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The Long-term Effect of Acupuncture for Migraine Prophylaxis
A Randomized Clinical Trial

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IMPORTANCE The long-term prophylactic effects of acupuncture for migraine are uncertain.

OBJECTIVE To investigate the long-term effects of true acupuncture compared with sham acupuncture and being placed in a waiting-list control group for migraine prophylaxis.

DESIGN, SETTING, AND PARTICIPANTS This was a 24-week randomized clinical trial (4 weeks of treatment followed by 20 weeks of follow-up). Participants were randomly assigned to true acupuncture, sham acupuncture, or a waiting-list control group. The trial was conducted from October 2012 to September 2014 in outpatient settings at 3 clinical sites in China. A total of 249 participants 18 to 65 years old with migraine without aura based on the criteria of the International Headache Society, with migraine occurring 2 to 8 times per month.

INTERVENTIONS Participants in the true acupuncture and sham acupuncture groups received treatment 5 days per week for 4 weeks for a total of 20 sessions. Participants in the waiting-list group did not receive acupuncture but were informed that 20 sessions of acupuncture would be provided free of charge at the end of the trial.

MAIN OUTCOMES AND MEASURES Participants used diaries to record migraine attacks. The primary outcome was the change in the frequency of migraine attacks from baseline to week 16. Secondary outcome measures included the migraine days, average headache severity, and medication intake every 4 weeks within 24 weeks.

RESULTS A total of 249 participants 18 to 65 years old were enrolled, and 245 were included in the intention-to-treat analyses. One hundred eighty-nine (77.1%) were women. Baseline characteristics were comparable across the 3 groups. The mean (SD) change in frequency of migraine attacks differed significantly among the 3 groups at 16 weeks after randomization ($P < .001$); the mean (SD) frequency of attacks decreased in the true acupuncture group by 3.2 (2.1), in the sham acupuncture group by 2.1 (2.5), and the waiting-list group by 1.4 (2.5); a greater reduction was observed in the true acupuncture than in the sham acupuncture group (difference of 1.1 attacks; 95% CI, 0.4-1.9; $P = .002$) and in the true acupuncture vs waiting-list group (difference of 1.8 attacks; 95% CI, 1.1-2.5; $P < .001$). Sham acupuncture was not statistically different from the waiting-list group (difference of 0.7 attacks; 95% CI, −0.1 to 1.4; $P = .07$).

CONCLUSIONS AND RELEVANCE Among patients with migraine without aura, true acupuncture may be associated with long-term reduction in migraine recurrence compared with sham acupuncture or assigned to a waiting list.

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Invited Commentary

Supplemental content

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Among neurological disorders, migraine is a leading cause of disability and significantly contributes to individual and societal burdens owing to pain and environmental sensitivities. The prevalence of migraine is 14.9% in the United States,[1] and 8.4% to 12.7% in Asia.[2] Approximately 25% to 38% of migraineurs need preventive therapy,[3,4] and pharmacotherapies, such as divalproex sodium, topiramate, metoprolol, and propranolol, are recommended for migraine prevention. However, such treatments are often associated with an increased risk of adverse events (AEs), including weight gain, fatigue, sleep disturbance, and gastrointestinal intolerance.[4,5] Excessive use of analgesics or specific antimigraine treatments could cause medication overuse–induced headache and an increase in headache frequency.[3,6] Because of the limitations associated with these conventional treatments, efforts have been made to identify effective, low-risk interventions.

Acupuncture is widely used for managing migraine in China and western countries, especially for drug-refractory patients.[7,8] The goals of acupuncture are usually 2-fold: relief of pain during migraine (acute effect)[9,10] and prevention of future migraine attacks (long-term effect). Several trials with a small sample size[11-14] have shown that true acupuncture (TA) may be more effective than sham acupuncture (SA) (simulated, or needling at nonacupoint locations) in the reduction of migraine intensity, frequency of migraine attacks, and number of migraine days; others,[15-18] however, have reported no differences. The inconsistency of these findings may result from variations in the design characteristics (eg, length of follow-up, interventions used) and study population.

The long-term effect of acupuncture is critical to successful prophylaxis and reduction of migraine recurrence. One important unanswered question is whether TA is superior to SA in preventing future migraine attacks. Therefore, we further conducted a 24-week, multicenter, 3-arm, parallel randomized clinical trial (RCT) to compare the long-term effect of TA vs SA or waiting list (WL) in migraineurs.

Key Points

Question What is the long-term efficacy of acupuncture for prophylaxis of migraine?

Findings In this 24-week, randomized clinical trial that included 249 patients with migraine without aura, we found that true acupuncture significantly reduced the frequency of migraine attacks, compared with sham acupuncture and being placed on a waiting list for treatment.

Meaning Among patients with migraine without aura, true acupuncture may be associated with long-term reduction in migraine recurrence compared with sham acupuncture or waiting list.

Methods

Study Population and Protocol

We recruited patients who had migraine without aura from the outpatient unit of the Departments of Acupuncture and Neurology in 3 clinical centers: the teaching hospital of Chengdu University of Traditional Chinese Medicine (TCM), the First Affiliated Hospital of Hunan University of TCM, and the Affiliated Hospital of Chongqing Medical University. Migraine without aura was diagnosed according to the classification criteria of the International Headache Society.[19] Patients who complained of recurrent headaches lasting 4 to 72 hours, unilateral headaches with pulsating quality, and also headaches aggravated by routine physical activity were recruited for further evaluation. Patients were enrolled in the study from October 2012 to September 2014. Patients were not reimbursed, but did receive free treatment. The protocol was approved by the local institutional ethics review boards and was performed in accordance with the Declaration of Helsinki and the Chinese version of the International Conference on Harmonization-Good Clinical Practice. The protocol was published previously and is available in the Supplement.[20]

The inclusion criteria were as follows: men or women 18 to 65 years old with initial onset of migraines prior to the age of 50 years; experience of acute migraine attacks at a frequency of 2 to 8 times per month 3 months before inclusion; experience of migraine attacks for at least 1 year; completion of a baseline headache diary; and provision of written, informed consent by the patients.

Patients with any of the following conditions were excluded: headache caused by organic disorders (eg, subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism, cerebral thrombosis, vascular malformation, arteritis, hypertension, or arteriosclerosis); the presence of neurological diseases, immunodeficiency, bleeding disorders, or allergies; prophylactic headache treatment with drugs during the previous 3 months; pregnancy, lactation, or plans to become pregnant within 6 months; or involvement in other clinical trials.

Randomization and Blinding

A total of 249 eligible patients were recruited and were randomly assigned at a 1:1:1 ratio to receive TA treatment or SA treatment, or to be place on a WL. Central randomization, using an online or messaging system, was performed by the Brightech Magnsoft Data Services. Randomization sequence was generated in blocks of varying sizes and stratified by centers.

The participants in the TA group and SA group were blinded, while those in the WL group were not. Acupuncturists could not be blinded to the treatment assignments given the nature of the interventions. Outcome assessors, data collectors, and statisticians were blinded to the treatment allocation.

Interventions

Electrostimulation generates an analgesic effect, as manual acupuncture does.[21] All acupuncturists were trained for at least 5 years and licensed with at least 4 years of clinical experience. Patients in the TA group and the SA group received 20 sessions of electroacupuncture treatment (once per day for 5 consecutive days followed by a 2-day break), each lasting 30

minutes, for 4 weeks. Migraineurs were not allowed to take any prophylactic medications. In cases of intolerable headache, the patients were instructed to take ibuprofen (300-mg capsules with sustained release) as a rescue medication, and the usage of ibuprofen was documented in the headache diary.

Four acupoints were used per treatment. All patients received acupuncture on 2 obligatory points, including GB20 and GB8. The 2 other points were chosen according to the syndrome differentiation of meridians in the headache region. The potential acupoints included SJ5, GB34, BL60, SI3, LI4, ST44, LR3, and GB40.[20] The use of additional acupoints other than the prescribed ones was not allowed. We chose the prescriptions as a result of a systematic review of ancient and modern literature,[22,23] consensus meetings with clinical experts, and experience from our previous study.[18] Sterile, single-use filiform acupuncture needles, each with a length of 25 to 40 mm and a diameter of 0.25 mm, were used in the treatment. Acupuncturists applied therapy unilaterally by alternatively using the left and right acupoints. Each point was acupunctured to achieve the *Deqi* sensation (a sensation of soreness, numbness, distention, or radiating that indicates effective needling). The HANS acupoint nerve stimulator (model LH 200A; Han Institute, TENS, Nanjing, China) was used after needle insertion. The stimulation frequency was 2/100 Hz (alternating every 3 seconds), and the intensity varied from 0.1 to 1.0 mA until the patients felt comfortable. This stimulation method was optimal for obtaining an analgesic effect[21] and was used successfully in our previous study.[18] In addition, more details of the procedure have been published.[20]

The number of needles, electric stimulation, and duration of treatment in the SA group were identical in the TA group except that an attempt was not made to induce the *Deqi* sensation. Four nonpoints were chosen according to our previous studies.[20,24]

Patients in the WL group did not receive acupuncture from the beginning of the clinical trial but were informed that they would be provided with 20 sessions of acupuncture treatment for free after 24 weeks.

Measures

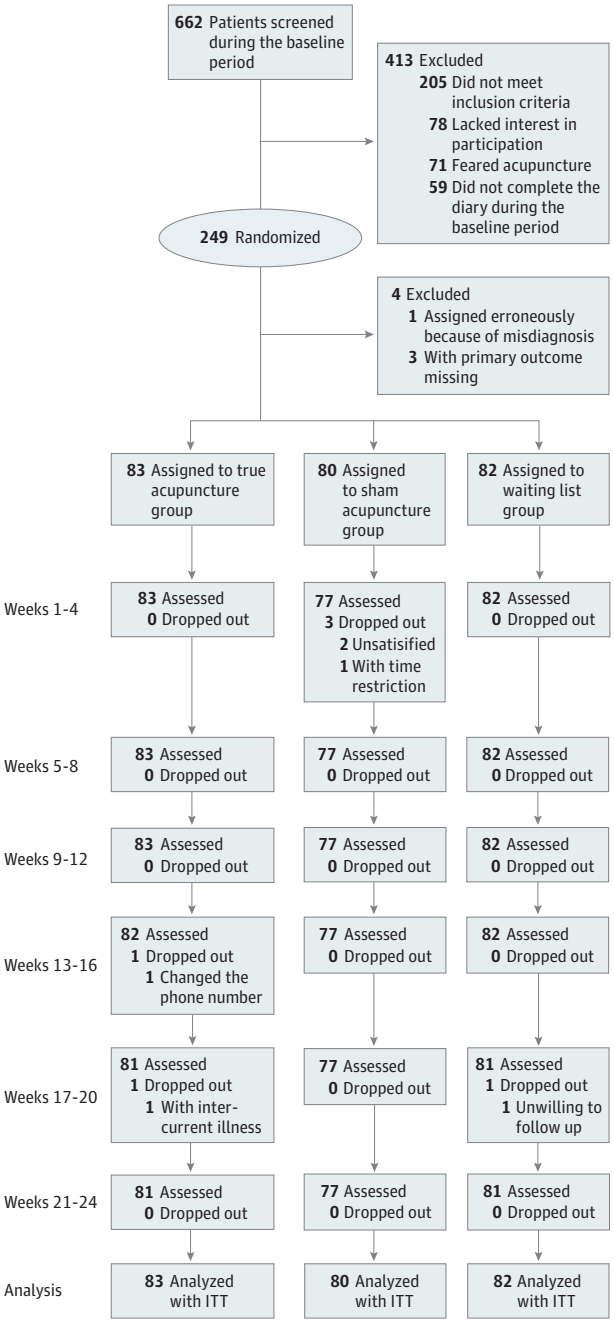
Data Collection

All patients were instructed to complete headache diary records every 4 weeks after inclusion. The headache diary documented the time of migraine onset, duration, severity (evaluated by the visual analog scale [VAS] score), and rescue medication use. The frequency of migraine attacks over 24 weeks, migraine days, and the intensity of each attack were calculated every 4 weeks. At each follow-up, 2 blinded evaluators at each clinical center reminded patients by phone calls or text messages to return the headache diary to the trial offices via emails or to outpatient offices at follow-up visits.

Outcome Measures

The primary outcome was the change in the frequency of migraine attacks between baseline and 16 weeks after randomization. Secondary outcome measures included the number of days with migraine (migraine days), average headache severity, and medication intake every 4 weeks within 24 weeks.

Figure 1. Flowchart of the Screening, Enrollment, Randomization, and Follow-up



ITT indicates intention to treat.

In addition, migraine-specific quality-of-life questionnaire (MSQ), and pain-related impairment of emotion (the Zung self-rating anxiety scale [SAS] and Zung self-rating depression scale [SDS]) were assessed at baseline and at the 4-week visit. Researchers documented acupuncture treatment and reasons for dropouts during the study period. Acupuncture-associated AEs, including bleeding, subcutaneous hemorrhage, hematoma, fainting, serious pain, and local infection, were recorded at each treatment session.

Table 1. Baseline Characteristics of 245 Patients Included in the Intention-to-Treat Analysis[a]

Characteristic	Group			All Patients (n = 245)
	TA (n = 83)	SA (n = 80)	WL (n = 82)	
Women	65 (78.3)	63 (78.8)	61 (74.4)	189 (77.1)
Age, mean (SD), y	36.4 (14.2)	39.1 (14.6)	38.8 (13.4)	38.1 (14.1)
Duration of illness, mean (SD), mo	115.7 (99.5)	113.0 (104.2)	104.6 (82.0)	111.1 (95.4)
Family history, yes vs no	19 (22.9)	16 (20.0)	21 (25.6)	56 (22.9)
Previous use of acupuncture	17(20.5)	15(18.8)	21 (25.6)	53 (21.6)
Use of acute pain medication	36 (43.4)	24 (28.9)	29 (34.9)	89 (36.3)
Accompanying symptoms				
Nausea or vomiting	55 (66.3)	52 (65.0)	45 (54.9)	152 (62.0)
Photophobia or phonophobia	22 (26.5)	23 (28.8)	33 (40.2)	78 (31.8)
Others	6 (7.2)	5 (6.3)	4 (4.9)	15 (6.1)
Acupuncture expectation of improvement				
None	0	0	1 (1.2)	1 (0.4)
Slight	6 (7.2)	9 (11.3)	9 (11.0)	24 (9.8)
Some	28 (33.7)	24 (30.0)	25 (30.5)	77 (31.4)
Significant	49 (59.0)	47 (58.8)	47 (57.3)	143 (58.4)

Abbreviation: SA, sham acupuncture; TA, true acupuncture; WL, waiting list.

[a] Data are given as No. (%) except where noted.

Sample Size Calculation and Statistical Analysis

We designed our trial to determine whether there was a difference among the TA group, the SA group, and the WL group in terms of the frequency of migraine attacks. According to our previous study,[18] we anticipated that the frequency of migraine attacks over 16 weeks would be 2.7 in the TA group and 3.7 in the SA group, considering a mean clinically relevant difference of 1.0 and a standard deviation (SD) of 1.81. With a 2-sided significance level of 5% and power of 90%, 70 participants per group would be required, as calculated by NQuery Advisor software (version 4.0; Statistical Solutions). With an estimated loss-to-follow-up rate of 15%, we planned to enroll 249 participants in the 3 groups, with 83 participants in each group.

The baseline characteristics and clinical outcomes described are based on the intention-to-treat (ITT) population, which included participants who had at least 1 treatment and 1 primary outcome measure (n = 245). Continuous variables are presented as the mean (SD) with 95% CIs. Categorical variables are described as numbers and percentages. The missing data of participants who dropped out were replaced by the last observation carried forward method. The significance level used for the statistical analysis with 2-tailed testing was 5%.

The analysis plan was determined before the study was conducted. If the data were normally distributed, we planned to use the analysis of covariance to detect differences among the 3 groups; if not, we planned to use the Kruskal-Wallis test. Secondary outcome measures were evaluated using the χ^2 test for categorical data, and analysis of variance or Kruskal-Wallis tests were used for quantitative variables according to the data distribution. If the global test among 3 arms was significant, the least significant difference (LSD) test was used for pairwise comparisons when the data were normally distributed; otherwise, the LSD was applied after rank-transformation when the variables showed nonnormality.

All data in this trial were commissioned to Brightech-Magnsoft Data Services for analysis using SAS statistical software (version 9.3; SAS Institute Inc).

Results

Participants and Baseline Characteristics

After the screening of 662 patients, 249 participants 18 to 65 years old were randomized. One hundred eighty-nine (77.1%) were women. A total of 245 patients (83 in the TA group, 80 in the SA group, and 82 in the WL group) were included in the ITT population (**Figure 1**). **Table 1** shows the patient characteristics at baseline and acupuncture expectation before treatment. They were comparable across the 3 groups. Six patients (2.4%) were unable to undergo follow-up (2 in the TA group, 3 in the SA group, and 1 in the WL group). During the treatment period, the mean number of treatments was 19.31 in the TA group and 19.23 in the SA group.

Primary Outcome

The change in frequency of migraine attacks differed significantly among the 3 groups at 16 weeks after randomization (**Table 2**). The frequency of attacks decreased in the TA group by 3.2, in the SA group by 2.1, and the WL group by 1.4; a greater reduction was observed in the TA than in the SA group (difference of 1.1 attacks; 95% CI, 0.4-1.9; $P = .002$) and in the TA vs WL group (difference of 1.8 attacks; 95% CI, 1.1 to 2.5; $P < .001$). The SA group was not statistically different from the WL group (difference of 0.7 attacks; 95% CI, −0.1 to 1.4; $P = .07$) (Table 2). The per-protocol analysis showed similar results.

Secondary Outcomes

The effects of acupuncture on the secondary outcomes seemed to be persistent during follow-up. The frequency of

Table 2. Headache Diary–Based Outcome Measurements During the Entire Study

Outcome Measure	TA (n = 83)	SA (n = 80)	WL (n = 82)	*P* Value	Pairwise Comparison TA vs SA Effect Size (95% CI)	TA vs SA *P* Value[a]	TA vs WL Effect Size (95% CI)	TA vs WL *P* Value[a]	SA vs WL Effect Size (95% CI)	SA vs WL *P* Value[a]
Difference From Baseline in Frequency of Migraine Attacks, mean (SD), No.[b,c]										
Baseline	4.8 (2.3)	5.0 (2.4)	4.9 (2.5)	.85	NA		NA		NA	
Treatment, 1-4 wk	2.7 (2.4)	1.5 (2.5)	0.8 (1.9)	<.001	0.5 (0.2 to 0.8)	.001	0.9 (0.6 to 1.2)	<.001	0.3 (0.0 to 0.6)	.07
After treatment, wk										
5-8	3.1 (2.1)	2.0 (2.2)	1.0 (2.4)	<.001	0.5 (0.2 to 0.8)	.002	0.9 (0.6 to 1.3)	<.001	0.4 (0.1 to 0.7)	.006
9-12	3.0 (2.0)	2.1 (2.5)	1.1 (2.1)	<.001	0.4 (0.1 to 0.7)	.005	0.9 (0.6 to 1.2)	<.001	0.4 (0.1 to 0.7)	.005
13-16	3.2 (2.1)	2.1 (2.5)	1.4 (2.5)	<.001	0.5 (0.2 to 0.8)	.002	0.8 (0.5 to 1.1)	<.001	0.3 (0.0 to 0.6)	.07
17-20	3.1 (1.8)	2.2 (2.5)	1.4 (2.3)	<.001	0.4 (0.1 to 0.7)	.008	0.8 (0.5 to 1.1)	<.001	0.3 (0.0 to 0.6)	.03
21-24	3.0 (2.0)	2.1 (2.4)	1.4 (2.6)	<.001	0.4 (0.1 to 0.7)	.01	0.7 (0.4 to 1.0)	<.001	0.3 (0.0 to 0.6)	.05
Days With Migraine per 4 Weeks, mean (SD), No.[b,d]										
Baseline	5.9 (3.9)	6.2 (4.4)	6.0 (4.6)	.80	NA		NA		NA	
Treatment, 1-4 wk	2.4 (1.7)	4.0 (2.9)	4.5 (2.4)	<.001	−0.7 (−1.0 to −0.4)	<.001	−1.0 (−1.3 to −0.7)	<.001	−0.2 (−0.5 to 0.1)	.18
After treatment, wk										
5-8	1.8 (1.9)	3.3 (2.3)	4.4 (2.3)	<.001	−0.7 (−1.0 to −0.4)	<.001	−1.2 (−1.6 to −0.9)	<.001	−0.5 (−0.8 to −0.2)	.001
9-12	2.1 (3.2)	3.2 (2.3)	4.2 (2.2)	<.001	−0.4 (−0.7 to −0.1)	.008	−0.8 (−1.1 to −0.4)	<.001	−0.4 (−0.8 to −0.1)	.01
13-16	2.0 (3.2)	3.1 (2.1)	3.8 (2.1)	<.001	−0.4 (−0.7 to −0.1)	.005	−0.7 (−1.0 to −0.4)	<.001	−0.3 (−0.6 to 0.0)	.06
17-20	2.0 (3.2)	3.0 (2.3)	3.9 (2.2)	<.001	−0.4 (−0.7 to −0.1)	.01	−0.7 (−1.0 to −0.4)	<.001	−0.4 (−0.7 to −0.1)	.03
21-24	2.1 (3.3)	3.1 (2.2)	3.8 (1.8)	<.001	−0.4 (−0.7 to −0.1)	.01	−0.6 (−0.9 to −0.3)	<.001	−0.3 (−0.7 to 0.0)	.07
VAS Score, mean (SD)[b]										
Baseline	5.7 (1.9)	5.6 (1.6)	5.1 (1.5)	.10	NA		NA		NA	
Treatment, 1-4 wk	3.6 (1.9)	4.2 (1.7)	4.9 (1.6)	.001	−0.3 (−0.6 to 0.0)	.04	−0.7 (−1.1 to −0.4)	<.001	−0.4 (−0.7 to −0.1)	.02
After treatment, wk										
5-8	3.7 (2.3)	4.3 (1.9)	5.0 (1.8)	.002	−0.3 (−0.6 to 0.0)	.04	−0.6 (−0.9 to −0.3)	<.001	−0.4 (−0.7 to −0.1)	.04
9-12	3.4 (2.1)	4.1 (1.9)	5.1 (1.5)	<.001	−0.3 (−0.7 to −0.0)	.01	−0.9 (−1.2 to −0.6)	<.001	−0.6 (−0.9 to −0.3)	.001
13-16	3.4 (2.3)	4.2 (1.9)	4.9 (1.4)	<.001	−0.4 (−0.7 to −0.1)	.01	−0.8 (−1.1 to −0.5)	<.001	−0.4 (−0.7 to −0.1)	.01
17-20	3.4 (2.0)	4.3 (1.8)	4.9 (1.4)	<.001	−0.5 (−0.8 to −0.2)	<.001	−0.9 (−1.2 to −0.5)	<.001	−0.4 (−0.7 to −0.1)	.03
21-24	3.2 (2.0)	4.2 (1.7)	4.9 (1.3)	<.001	−0.5 (−0.8 to −0.2)	<.001	−1.0 (−1.3 to −0.7)	<.001	−0.5 (−0.8 to −0.1)	.01
Use of Acute Pain Medication, No. (%)[e]										
Baseline	36 (43.4)	24 (28.9)	29 (34.9)	.15	NA		NA		NA	
Treatment, 1-4 wk	5 (6.0)	4 (4.8)	13 (8.8)	.03	NA		NA		NA	
After treatment, wk										
5-8	3 (3.6)	3 (3.6)	15 (18.1)	.001	NA		NA		NA	
9-12	5 (6.0)	4 (4.8)	13 (8.8)	.03	NA		NA		NA	
13-16	5 (6.0)	5 (6.0)	16 (19.3)	.006	NA		NA		NA	
17-20	5 (6.0)	7 (8.4)	18 (21.7)	.004	NA		NA		NA	
21-24	5 (6.0)	7 (8.4)	19 (22.9)	.002	NA		NA		NA	

Abbreviation: NA, not applicable; SA, sham acupuncture; TA, true acupuncture; VAS, visual analog scale; WL, waiting list.

[a] *P* value based on the least significant difference.

[b] *P* values based on Kruskal-Wallis analysis among the 3 groups.

[c] The frequency of migraine attack was defined as the number of episodes of migraine attack separated by pain-free intervals of at least 48 h, as recorded in the headache diary.

[d] Number of days with migraine was defined as the duration of migraine attacks.

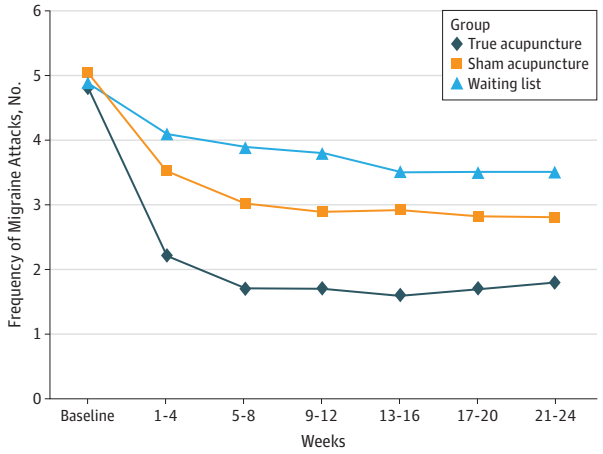
[e] *P* values based on χ^2 test among the 3 groups.

migraine attacks (**Figure 2**), migraine days, and VAS scores were significantly lower in the TA group than in the other 2 control groups in each interview during weeks 4 to 24 (Table 2). Significant differences in frequency of migraine and migraine days between the 2 control groups were only found at weeks 8, 12, and 20 after inclusion within the follow-up period (Table 2).

At the end of week 4, no differences were observed between the TA group and the SA group in the MSQ, SAS, or SDS scores ($P > .05$ for all comparisons) except for the emotional functional subscale in MSQ. Compared with the WL group, however, the TA group showed a significant improvement in all subscales of the MSQ and SAS scores ($P < .05$ for all comparisons). Furthermore, patients in the SA group only had a better score in the restrictive subscale of MSQ than those in the WL group (**Table 3**).

The number of patients using acute pain medication, such as ibuprofen, significantly differed among the 3 groups both at the treatment and at follow-up. Compared with the WL control group, TA and SA group have reduced acute medication (Table 2).

Figure 2. Frequency of Migraine Attacks Throughout the Study



Safety

Seven patients (5 in the TA group and 2 in the SA group) reported AEs during the 24 weeks. Three patients from the TA group complained of a tingling sensation after insertion in the acupoints located on the head. One described swelling of the left ankle after a needle was removed from GB40. The other 3 patients (1 in the TA group and 2 in the SA group) had subcutaneous hemorrhage in the needle insertion area. All AEs were reported as mild or moderate, and none required special medical interventions. The 7 patients fully recovered from the AEs and did not withdraw from the trial.

Discussion

True acupuncture exhibited persistent, superior, and clinically relevant benefits for migraine prophylaxis, reducing the migraine frequency, number of days with migraine, and pain intensity to a greater degree than SA or WL. Improvements in the emotional domain of quality of life were also found. Moreover, compared with no treatment, SA may obtain a relatively better effect in controlling the migraine frequency and number of days with migraine within 8 weeks after treatment rather than at the end of the treatment session. Acupuncture should be considered as one option for migraine prophylaxis in light of our findings. To the best of our knowl-

Table 3. MSQ Score, SAS Score, and SDS Score at the End of Treatment[a]

Outcome Measure	Mean (SD) [95% CI] TA (n = 83)	SA (n = 80)	WL (n = 82)	*P* Value	*P* Value for Pairwise Comparison[b] TA vs SA	TA vs WL	SA vs WL
MSQ Score, Restrictive Subscale							
Baseline	65.1 (16.7) [61.4-68.7]	64.3 (13.6) [61.3-67.3]	65.5 (17.7) [61.6-69.4]	.58	.13	<.001	.01
Treatment, 1-4 wk	79.3 (14.5) [76.1-82.4]	75.7 (14.7) [72.4-79.0]	69.9 (15.5) [66.5-73.3]	<.001			
MSQ Score, Preventive Subscale							
Baseline	73.2 (18.5) [69.2-77.2]	73.4 (16.9) [69.6-77.1]	76.4 (20.0) [72.0-80.8]	.20	.054	.01	.49
Treatment, 1-4 wk	86.1 (14.2) [83.1-89.2]	81.4 (16.1) [77.8-85.1]	79.8 (15.8) [76.3-83.2]	.02			
MSQ Score, Emotional Functional Subscale							
Baseline	76.6 (15.4) [73.2-80.0	75.5 (17.2) [60.0-86.7]	73.3 (18.2) [60.0-86.7]	.61	.01	<.001	.22
Treatment, 1-4 wk	86.2 (12.7) [83.4-89.0]	80.2 (16.2) [76.5-83.9]	77.2 (16.4) [73.6-80.8]	.002			
SAS Score							
Baseline	44.5 (9.4) [42.4-46.5]	44.7 (8.4) [42.8-46.5]	45.3 (9.1) [43.3-47.3]	.82	.43	.01	.09
Treatment, 1-4 wk	39.0 (8.4) [37.2-40.8]	40.1 (8.3) [38.2-41.9]	42.4 (8.6) [40.4-44.2]	.03			
SDS Score							
Baseline	44.94 (11.2) [42.5-47.4]	44.63 (11.7) [42.0-47.2]	44.3 (11.5) [41.8-46.8]	.94	NA	NA	NA
Treatment, 1-4 wk	40.08 (12.0) [37.5-42.7]	40.65 (11.4) [38.0-43.0]	43.49 (12.2) [40.8-46.2]	.15			

Abbreviations: MSQ, Migraine-Specific Quality of Life Questionnaire; NA, not applicable; SA, sham acupuncture; SAS, Zung Self-rating Anxiety Scale; SDS, Zung Self-rating Depression Scale; TA, true acupuncture; WL, waiting list.

[a] Four weeks after randomization.

[b] *P* value based on the least significant difference.

edge, our study is one of the largest trials that have used rigorous methods to test the efficacy of true acupuncture over 24 weeks of follow-up. We provided daily treatment during workdays for 4 weeks to achieve a long-lasting effect for 20 weeks. We had a lower loss to follow-up rate (1.61%) than other migraine prophylaxis studies.[12,15,16,18]

We found that TA was more effective than the WL control group for migraine prophylaxis. Our findings were congruent with those of a previous clinical trial[15] and individual patient data meta-analysis for chronic pain.[25] Furthermore, the findings of the current study demonstrated that TA was significantly better than SA for migraine prophylaxis, which has been supported by several other RCTs.[11,12,14,26] These findings were not completely in accordance with those of our previous study,[18] which showed no significant differences between the TA group and the SA group in weeks 5 to 8; instead, the difference appeared later, in weeks 13 to 16. We speculate that the inconsistency was attributed to the different acupoints prescribed. A standardized prescription was used in our previous study; however, semistandard therapy according to syndrome differentiation of meridians—a more practical approach—was used in the TA group in the present study.

Of note, a large trial from Germany demonstrated no statistical difference between TA and SA.[15] We speculate that the clinical benefits and superiority found in our trial were due to several factors. The first was the type of treatment. We added electrostimulation to manual acupuncture because manual acupuncture requires more time until it reaches a similar analgesic effect as electrical stimulation.[27] Previous studies have reported that electrostimulation is better than manual acupuncture in relieving pain[27-30] and could induce a longer-lasting effect.[28]

Second, only patients with migraines without aura were chosen in the present study; however, all other similar studies have included migraineurs with other types. As an acute therapy, sumatriptan was less effective for migraine attacks with aura than that for attacks without aura.[31] We hypothesized that the type of migraine attack may have an impact on the therapeutic outcome, and that patients with migraine without aura are more responsive to acupuncture than migraine with aura owing to their distinct pathogeneses.

Finally, the severity of pain that patients reported during the baseline period might have influenced the therapeutic effects. The mean days with migraine in our trial ranged from 5.9 to 6.0 days per 4 weeks, and the mean attack frequency was approximately 4.9 during the baseline. However, Linde et al[15] reported fewer days with migraine and fewer migraine attacks during the baseline, and no significant difference between TA and SA was observed either at the end of treatment or at the 12-week follow-up. Reductions in migraine severity and frequency increased benefits in patients with more severe headaches.[12,32] This finding might explain the significant difference between the TA and SA groups in our study, and the absence of such a finding in the aforementioned RCT[15] with a similar study design.

We suspected that the slight improvement in the WL group was probably due to the Hawthorne effect or the effect of regression to the mean, a finding that is consistent with those of a previous report.[15] Although inferior to TA, SA was still associated with clinical improvement and was possibly a result of the nonspecific physiological effect experienced during needling or a placebo effect originating from frequent patient-acupuncture practitioner interactions. This could explain why a significant difference between SA control and WL control was observed only during the follow-up period instead of at the end of treatment.

These results are beneficial to patients with aura-free migraine who had at least 2 monthly attacks during the 4-week of pretreatment. Among such patients, TA was more efficacious for migraine prophylaxis than SA or no acupuncture, and the improvement induced by acupuncture persists for at least 24 weeks.

Limitations

Our study also has 3 limitations. First, our study used a semistandard prescription with fewer acupoints stimulated; because we focused on efficacy in the present study, we did not use personalized treatment planning that is based on the acupuncturists' experiences, which might cause performance bias. Second, blinding was not possible for patients in the WL group. This means that we may have overestimated both the differences between TA and WL groups and that between SA and WL groups owing to nonspecific effects of needling. Finally, our study did not test the comparative effect of acupuncture and standard therapy on migraine prophylaxis. Further studies are warranted to investigate this important issue, particularly in a pragmatic environment.

Conclusions

Compared with SA and WL control groups, TA manifested persisting superiority and clinically relevant benefits for at least 24 weeks in migraine prophylaxis, including reducing the number of migraine frequency and days with migraine, as well as decreasing pain intensity.

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REFERENCES

1. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache*. 2015;55(1):21-34.

2. Wang SJ. Epidemiology of migraine and other types of headache in Asia. *Curr Neurol Neurosci Rep*. 2003;3(2):104-108.

3. Pringsheim T, Davenport W, Mackie G, et al; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2012;39(2)(suppl 2):S1-S59.

4. Tfelt-Hansen PC. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2013;80(9):869-870.

5. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*. 2013;6(6):CD010611.

6. Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition: a guide for investigators. *Cephalalgia*. 2012;32(1):6-38.

7. Wells RE, Bertisch SM, Buettner C, Phillips RS, McCarthy EP. Complementary and alternative medicine use among adults with migraines/severe headaches. *Headache*. 2011;51(7):1087-1097.

8. Kristoffersen ES, Grande RB, Aaseth K, Lundqvist C, Russell MB. Management of primary chronic headache in the general population: the Akershus study of chronic headache. *J Headache Pain*. 2012;13(2):113-120.

9. Li Y, Liang F, Yang X, et al. Acupuncture for treating acute attacks of migraine: a randomized controlled trial. *Headache*. 2009;49(6):805-816.

10. Wang LP, Zhang XZ, Guo J, et al. Efficacy of acupuncture for acute migraine attack: a multicenter single blinded, randomized controlled trial. *Pain Med*. 2012;13(5):623-630.

11. Vincent CA. A controlled trial of the treatment of migraine by acupuncture. *Clin J Pain*. 1989;5(4):305-312.

12. Wang Y, Xue CC, Helme R, Da Costa C, Zheng Z. Acupuncture for frequent migraine: a randomized, patient/assessor blinded, controlled trial with one-year follow-up. *Evid Based Complement Alternat Med*. 2015;2015:920353.

13. Facco E, Liguori A, Petti F, et al. Traditional acupuncture in migraine: a controlled, randomized study. *Headache*. 2008;48(3):398-407.

14. Alecrim-Andrade J, Maciel-Júnior JA, Carnè X, Severino Vasconcelos GM, Correa-Filho HR. Acupuncture in migraine prevention: a randomized sham controlled study with 6-months posttreatment follow-up. *Clin J Pain*. 2008;24(2):98-105.

15. Linde K, Streng A, Jürgens S, et al. Acupuncture for patients with migraine: a randomized controlled trial. *JAMA*. 2005;293(17):2118-2125.

16. Diener HC, Kronfeld K, Boewing G, et al; GERAC Migraine Study Group. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurol*. 2006;5(4):310-316.

17. Alecrim-Andrade J, Maciel-Júnior JA, Cladellas XC, Correa-Filho HR, Machado HC. Acupuncture in migraine prophylaxis: a randomized sham-controlled trial. *Cephalalgia*. 2006;26(5):520-529.

18. Li Y, Zheng H, Witt CM, et al. Acupuncture for migraine prophylaxis: a randomized controlled trial. *CMAJ*. 2012;184(4):401-410.

19. International Classification of Headache Disorders, 2nd edition. *Cephalalgia*. 2004;24(suppl 1):9-160.

20. Chen J, Zhao L, Zheng H, et al. Evaluating the prophylaxis and long-term effectiveness of acupuncture for migraine without aura: study protocol for a randomized controlled trial. *Trials*. 2013;14:361.

21. Ulett GA, Han S, Han JS. Electroacupuncture: mechanisms and clinical application. *Biol Psychiatry*. 1998;44(2):129-138.

22. Chen Q, Wu X, Zhu H, et al. Analysis of acupuncture points used in clinical controlled trials of acupuncture for migraineurs. *J Chengdu Univ Trad Chinese Med*. 2007;30:1-9.

23. Yang XG, Ying L, Tian XP, Liang FR. Comments on selection of non-acupoints beyond meridians in studies of acupuncture and moxibustion. *J Tradit Chin Med*. 2010;30(4):309-313.

24. Li Y, Liang F, Yu S, et al. Randomized controlled trial to treat migraine with acupuncture: design and protocol. *Trials*. 2008;9:57.

25. Vickers AJ, Cronin AM, Maschino AC, et al; Acupuncture Trialists' Collaboration. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med*. 2012;172(19):1444-1453.

26. Foroughipour M, Golchian AR, Kalhor M, Akhlaghi S, Farzadfard MT, Azizi H. A sham-controlled trial of acupuncture as an adjunct in migraine prophylaxis. *Acupunct Med*. 2014;32(1):12-16.

27. Schliessbach J, van der Klift E, Arendt-Nielsen L, Curatolo M, Streitberger K. The effect of brief electrical and manual acupuncture stimulation on mechanical experimental pain. *Pain Med*. 2011;12(2):268-275.

28. Zheng Z, Feng SJ, Costa Cd, Li CG, Lu D, Xue CC. Acupuncture analgesia for temporal summation of experimental pain: a randomised controlled study. *Eur J Pain*. 2010;14(7):725-731.

29. Tsui P, Leung MC. Comparison of the effectiveness between manual acupuncture and electro-acupuncture on patients with tennis elbow. *Acupunct Electrother Res*. 2002;27(2):107-117.

30. Baeumler PI, Fleckenstein J, Benedikt F, Bader J, Irnich D. Acupuncture-induced changes of pressure pain threshold are mediated by segmental inhibition: a randomized controlled trial. *Pain*. 2015;156(11):2245-2255.

31. Hansen JM, Goadsby PJ, Charles A. Reduced efficacy of sumatriptan in migraine with aura vs without aura. *Neurology*. 2015;84(18):1880-1885.

32. Vickers AJ, Rees RW, Zollman CE, et al. Acupuncture for chronic headache in primary care: large, pragmatic, randomised trial. *BMJ*. 2004;328(7442):744.