of expertise from multiple disciplines; selection of acupoints based on literature and expert experience; and randomized allocation of nonspecific acupoints to minimize the treatment effects of sham acupuncture.

The main limitation of the trial is the short length of the treatment and follow-up periods. In order to blind the patients, we adopted a double-dummy method of verum acupuncture plus placebo drug with flunarizine plus sham acupuncture. However, different types of placebos might have different nonspecific effects. Therefore, the placebo effects on patients produced by placebo drug and sham acupuncture might be different, which could affect the therapeutic outcomes. In addition, the sample size was relatively smaller.

In conclusion, compared with 4-week flunarizine treatment, acupuncture is superior in reduction of the number of migraine days and in acute medication intake, but not in relieving the intensity of pain and improving quality of life. Despite the unknown mechanism of this therapy, acupuncture could be adopted as a migraine treatment for the prevention of relapse and aggravation. Further research could be conducted on the mechanism of acupuncture for migraine prophylaxis.

Acknowledgements

This trial was funded by the Capital Medical Development Research Fund (No. SF-2005-2). The agency had no role in study design, data collection and analysis, data interpretation, writing the manuscript, or the decision to submit the manuscript for publication. The authors thank YiMing Zhao, PhD, (Research Center of Clinical Epidemiology Affiliated with Peking University) for statistical advice. The authors also appreciate the approval of Xi’an Janssen Pharmaceutical Ltd for medication supply. The authors declare that they have no conflicts of interest.

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