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Acupuncture for menstrual migraine: a systematic review

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ABSTRACT

Background and objective In clinical practice, the evidence of acupuncture used as a treatment for migraine without aura is employed interchangeably to guide treatment for menstrual migraine. However, its effect and safety are not substantiated. This study aimed to assess the efficacy of acupuncture on the frequency and pain intensity of menstrual migraine.

Methods We searched PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI) and other two Chinese databases from their inception to 1 May 2019. This study included randomised controlled trials of women with menstrual migraine receiving acupuncture or a valid control. Two reviewers independently completed study selection, data extraction and risk of bias assessment. We combined data with a fixed-effect model in RevMan. Clinical outcomes included migraine frequency and duration, headache intensity, and adverse events.

Results Thirteen studies with 826 subjects were included, 9 of which had data suitable for meta-analyses. Current evidence showed that acupuncture was not superior to sham acupuncture in reducing monthly migraine frequency and duration, average headache intensity, and analgesic use at completion of treatment or follow-up. Pooled data demonstrated a significant improvement in mean headache intensity in the acupuncture group compared with drugs. However, all studies were underpowered and associated with moderate to high risk of bias. No serious adverse event was related to acupuncture treatment.

Conclusions There is no convincing evidence to support the use of acupuncture in treating menstrual migraine. Acupuncture cannot yet be recommended to patients with menstrual migraine until more solid evidence is produced.

Trial registration number CRD42019119337.

INTRODUCTION

An estimated 3%–7.6% of the German and Norwegian populations experience

menstrual migraine (MM).^{1 2} The onset of migraine attack is pathologically associated with menstruation and could be related to drastic fluctuations in sex hormones (such as progesterone and oestrogen) throughout the menstrual cycle.^{3 4} The International Classification of Headache Disorders (ICHD) defined MM as migraine without aura occurring on days –2 to +3 of menstruation in at least two out of three menstrual cycles.⁵ Two subtypes of MM can be further diagnosed in clinical setting, namely pure menstrual migraine (PMM) and menstrually related migraine (MRM). According to the 2017 Migraine in America Symptoms and Treatment (MAST) study, only 4.3% of female migraineurs are patients with PMM, but 38% who are MRM sufferers are more likely to experience moderate-to-severe headache-related disability and to report attack-related allodynia than women with PMM or non-menstrual migraine.⁶ MM often induces more severe pain, longer disease course and more comorbid symptoms, and is associated with relatively low rate of response to treatment.^{7 8} The MAST study demonstrated that MRM led to the highest overall level of pain interference among all women with migraine.⁹ Conventional treatments for MM are triptans, non-steroid anti-inflammatory drugs, combined therapy, contraceptives and hormones, which are frequently prescribed for acute, short-term treatments and daily prevention.^{7 10}

Many patients tend to pursue better clinical efficacy by seeking complementary and alternative therapy in their daily life.¹¹ Acupuncture is a non-pharmacological treatment that has been used to alleviate pain for over a thousand years. Its analgesic effect on a number of pain conditions has been well documented, such as knee pain, headache and low back pain.¹² Such clinical evidence is frequently used interchangeably in the treatment of MM.

However, until now the efficacy and safety of acupuncture for MM are underevaluated. As available clinical studies are still emerging, we performed this systematic review, following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (<http://www.prisma-statement.org/>), to synthesise current evidence and assess the efficacy of acupuncture in treating women with MM.

METHODS

Criteria for considering studies in this review

Types of studies

Randomised controlled trials were included in this study without language or publication status restrictions. Any study with a sample size of fewer than 10 participants can be included in this systematic review, but will be excluded from relevant meta-analyses due to concerns of potentially high risk of publication bias and an inflated magnitude of OR. In the study selection phase, we found no studies with fewer than 10 participants.

Types of participants

This study included female participants who were diagnosed with MM, either PMM or MRM, regardless of their age, race, sex or marital status. Only studies with explicit diagnosis of MM were included in this trial. However, studies on general migraine without aura that did not take measures to isolate MM from the population or even mentioned menstrual migraine in their study protocol and final report were excluded. Those with overt acupuncture contraindications (bleeding disorders and anticoagulation) were excluded.

Types of interventions

Experimental interventions

The experimental arm was explicitly claimed as a modality of acupuncture or its related acupoint stimulation such as needle, heat, electricity, physical pressure, laser and so on. The combinational use of acupuncture to medications was considered in this review. Studies that compared the efficacy of different forms of acupuncture were excluded.

Control interventions

The following control groups were considered: (1) acupuncture versus sham devices; (2) acupuncture versus routine care; (3) acupuncture versus medications; and (4) acupuncture in addition to active treatment (medications conventionally used for immediate pain relief) versus active treatment alone.

Types of outcome measures

Primary outcome

The primary outcome was the number of migraine attacks per month at completion of acupuncture treatment.

Box 1 Search strategy used in PubMed

► (((((((((((acupuncture[(MeSH Major Topic)]) OR acupuncture therapy[(MeSH Subheading)]) OR electroacupuncture[Title/Abstract]) OR electroacupuncture therapy[Title/Abstract]) OR manual acupuncture[Title/Abstract]) OR acupressure[Title/Abstract]) OR auricular acupressure[Title/Abstract]) OR moxibustion[Title/Abstract]) OR dry needle[Title/Abstract]) OR acupoint[Title/Abstract])) AND (((((((migraine disorders[(MeSH Major Topic)]) OR migraine[Title/Abstract]) OR menstrual migraine[Title/Abstract]) OR menstrual[Title/Abstract]) OR menstrually[Title/Abstract]) OR menses[Title/Abstract]) OR menstruation[Title/Abstract])) AND (((((((randomized controlled trial[(Publication Type)]) OR controlled clinical trial[(Publication Type)]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR clinical trials[(MeSH Major Topic)]) OR randomly[Title/Abstract]) OR trial[(Title)])) NOT ((animals[(MeSH Major Topic)]) NOT humans[(MeSH Major Topic)]))

Secondary outcomes

Secondary outcomes included (1) days with migraine per month; (2) mean headache intensity measured by the Visual Analogue Scale (VAS); (3) amount of headache medication use; (4) number of migraine attacks per month at the last post-treatment visit (3–6 months); and (5) adverse events (AEs).

Search methods for identification of studies

Five major online databases, namely PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang and SinoMed databases, were searched without language or publication status restrictions from their inception to 1 May 2019. Only randomised controlled trials that evaluated the effect of acupuncture in comparison with a valid comparator were included. The search strategy for PubMed and CNKI is provided in [Box 1](#). Moreover, the list of all identified publications including relevant systematic reviews (related to acupuncture treating migraine) and meta-analyses was investigated to further identify additional trials. Missing data for studies with useful but incomplete data were obtained from the contact trial personnel for data synthesis.

Data collection and analysis

Selection of studies

The list of publication records generated from the literature search was imported to EndNote V.X8.1 (Clarivate Analytics, Philadelphia, USA). Two reviewers independently assessed the eligibility of each record according to the inclusion criteria. Preliminary screening included reading the title and abstract only, and further evaluation was based on reading the full text of each study. The reference list of related systematic review was checked to identify potentially missing trials.

Data extraction and management

Two reviewers used the Cochrane Data Collection Form, with modifications in intervention specifics, to extract data on the study characteristics of each report. This acquisition form included four major domains: citation information, design (design, participants, trial methods, duration, intervention details, caregiver information), results (outcome measures, AEs) and conclusion. Features of acupuncture used in MM treatment were identified. Any disagreement/inconsistency on the eligibility of a study or the information extracted from one study was resolved by involvement of a senior reviewer. The predefined inclusion/exclusion criteria and/or original full text of a study were revisited for confirmation.

Assessment of risk of bias in included studies

The risk of bias for each included trial was evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials. The required parameters for the six domains were added into RevMan for trial assessment (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias if necessary). The trial was rated high, unclear or low risk of bias according to each domain.

Qualitative analysis of the characteristics of acupuncture interventions

We have summarised the characteristics of the included studies according to the metadata of the study, including the origin of the study, trial status (completed or ongoing), sample size, characteristics of participants (age, disease course and subtype, number of patients in the experimental and control group), acupuncture type (electroacupuncture or manual), treatment frequency and duration, control arm, and primary outcome (table 1). We further employed the R programming application called 'tm: Text Mining Package' (<https://cran.r-project.org/web/packages/tm/index.html>) to identify the pattern of acupoint selection during the treatment of MM. The acupoint prescription in each study was imported as an individual document to R platform (both the Chinese name and English code of each acupoint) to form a data set. The 'data.frame()' function was used to build the fundamental data structure. We constructed data matrix using the 'DocumentTermMatrix()' function and further identified the correlation coefficient between acupoints using 'Find-Assocs()' function. The stimulation approaches, time course and qualifications of acupuncturist were also summarised bibliographically.

Adequately reporting acupuncture treatment is essential for the interpretation, evaluation and reproduction of such trials. The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) is a well-recognised tool that ensures adequate reporting of acupuncture in clinical trials.¹³ The STRICTA

checklist, containing 6 reporting categories and 17 items, was used to evaluate the quality of reporting of each trial. A score of 1 was given to each item if designated information was reported in full, and 0 otherwise. Specifically, item (4a) of STRICTA reports other treatments in addition to acupuncture. However, for some trials, there were no additional interventions used, in which case this item was marked as 'N/A' and not included in the sum of score. A reporting quality rate was calculated by the following formula: *reporting quality rate = sum of reported items / total score * 100%*. (*The total score is equal to 17 or 16, depending on whether additional treatment was used. If used, the total score was 17, and 16 otherwise.)

Measures of treatment effect

Clinical data were imported into RevMan V.5.3 software for data synthesis. RevMan V.5.3 was used to synthesise and statistically analyse efficacy data. Dichotomous data were analysed using risk ratio with 95% CI. For continuous outcomes, data were analysed using a weighted mean difference (WMD) or standard mean difference (SMD) of effect size with 95% CI. WMD was used for the same scale or same assessment instrument; SMD was used for different assessment tools.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Available data were analysed following confirmation by investigators that the data were missing 'at random'. If missing data were inaccessible, we imputed the missing data with replacement values, treating these as if they were observed. The last observation carried forward imputation method was used to assume a missing value, and then an intention-to-treat analysis was performed. Moreover, if possible, we performed sensitivity analyses to assess how sensitive the results were to reasonable changes in the assumptions that were made.

Assessment of heterogeneity

χ^2 tests were performed in the forest plot using RevMan V.5.3 to investigate statistical heterogeneity, and a p value less than 0.10 was considered significant, in line with the Cochrane Handbook. Moreover, the I^2 value was calculated to quantify the impact of statistical heterogeneity on the meta-analysis.

Assessment of reporting bias

A funnel plot was generated to observe for reporting bias when more than 10 trials were included in each meta-analysis.

Table 1 Characteristics of included studies and the risk of bias associated with each study

Study identification	Participants		Interventions		Timing of intervention	Primary outcome	Risk of bias summary					
	Age (years)	Course (years)	Acupuncture	Control			①	②	③	④	⑤	⑥
Ling Cao ²³	A: 33.82±4.34 C: 33.86±4.85	A: 0.25–11 C: 0.17–13	Electroacupuncture; 14 sessions in 2 weeks	NSAIDs (Celebrex)	Premenstruation	Number of patients with improvement	+	+	+	?	+	+
Lina Chen <i>et al</i> ²⁰	A: 29.81±4.32 C: 28.43±4.63	A: 0.02–8 C: 0.01–9	Manual acupuncture; 14 sessions in 2 weeks	NSAIDs (Celebrex)	Acute treatment	Time for headache relief	+	+	+	?	+	+
Xiaoting Fan <i>et al</i> ¹⁸	A: 26.65±4.58 C: 26.10±4.81	A: 3.50±1.20 C: 3.20±0.90	Moxibustion; 21 sessions in 3 weeks	NSAIDs (ibuprofen)	Premenstruation	Pain intensity measured by VAS	?	+	+	?	+	+
Lj ²²	A: 29.77±5.43 C: 31.31±5.65	A: 1.13±0.44 C: 1.04±0.58	Manual acupuncture; 18 sessions in 3 weeks	NSAIDs (ibuprofen)	Intramenstruation and premenstruation	Pain intensity measured by PRI	+	+	+	+	+	+
Linde <i>et al</i> ¹⁶	A: 35.20±7.5 S: 37.40±8.6	Not reported	Electroacupuncture; 9 sessions in 3 weeks	Sham acupuncture (sham device)	Premenstruation	Monthly migraine attack frequency	+	?	+	+	+	+
Liu ²⁶	A: 26.40±1.71 C: 25.30±2.01	A: 6.04±0.51 C: 5.22±1.01	Manual acupuncture; 28 sessions in 4 weeks	NSAIDs (aspirin)	Premenstruation	Pain intensity measured by VAS	+	+	+	?	+	+
Lv ¹⁹	A: 29.72±5.33 C: 28.57±5.43	A: 6.17±1.81 C: 6.42±2.51	Manual acupuncture; 21 sessions in 2 weeks	Flunarizine	Intramenstruation and premenstruation	Pain index score	+	+	+	?	+	+
Ma ¹⁷	A: 18–39 C: 19–40	A: 1–4 C: 1–6	Manual acupuncture; 9 sessions in 9 days	Flunarizine	Intramenstruation and premenstruation	Number of patients with improvement	+	+	+	+	+	+
Sun ²⁵	17–45	0.25–15	Manual acupuncture; 15 sessions in 3 weeks	NSAIDs (ibuprofen)	Premenstruation	Number of patients with improvement	+	+	+	+	+	+
Liqiong Tian ²⁴	A: 30.22±3.21 S: 31.65±3.12	A: 2.14±1.22 S: 2.12±0.22	Manual acupuncture; 20 sessions in 2 cycles	Sham acupuncture (non-acupoint)	Intramenstruation and premenstruation	Number of patients with improvement	?	+	?	?	+	+
Lihong Wang <i>et al</i> ²¹	A: 31.60±9.60 C: 32.60±8.90	A: 0.98±0.33 C: 1.07±0.66	Electroacupuncture; 24 sessions in 3 cycles	Flunarizine	Intramenstruation and premenstruation	Pain intensity measured by VAS	+	?	+	?	+	+
Yu and Salmoni ¹⁵	22–52	Not reported	Manual acupuncture; 9 sessions in 3 cycles	Sham acupuncture (irrelevant acupoint)	Premenstruation	Monthly migraine attack days	+	?	?	?	+	?
Zhou ¹⁴	A: 33.10±6.14 S: 33.27±6.87	A: 7.40±6.31 S: 6.48±4.66	Electroacupuncture; 27 sessions in 3 cycles	Sham acupuncture (non-acupoint)	Intramenstruation, premenstruation and postmenstruation	Monthly migraine attack frequency	+	+	?	+	+	+

① random sequence generation (selection bias); ② allocation concealment (selection bias); ③ blinding of participants and personnel (performance bias); ④ blinding of outcome assessment (detection bias); ⑤ incomplete outcome data (attrition bias); ⑥ selective reporting (reporting bias).

⊕ low risk of bias; ⊕ unclear risk of bias; ⊕ high risk of bias.

A, acupuncture; C, control; NSAID, non-steroidal anti-inflammatory drug; PRI, Pain Rating Index; S, sham; VAS, Visual Analogue Scale.

Data synthesis

Data were synthesised and analysed depending on the level of statistical heterogeneity. If the heterogeneity test showed little or no statistical heterogeneity in these trials, the fixed-effects model was used for the pooled data. The random-effects model was not used for data synthesis as no significant heterogeneity was detected (all $I^2 < 50\%$).

Subgroup analysis and investigation of heterogeneity

If there was considerable heterogeneity in the trials ($I^2 \geq 75\%$), we identified the source of heterogeneity from both clinical and methodological aspects, and a narrative, qualitative summary was provided. If data were available, a subgroup analysis was conducted to address the heterogeneity according to selected study characteristics.

Sensitivity analysis

Sensitivity analysis was used to monitor the robustness of the primary decision made in the review process from multiple nodes, such as small studies, methodological weaknesses and missing data. The sensitivity analysis involved two steps, as suggested by the Cochrane Handbook: first including all studies as the primary meta-analysis does, and second including those that were definitely known to be eligible.

RESULTS

Results of literature search and screening

Initial search with duplicates removed yielded 428 publication records, including 426 records from electronic databases and 2 records from books/journals. Preliminary screening excluded 307 records by title, due to either not being a randomised trial or not being related with migraine. Subsequent abstract reading in relay to preliminary screening excluded 99 records, due to studies either enrolling subjects without MM ($n=77$) or not being a randomised controlled trial ($n=22$). The final screening was based on checking the full-text report of the trial, further excluding eight studies due to duplication, unspecified headache, unmatched acupuncture therapy or control arm (figure 1).

Characteristics of included studies

Clinical characteristics of participants

The review included 13 completed trials^{14–26} and 1 ongoing trial.²⁷ These studies were from Germany,¹⁶ Canada¹⁵ and China.^{14 17–27} Due to data availability, only 13 finished trials with 826 participants (aged between 17 and 52 years) were included and assessed in further analysis. Of these participants, 641 entered medication-controlled trials (9 trials, $n_{\text{acupuncture}}=330$, $n_{\text{medication}}=311$) and the remaining 185 were included in sham acupuncture-controlled trials (4 trials,^{14–16 24} $n_{\text{acupuncture}}=98$, $n_{\text{sham}}=87$). All participants were diagnosed at baseline with one of the two types of MM according

to the ICHD classification (338 subjects) or some national standards in China (488 subjects). According to ICHD-II/III, there were 28 participants with MRM, 68 participants with PMM and 242 participants with unspecified MM included in this study.

Risk of bias for included studies

Among the 13 completed studies, no study was associated with low risk of bias. Only three^{14–16} were identified to have unclear risk of bias, while the remaining ten studies had high risk of bias. The bias resulted from the lack of allocation concealment (selection bias), blinding of participants and personnel (performance bias), and blinding of outcome assessment (detection bias). The details of the risk of bias for each study are shown in table 1.

Features of acupuncture used in MM treatment

A total of 11 studies applied manual acupuncture, among which 3 additionally administered electric current stimulation,²³ moxibustion²² and auricular acupressure,¹⁷ respectively. One study (Xiaoting Fan *et al*¹⁸) used moxibustion treatment only and another (Lihong Wang *et al*²¹) applied transcutaneous electric nerve stimulation plus acupoint injection. A total of seven studies used fixed acupuncture treatment scheme and five studies employed a semistandardised acupuncture protocol. Text mining showed that the most frequently used acupoints were Taichong (LR3), Sanyinjiao (SP6), Shuaigu (GB8), Baihui (DU20), Fengchi (GB20), Taiyang (EX-HN5), Hegu (LI4) and Zusanli (ST36) (figure 2). During acupuncture, Deqi was achieved by all 11 studies. Further correlation analysis between acupoints showed that when selected for treating MM, LR3 has a higher correlation coefficient with SP6 ($r=0.66$), LI4 ($r=0.56$) and GB20 ($r=0.40$). SP6 was highly correlated with GB20 ($r=0.48$) and LI4 ($r=0.4$). DU20 was closely associated with EX-HN5 ($r=0.53$) (table 2). The results indicated that common acupoint combinations of LR3+SP6, SP6+GB20 and DU20+EX-HN5 were used synergistically to reduce MM in these trials.

With regard to needle manipulation methods, twirling and rotating were performed to achieve an optimal effect, as reported in six studies.^{17 19 22–24 26} The frequency of twirling or rotation varied from 80 times to 200 times per minute. During retention, the needles were manipulated two to three times with a 10 min interval. Premenstrual treatment was reported in all trials, except for one study²⁰ which administered acupuncture at the time when pain attacked. Four studies^{17 19 22 24} provided acupuncture treatment during menses in addition to premenstrual period. In another two studies,^{14 23} acupuncture was administered during the whole menstrual cycle. The frequency of premenstrual acupuncture was three to seven times per week for three menstrual cycles.

Figure 1 Study flow chart.

Reporting quality of the practice of acupuncture

The average reporting quality rate of 11 studies that applied acupuncture treatment is 76.60%, indicating a moderate quality of reporting. A further analysis of each category showed that the rationales of acupuncture (reporting rate=100%) and the treatment regimen (100%) were satisfactorily reported by all studies. The details of needling were also reported with sufficient information, except that the number of needle insertions per subject per session (9.09%) and the depth of insertion (27.27%) were only reported by few studies. The setting and context of treatment (9.09%), the qualification of acupuncturist (27.27%),

and the rationales of comparator (45.45%) were not adequately reported by most studies.

Efficacy of acupuncture for the treatment of MM as compared with sham control

Monthly migraine attack frequency

Due to substantial heterogeneity and insufficient number of studies, the data on migraine attack frequency could not be pooled. However, neither of the two trials^{14 16} that monitored the monthly migraine attack frequency showed a significant improvement in migraine attack frequency in association with true acupuncture at the completion of three-cycle treatment

Figure 2 Ranking of common acupoints frequently used in treating menstrual migraine.

when compared with sham acupuncture. Linde *et al*'s¹⁶ study measured the residual effect of acupuncture at 2 months and 6 months after treatment and also found no significant difference between the two groups.

Migraine days per month

Yu and Salmoni's¹⁵ study showed that acupuncture treatment was associated with a significant reduction in migraine days per cycle/month when compared with sham acupuncture both at the completion of treatment (n=18, MD: -1.84, 95% CI -3.07 to 0.60, p<0.05) and at 3 months after treatment (n=18, MD: -1.26, 95% CI -2.39 to 0.13, p<0.05). On the contrary, Linde *et al*'s¹⁶ study suggested no significant difference between acupuncture and sham acupuncture groups in migraine days per cycle/month during the whole course of treatment (n=28, MD: 0.69, 95% CI -0.08 to 1.46, p>0.05) or at 6 months after treatment (n=28, MD: 0.46, 95% CI -0.29 to 1.21, p>0.05).

Data from these two studies were not combined as a result of substantial heterogeneity.

Mean headache intensity

Pooled analysis suggested that acupuncture was not superior to sham acupuncture in reducing mean headache intensity (measured by VAS) either at the end of treatment (3 studies, n=101, MD: 0.25, 95% CI -0.41 to 0.91, p=0.45, I²=20%) or at 3+ months after treatment (2 studies, n=46, MD: -1.08, 95% CI -2.08 to 0.08, p=0.03, I²=0%)¹⁴⁻¹⁶ (figure 3). Another study indicated that acupuncture was associated with greater reduction in average migraine pain intensity than sham acupuncture at the end of treatment (n=59, MD: -1.09, 95% CI -1.64 to 0.54, p<0.05).²⁴ However, due to significant heterogeneity (I²=77%), it was excluded from data pooling during sensitivity analysis.

Table 2 Correlation coefficient for associations between acupoints used for menstrual migraine

	Taichong (LR3)	Sanyinjiao (SP6)	Shuaigu (GB8)	Baihui (DU20)	Fengchi (GB20)	Taiyang (EX-HN5)	Hegu (LI4)	Zusanli (ST36)
Taichong (LR3)	1	0.66*	0.03	—	0.40*	0.17	0.56*	—
Sanyinjiao (SP6)	0.66*	1	—	0.03	0.48*	0.03	0.40*	0.21
Shuaigu (GB8)	0.03	—	1	0.20	0.20	—	—	—
Baihui (DU20)	—	0.03	0.20	1	0.06	0.53*	—	0.12
Fengchi (GB20)	0.40*	0.48*	0.20	0.06	1	0.01	—	—
Taiyang (EX-HN5)	0.17	0.03	—	0.53*	0.01	1	0.16	0.12
Hegu (LI4)	0.56*	0.40*	—	—	—	0.16	1	0.19
Zusanli (ST36)	—	0.21	—	0.12	—	0.12	0.19	1

*Correlation coefficient ≥ 0.40 indicates a moderate correlation between two different acupoints.

Figure 3 Forest plot of comparison between acupuncture and sham acupuncture in mean headache intensity at the end of 3-month treatment.

Pain medication use

In Zhou's¹⁴ study, 10 participants in the true acupuncture group and 8 participants in the sham acupuncture group administered additional analgesic medications. In Linde *et al*'s¹⁶ study, no significant difference in the doses of monthly analgesic medication use was found between acupuncture and sham acupuncture groups either at the end of treatment ($n=28$, MD: 0.16, 95% CI -0.59 to 0.90, $p>0.05$) or at 6 months after treatment ($n=28$, MD: -0.34, 95% CI -1.09 to 0.41, $p>0.05$).

Efficacy of acupuncture for treatment of MM as compared with medication

Only five out of nine studies comparing acupuncture with analgesic medications reported on the average headache intensity (measured by VAS).^{17 18 21 22 26} Pooled analysis suggested that, immediately at the completion of treatment, acupuncture resulted in greater reduction in headache intensity than analgesic medications (5 studies, $n=362$, MD: -1.88, 95% CI -2.19 to -1.58, $p<0.00001$, $I^2=47\%$) (figure 4). The drugs used in these studies were ibuprofen^{18 22 26} and flunarizine.^{17 21} Two studies evaluated the persistence of the clinical effect and found a better effect with acupuncture than with medications at 3 and 6 months after treatment.^{17 21} Other outcomes were not evaluated by these studies.

Safety and AEs

Nine studies reported the incurrence of AEs during the trial process. No serious AE was reported by any of these studies. There were 22 AEs that occurred

in the acupuncture group and 34 AEs in the control group. The common AEs that were identified relevant to acupuncture treatment were in mild to moderate severity, including bleeding, subcutaneous haematoma, tingling sensation and pain, bruises, and vertigo. There were seven AEs associated with the sham acupuncture treatment, including bleeding at acupoint, subcutaneous haematoma, tenderness at acupoint and tiny bruises. These symptoms resolved rapidly after treatment. In the medication group, 27 AEs including stomach-ache, nausea and vomiting, heart burning sensation, dizziness, and sleepiness were reported.

DISCUSSION

This study is to date the first systematic review performed to evaluate clinical trials on the use of acupuncture to treat women with MM. Our study found that acupuncture was unlikely to cause greater reductions in migraine attack frequency/duration, pain intensity or drug use than sham control. Nevertheless, current evidence demonstrated that acupuncture is superior to analgesic medications in alleviating average headache intensity. Unlike analgesic medications, acupuncture was rather safe and only associated with minor AEs and required no additional treatment. The quality of evidence was generally low. All included studies were underpowered.

In clinical practice, patients with migraine/headache represent a considerable proportion of the population who uses acupuncture for pain management, and many patients accept acupuncture treatment willingly.²⁸⁻³⁰ Acupuncture in recent years has undergone a

Figure 4 Forest plot of comparison between acupuncture and medication in mean headache intensity at the end of 3-month treatment.

series of scientific assessment for its efficacy and safety in treating headache. At present, there is a growing body of evidence supporting the use of acupuncture in migraineurs.^{31–33} A systematic review by Linde *et al*³¹ showed that acupuncture as an adjuvant to symptomatic treatment of attacks reduces the frequency of headache. Moreover, there is evidence indicating that acupuncture is more effective than sham control and has equivalent effect as prophylactic drugs in preventing migraine attacks. When making clinical decisions, physicians and neurologists tend to assume previous evidence could be used interchangeably to convince patients with MM to pursue acupuncture treatment. However, our study synthesised 13 clinical trials including 826 subjects and found that current evidence was not able to support the use of acupuncture in patients with MM, which does not agree with previous evidence and consequently its further use.³¹ The results showed that acupuncture did not outperform placebo treatment in reducing monthly migraine attacks, migraine days or average headache intensity at the end of a 3-month treatment or beyond. No significant reduction of drug use was confirmed. Conversely, a significant improvement in mean headache intensity was found to be associated with acupuncture treatment when compared with analgesic medications.

Nevertheless, such insignificant changes in clinical outcomes may be a result of possibility as most trials were underpowered and associated with high risk of biases. We also speculate that the inconsistent results could be related to the overt selection bias, as previous clinical studies rarely isolated the MM subgroup from the small clinical sample of migraine for efficacy stratification. It is well demonstrated that MM is more severe, longer lasting and more resistant to conventional treatment than non-menstrual migraine as a result of complicated oestrogen-related pathophysiological process.^{34–37} Even though a group of pharmacological agents such as triptans have been found effective for acute and preventive treatments,^{7 10} it is largely unknown whether acupuncture should be recommended for use. Another possible reason leading to this discrepancy could be performance bias. Unlike daily practice, acupuncture administered in over 50% of the included studies only included fixed treatment scheme and was performed at the perimenstrual period. In Chinese medicine, the treatment of menstruation-related diseases emphasises pattern differentiation and adaptations of treatment principles in synchronisation with different phases of the menstrual cycle.^{38 39} This may cause an underestimation of the effect. The better effect observed in the comparison with drugs could be explained by the adjuvant use of acupuncture to medications. Other studies with a large cohort of patients also revealed a smaller effect size of acupuncture versus sham acupuncture than that of acupuncture versus waitlist, for pain relief.^{12 40}

In addition to methodological rigour, this systematic review also provided future studies with valuable information on formulating effective acupuncture paradigm for MM, even though little clinical effect was detected. Eight acupoints were highly chosen in the selected trials, namely LR3, SP6, GB8, DU20, GB20, EX-HN5, LI4 and ST36 (figure 2). Our study indicated that these points were not powerful enough to alter MM symptom in an experimental setting. Only a limited number of studies selected acupoints to restore the function of the reproductive organ in their prescriptions. Optimal combination of acupoints could be established by adding more reproductive function-related acupoints, such as acupoints on the liver/kidney meridian and some extraordinary acupoints, as novel evidence highlights the potential significance of meridian-related acupoint specificity.⁴¹ Furthermore, when and how acupuncture should be administered to induce better efficacy have to be determined prospectively. Many studies were designed only with a premenstrual treatment schedule but showed little effect in treating MM. From the theory of traditional Chinese medicine, personalised acupuncture treatments in terms of acupoint selection and intervention timing should be investigated more thoroughly in future trials.

This review might have some biases. First, the diagnosis of MM in the included studies was inconsistently based on ICHD-Third Edition. All studies determined MM based on clinical interviews, but few were further confirmed by using prospective headache diaries, which might lead to chances of diagnostic error.⁴² Moreover, most trials did not provide complete information on MM subgroups and those data were not included in the analysis. An ongoing trial was not included in the final analysis.²⁷ Communications were attempted to retrieve unpublished data from researchers of the individual studies, but no one responded. These problems may lead to selection bias. Second, the sample size of each study was small, which could introduce bias to meta-analyses due to sampling error.⁴³ Furthermore, this systematic review could not perform funnel plot test to determine potential publication bias due to an insufficient number of included trials.

CONCLUSIONS

Our study with a focus on patients with MM provided new information, but was not adequate to provide convincing evidence to support the use of acupuncture in treating patients with MM. Acupuncture cannot yet be recommended for MM treatment until more solid evidence is produced.

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