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A randomized controlled trial of acupressure as an adjunctive therapy to sodium valproate on the prevention of chronic migraine with aura

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Abstract

Background: The primary objective of the present study was to evaluate the efficacy and safety of using acupressure as an adjunctive therapy to sodium valproate (SV) combined with acupressure (ASV) on the prevention of chronic migraine with aura (CMA).

Methods: A total of 98 patients with CMA were randomly divided into an intervention group and a control group, with 49 patients in each group. The patients in the intervention group received ASV, while the participants in the control group received SV alone. The primary outcome was measured by the numeric rating scale (NRS). The secondary outcomes including frequency of migraine attacks, the times of using analgesics, and quality of life, measured by the short-form 36 Health Survey Scale (SF-36) score. In addition, adverse events (AEs) were also recorded throughout the trial. The outcomes were measured at the end of the 8-week treatment, and 4-week follow-up.

Results: After the 8-week treatment and 4-week follow-up, ASV efficacy was not greater than that of SV alone regarding pain relief, as measured using the NRS, and frequency of migraine attacks, consumption of analgesics, and quality of life, as measured using the SF-36. However, ASV can significantly reduce the nausea when compared with SV (P = .04).

Conclusion: The present results indicate that ASV can decrease migraine-related nausea during treatment, but cannot relieve pain or enhance quality of life in patients with CMA.

Abbreviations: AEs = adverse events, ARB = angiotensin receptor blockers, ASV = acupressure combined with sodium valproate, BP = body pain, CCB = calcium channel blockers, CMA = chronic migraine with aura, DU20 = *Baihui*, EX-HN5 = *Taiyang*, GB 20 = *Fengchi*, GH = general health, ICHD-II = International Classification of Headache Disorders, ITT = intention to treat, MCS = mental component summary, MH = mental health, NRS = numeric rating scale, PC6 = *Neiguan*, PCS = physical component summary, PF = physical functioning, RE = role emotional, RP = role physical, SF = social functioning, SF-36 = short-form 36 health survey scale, SV = sodium valproate, VT = vitality.

Keywords: acupressure, efficacy, migraine, safety, sodium valproate

1. Introduction

Migraine is a very common disorder, often characterized by recurrent, unilateral, throbbing headaches with moderate or severe intensity. It is often aggravated by routine physical activities, and is associated with the nausea, vomiting, photophobia, and phonophobia.[1] It is the third-to-most common disorder with a worldwide prevalence of 14.7%, thereby rendering it a very important social issue for public health intervention.[2] This condition occurs mainly in women, with a female:male ratio of approximately 3:1.[3,4] If not treated effectively, it can result in various comorbidities such as psychiatric disorders, sleep disorders, and other chronic pain-related conditions, which greatly affects quality of life.[5–14]

Migraine is often classified into 2 categories based on acute episodes and chronic remission periods. Both specific and nonspecific therapies have been used to treat acute migraine. However, for chronic migraine, treatment is mainly aimed at the prevention of its occurrence. Several medications, such as angiotensin receptor blockers (ARB), antidepressant drugs, calcium channel blockers (CCB), beta-receptor blockers, and other interventions, are effective for the chronic migraine prevention. However, owing to their severe side effects, these drugs are not widely used to treat patients with chronic migraine.[15] Thus, it is necessary to explore alternative therapy leading to few or no adverse events (AEs), for the prevention of migraine.

Among the available drugs, sodium valproate (SV), having been approved by the FDA, is also used for managing chronic migraine. It also has been indicated as a prophylactic monotherapy to treat chronic migraine and reported to greatly reduce headache frequency and intensity.[16] Additionally, previous studies also reported that acupressure played a promising role in preventing migraine without resulting in AEs.[17,18] However, no studies have reported to use acupressure as an adjunctive therapy to SV to prevent migraine. Thus, in this study, we aimed to explore the efficacy and safety of acupressure as an adjunctive therapy to SV (ASV) for relieving pain in patients with chronic migraine with aura (CMA). We hypothesized that for the treatment of CMA, the effect of ASV would be superior to the effect of SV alone.
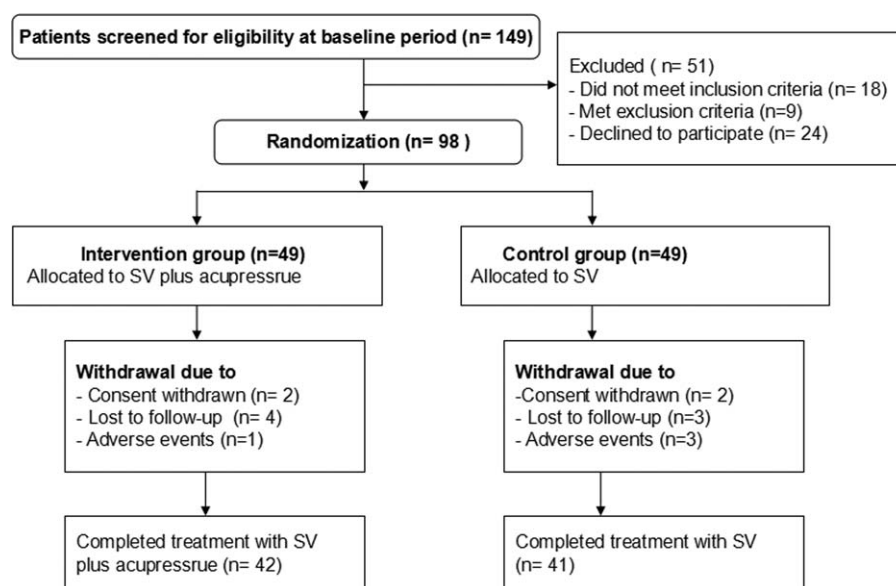
Figure 1. Flow diagram of study selection.

2. Methods and materials

2.1. Study design

This randomized controlled trial was approved by the ethics committee of Beijing ChaoYang Hospital and was conducted at the same hospital from February 2015 to January 2017. Ninety-eight eligible patients were randomly divided into an intervention group or a control group at a ratio of 1:1. Participants in the intervention group received ASV, while those in the control group received SV alone. Outcomes were measured at the end of 8-week treatment, and 4-week follow-up.

2.2. Patients

The patients in this study met the following criteria: diagnosis of migraine with aura, according to the second edition of diagnostic criteria of the International Classification of Headache Disorders (ICHD-II)[19]; age between 18 and 60 years; a history of migraine with aura as defined by the criteria of ICHD-II in 2004 for more than 12 months; more than 2 average migraine attacks each month at baseline period; no migraine prevention therapies were given, including acupressure, and drugs like ARB, CCR, etc, within 1 month prior to enrollment in the study; and provision of informed consent prior to enrollment in the study. However, patients were excluded if they were pregnant or breastfeeding; took analgesics more than 10 times each month; took SV 1 month prior to this study; combined with psychiatric, cardiovascular, cerebrovascular, and other system diseases, etc; and allergic to the SV.

2.3. Randomization and blinding

The stratified randomization sequence was operated by a computerized number generated using SAS package (Version 9.3; SAS Institute Inc, Cary, NC). All the participants were randomly assigned to the intervention group or sham group at a 1:1 ratio. The randomization assignments and their allocation information were concealed in sequentially numbered, opaque, sealed envelopes. The outcome assessors and data analysts were masked to the treatment allocation information throughout the study.

2.4. Intervention

The participants in both the groups were given SV, 800 mg/d for 8 weeks. In addition, patients in the intervention group also received acupressure at acupoints *Baihui* (DU20), *Fengchi* (GB 20), and *Taiyang* (EX-HN5), and *Neiguan* (PC6) of attacked side for 20 minutes, with each point 5 minutes daily, 3 times weekly for a total of 8 weeks.

2.5. Outcome measurements

The primary outcome of the intensity of CMA pain was measured by numeric rating scale (NRS). The secondary outcomes included the frequency of migraine attacks, the times of using analgesics, and quality of life, as measured by the short-form 36 Health Survey Scale (SF-36) score. SF-36 consists of 10 domains as follows: mental health (MH), role emotional (RE), social functioning (SF), vitality (VT), general health (GH), body pain (BP), role physical (RP), physical functioning (PF), mental component summary (MCS), and physical component summary (PCS). In addition, any AEs were recorded to evaluate the safety of ASV. The outcomes were evaluated at the end of 8-week treatment and 4-week follow-up after the treatment.

2.6. Statistical analysis

All data in the present study were analyzed by the SAS package (Version 9.3; SAS Institute Inc, Cary, NC). Sample size was calculated based on the difference in mean change of the NRS score with $\alpha = 0.5$, $\beta = 0.8$, and assuming a 15% drop-out rate. Therefore, the required sample size of this study was estimated to be 98 patients, with 49 assigned to each group. *t* test or Mann–Whitney rank sum test was used to analyze the continuous data. Pearson χ^2 test or Fisher exact test was used to analyze the categorical data. All outcome data were analyzed by intention-to-treat (ITT). The statistical significance level was set at $P < .05$.

3. Results

One hundred forty-nine patients were screened for eligibility at baseline period (Fig. 1). Of those 149 subjects, 51 were excluded

Table 1

Baseline characteristics of study population.

Parameters	Intervention group (n=49)	Control group (n=49)	P value
Mean age, y	38.4 (10.7)	39.2 (11.3)	.72
Sex (female/male)	35/14	38/11	.49
Race (Chinese)	49 (100.0)	49 (100.0)	1.00
Ethnicity (Han)	49 (100.0)	49 (100.0)	1.00
Duration of CMA, mo	18.3 (6.8)	19.5 (7.1)	.35
Migraine attacks	3.4 (1.2)	3.5 (1.3)	.69
NRS score	5.8 (1.3)	6.0 (1.4)	.46
Analgesic consumptions (times)	1.4 (1.5)	1.5 (1.7)	.76
SF-36			
PF	92.4 (7.8)	92.7 (8.0)	.85
RP	63.5 (24.6)	64.2 (26.8)	.89
BP	53.3 (14.1)	52.9 (13.8)	.89
GH	60.7 (15.8)	61.0 (16.4)	.93
VT	72.8 (13.9)	71.9 (14.1)	.75
SF	76.2 (13.7)	75.9 (13.4)	.91
RE	67.5 (22.4)	65.8 (21.6)	.70
MH	72.7 (14.6)	71.8 (14.1)	.76
MCS	73.1 (14.5)	71.7 (16.2)	.65
PCS	67.9 (14.3)	68.3 (14.7)	.89

Data are present as mean ± standard deviation or number (%).
BP = body pain, CMA = chronic migraine with aura, GH = general health, MCS = mental component summary, MH = mental health, NRS = numeric rating scale, PCS = physical component summary, PF = physical functioning, RE = role emotional, RP = role physical, SF = social functioning, SF-36 = short-form 36 health survey scale, VT = vitality.

because they did not meet the inclusion criteria (n=18), met the exclusion criteria (n=9), and declined to participate this study (n=24). Thus, 98 patients were randomly allocated to the intervention group or control group, each group 49 patients. All outcome data were analyzed using ITT approach. However, 15

patients withdrew from the study, because of the consent withdrawal (n=4), lost to follow-up (n=7), and adverse events (n=4) (Fig. 1). The baseline characteristics of all patients are shown in Table 1. No significant differences were found in all baseline characteristics between 2 groups (Table 1).

All outcome data were measured by the change of differences from baseline (with a 95% confidence interval) to assess the efficacy and safety of ASV at the end of 8-week treatment, and 4-week follow-up after the treatment (Table 2). The results of all outcome measurements are summarized in Tables 2 and 3. Compared with SV, ASV neither decreased the intensity of the pain associated with CMA, as measured by NRS, frequency of migraine attacks, and the times of using analgesics, nor enhanced quality of life, as measured by SF-36.

Additionally, no significant differences in AEs were found between 2 groups, except ASV significantly reduced the frequencies of nausea, compared with SV alone (n=0.04) (Table 4).

4. Discussion

The present results did not confirm the hypothesis that compared with SV alone, ASV can show promising preventive outcomes after 8-week treatment in patients with CMA. To our knowledge, this study is the first randomized controlled trial using acupressure as an adjunctive therapy for preventing CMA in individuals in China. The findings did not indicate positive effects of ASV in preventing CMA in individuals.

Previous studies have reported favorable effects of acupressure for treating patients with migraine and in preventing its occurrence.[18,19] One study recruited 40 women without aura and found that acupressure at PC6 can control the treatment of migraine-associated nausea.[19] Another study reported that acupressure effectively relieved migraine and stress-related

Table 2

Outcome measurements for pain relief (differences from baseline).

Outcome measurements	8-week treatment			4-week follow-up		
	Intervention group (n=49)	Control group (n=49)	P value	Intervention group (n=49)	Control group (n=49)	P value
NRS score	−3.5 (1.0)	−3.3 (1.2)	.37	−3.7 (1.1)	−3.6 (1.4)	.69
Migraine attacks	−2.0 (1.2)	−1.9 (1.1)	.67	−1.8 (1.1)	−1.7 (0.9)	.62
Analgesic consumption (times)	−0.8 (1.4)	−0.7 (1.2)	.70	−0.7 (1.3)	−0.7 (1.1)	.95

Data are present as mean ± standard deviation.
NRS = numeric rating scale.

Table 3

Outcome measurements for quality of life, measured by SF-36 (differences from baseline).

Outcome measurements	8-week treatment			4-week follow-up		
	Intervention group (n=49)	Control group (n=49)	P value	Intervention group (n=49)	Control group (n=49)	P value
PF	1.2 (0.5)	1.0 (0.6)	.07	1.1 (0.5)	1.0 (0.4)	.27
RP	10.4 (2.5)	9.7 (2.1)	.13	10.1 (2.6)	9.5 (2.0)	.20
BP	18.2 (3.3)	18.7 (3.5)	.43	17.9 (3.4)	18.4 (3.7)	.49
GH	7.3 (1.8)	6.8 (1.6)	.15	7.1 (1.9)	6.6 (1.7)	.17
VT	3.8 (0.7)	3.6 (0.6)	.13	3.6 (0.6)	3.4 (0.7)	.14
SF	5.3 (1.4)	5.7 (1.6)	.19	5.2 (1.5)	5.5 (1.5)	.32
RE	9.9 (1.7)	10.4 (1.8)	.16	10.1 (1.9)	10.3 (1.8)	.59
MH	3.4 (0.6)	3.2 (0.6)	.33	3.5 (0.7)	3.4 (0.6)	.45
MCS	5.8 (1.6)	5.5 (1.5)	.34	5.9 (1.7)	5.7 (1.6)	.55
PCS	11.2 (2.3)	10.6 (2.1)	.18	10.9 (2.4)	10.5 (2.0)	.37

Data are present as mean ± standard deviation.
BP = body pain, GH = general health, MCS = mental component summary, MH = mental health, PCS = physical component summary, PF = physical functioning, RE = role emotional, RP = role physical, SF = social functioning, SF-36 = short-form 36 health survey scale, VT = vitality.

Table 4

Adverse events reported in both groups, n (%).

Adverse event	Intervention group (n = 49)	Control group (n = 49)	P value
Nausea	1 (2.0)	8 (16.3)	.04
Vomiting	0 (0)	4 (8.2)	.13
Worsening migraine	0 (0)	1 (2.0)	.50
Diarrhea	1 (2.0)	1 (2.0)	1.00
Hair loss	4 (8.2)	6 (12.2)	.51
Back pain	0 (0)	2 (4.1)	.29
Neck pain	1 (2.0)	3 (6.1)	.33
Flu-like syndrome	2 (4.1)	4 (8.2)	.41
Pruritus	1 (2.0)	1 (2.0)	1.00

Data are present as number (%).

headaches.[18] Moreover, acupressure should replace pharmacotherapy for outpatients, owing to its ease of application and no toxic effects.[18]

In this study, no significant differences were found in the pain associated with CMA, as measured using the NRS, the frequency of migraine attacks, and the consumption of analgesics in the intervention group than in the control group. These results indicate that ASV can neither relieve pain in patients with CMA nor improve quality of life, as measured using the SF-36. However, we found that ASV significantly reduced the frequency of migraine-related nausea.

This study has the following limitations. First, the observed effect in this study is the synergistic effect of acupressure and SV, and not acupressure alone, because it was impossible for all participants to interrupt their pain medications. Second, this is a single-center study and only included individuals of the Chinese Han ethnicity; hence, our results may not be generalizable to other hospitals and ethnicities in China. Third, patients were not blinded in this study, which might also have affected our results.

5. Conclusion

Our results indicate that ASV can neither reduce the intensity of the pain in CMA nor improve quality of life, except that it can significantly decrease the frequency of migraine-related nausea.

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