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Systematic Review

Acupuncture for migraine without aura: a systematic review and meta-analysis

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ABSTRACT

Background: Migraine without aura (MWoA), the most common type of migraine, has great impacts on quality of life for migraineurs. Acupuncture is used in the treatment and prevention of migraine for its analgesic effects.
Objective: The aim of this systematic review and meta-analysis is to systematically assess the therapeutic and preventive effect of acupuncture treatment and its safety for MWoA.
Search strategy: Nine electronic databases (PubMed, MEDLINE, Cochrane Library, Lilacs, Embase, China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Wanfang Data and Chinese Clinical Trial Registry (ChiCTR)) were systematically searched from their beginning through June 2017 using MeSH terms such as "acupuncture, acupuncture therapy, electro-acupuncture, ear acupuncture, acupuncture points, acupuncture analgesia," and "migraine disorders, cluster headache." Manual searching included other conference abstracts and reference lists.
Inclusion criteria: Randomized controlled trials (RCTs) with a clinical diagnosis of MWoA, which were treated with acupuncture versus oral medication or sham acupuncture treatment.
Data extraction and analysis: Two evaluators screened and collected literature independently; they extracted information on participants, study design, interventions, follow-up, withdrawal and adverse events and assessed risk of bias and quality of the acupuncture intervention. The primary outcomes were frequency of migraine (FM) and number of migraine days (NM). Secondary outcomes included the visual analogue scale (VAS) score, effective rate (ER) and adverse events. Pooled estimates were calculated as mean difference (MD) with 95% confidence interval (CI) for continuous data and relative risk (RR) with 95% CI for dichotomous data.
Results: Overall, 14 RCTs including 1155 participants were identified. The analysis found that acupuncture had a significant advantage over medication in reducing FM (MD = −1.50; 95% CI: −2.32 to −0.68; $P < 0.001$) and VAS score (MD = 0.97; 95% CI: 0.63–1.31; $P < 0.00001$) and had a higher ER (RR = 1.30; 95% CI: 1.16–1.45; $P < 0.00001$). Acupuncture also had a significant advantage over sham acupuncture in the decrease of FM (MD = −1.05; 95% CI: −1.75 to −0.34; $P = 0.004$) and VAS score (MD = −1.19; 95% CI: −1.75 to −0.63; $P < 0.0001$). Meanwhile, acupuncture was more tolerated than medication because of less side effect reports (RR = 0.29; 95% CI: 0.17–0.51; $P < 0.0001$). However, the quality of evidence in the included studies was mainly low (to very low), making confidence in the FM and VAS score results low.
Conclusion: Our meta-analysis shows that the effectiveness of acupuncture is still uncertain, but it might be relatively safer than medication therapy in the treatment and prophylaxis of MWoA. Further proof is needed.

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Contents

1. Introduction

Acupuncture is traditionally used to treat many symptoms and diseases. A recent study [1] reported a mechanism for acupuncture's analgesic activity, which involves release of nitric oxide (NO) from the skin near acupoints, with higher levels at the acupoints; this local NO release may improve local circulation and allow for a flush of analgesic or desensitizing substances, contributing to the beneficial effects of pain relief. Another study showed that the use of electrotherapy and acupuncture, for analgesic benefits, after total knee arthroplasty is associated with reduced opioid consumption [2]. As a key part of traditional Chinese medicine (TCM), acupuncture is practised worldwide for its analgesic effects, due to its efficacy and safety. Some of these effects have been attributed to triggering the adenosine A1 receptor and interfering with adenosine metabolism [3].

Currently migraine poses a great problem to modern medicine [4], and places a great burden on patients, their families, coworkers and society in general. Migraine without aura (MWoA) is the most common form of the disease [5]. Its attacks are often more severe than migraine with aura, and sufferers take medicine frequently, where available. The pharmacological therapy includes two parts: an analgesic given during the acute stage to relieve pain, and prophylaxis during remission to reduce the duration, frequency and severity of headaches. Certainly, both are effective, but they cause their own side effects, including nonmigraine headaches [6,7]. As a nondrug therapy, acupuncture is also recommended by *Guidelines for the Diagnosis and Treatment of Migraine in China* [5]. Thus, the number of clinical trials of acupuncture therapy for MWoA has increased in recent years. However, these studies vary considerably in quality and type, and the efficacy and safety of the treatment have not been confirmed. There have been few systematic reviews focusing on acupuncture therapy in treating MWoA alone.

To address this issue, in the present review, we followed the Cochrane systematic review methods and *Evidence-based Guidelines of Clinical Practice with Acupuncture and Moxibustion: Migraine* [8], assessed studies focusing on acupuncture for the treatment of MWoA and used the grading of recommendations assessment, development and evaluation (GRADE) approach to objectively score the evidence for efficacy and safety.

2. Methods

2.1. Protocol and registration

This study was registered on PROSPERO in University of York (registration number: RD42017078276).

2.2. Criteria for considering studies

2.2.1. Types of studies

Randomized controlled trials (RCTs) in any language, whether blinded or not, were included. Any repeated reports or any trials with sample sizes less than ten were excluded.

2.2.2. Types of participants

Patients diagnosed with MWoA, based on the *International Classification of Headache Disorders MWoA criteria* [9–11], were included. Patients with other systemic diseases were excluded.

2.2.3. Types of interventions

In our analysis, acupuncture therapy was considered to be the treatment group, while medication, sham acupuncture and placebo were considered to be controls.

For the purposes of this study, acupuncture interventions included body acupuncture, electro-acupuncture, auricular acupuncture, eye-acupuncture, abdominal acupuncture, scalp acupuncture, elongated needle, warm acupuncture, and fire needle. Other similar TCM interventions, such as cupping, laser acupuncture and acupressure were excluded. Comparison interventions included oral medicine, sham acupuncture or placebo. Any combination of therapies in the treatment group was excluded from this review (e.g., acupuncture combined with massage or Chinese herbal medicine).

2.2.4. Types of outcome measures

The outcome categories were classified according to clinical importance. (1) Critical and important outcomes: frequency of migraine (FM), number of migraine days (NM). Patients were asked to record headache diaries [12] (including the dates of attack, duration, intensity, etc.) and then researchers calculated FM and NM per 4 weeks both before and after the intervention. (2) Important but not critical outcome: the visual analogue scale (VAS) score [5] for the intensity of pain and effective rate (ER). ER was measured according to Guiding Principles of Clinical Research on New Drugs of TCM in China [13].

2.3. Literature search

We searched nine electronic databases (PubMed, MEDLINE, Cochrane Library, Lilacs, Embase, China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Wanfang Data and Chinese Clinical Trial Registry (ChiCTR)) from their beginning through June 2017, using MeSH terms such as "acupuncture, acupuncture therapy, electro-acupuncture, ear acupuncture, acupuncture points, acupuncture analgesia," and "migraine disorders, cluster headache." We also searched conference abstracts and reference lists of all available records identified in the initial publications to avoid missing relevant RCTs. There were no restrictions on publication language.

2.4. Study selection and data extraction

Two evaluators screened and collected literature independently. They eliminated studies that did not meet data quality standards and recorded the reasons for the exclusion. Then, they crosschecked the search results. Disagreements were resolved through discussion or the input of a third evaluator. Meanwhile, they made a data abstraction table independently, and merged the two into a final table. The main contents were as follows: general information of study, baseline data of participants, study design, interventions, follow-up, withdrawal and adverse events.

2.5. Assessment of risk of bias

Two researchers evaluated all the studies independently, using a collaboration tool recommended by the Cochrane Handbook 5.1, for assessing the risk of bias. There were six points that had to be evaluated: random allocation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and "other" [14]. Disagreement was also resolved by discussion. Each domain was assessed in Table 1.

Table 1
Assessment of risk of bias.

Risk of bias	Random allocation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other bias
Low	Using computer-made randomization list or a random number table	Using sequentially numbered, sealed and opaque envelopes or similar	Blinding was performed adequately, or the outcome measurement was not influenced by the lack of blinding. As the acupuncturists in our research were hard to be blinded, lack of blind was a relatively low risk factor	The reasons for dropout were unlikely to make treatment effects a departure from plausible values, or proper methods were used to handle missing data	Predefined, or clinically relevant and reasonably expected outcomes were reported (e.g., protocols were reported, or clinical trials were registered)	The trial appeared to be free of other components. Regarding the characteristics of acupuncture randomized controlled trials, the method of acupuncture operation and Deqi sensation were reported
Uncertain	Just mentioned randomization without details	Just mentioned randomization without details	Information was insufficient to assess whether the type of blinding used was likely to induce bias on the estimate of effect	Insufficient evidence was obtained to assess whether the reasons for missing data and the methods used to handle missing data were likely to induce bias on the estimate of effect	Not all predefined or clinically relevant outcomes were reported, or they were not reported fully, or it is unclear whether or not data on these outcomes were recorded	Descriptions were insufficient to assess whether the method of acupuncture operation was used effectively, and descriptions of Deqi sensation were unclear
High	Using visiting order, dates or names	The sequence generation was known to the researchers who assigned participants, or the study was quasirandomized	No blinding or incomplete blinding was used, which may influence the outcome	The improper estimate of effects was clearly biased because of the underlying reasons for dropout, and the methods used to handle missing data were unsatisfactory	One or more clinically relevant and reasonably expected outcomes were not reported; data on these outcomes were likely to have been recorded	Other factors in the trial could have put it at risk of bias

2.6. The GRADE method

Only RCTs were included in this study, providing evidence of the highest quality [15]. According to GRADE Working Group [16], the evidence quality would be reduced by five factors (risk of bias, inconsistency, indirectness, imprecision and publication bias), and graded into four levels (high, moderate, low and very low). Two authors evaluated the quality of evidence for each outcome independently, using GRADEpro Guideline Development Tool online software [17] to evaluate and produce forms.

2.7. Data synthesis and statistical analysis

Review Manager 5.3 provided by the Cochrane Collaboration [18] was used for the statistical analysis in this meta-analysis.

The chi-square test was used to assess the heterogeneity among trials. The significance threshold for this test was set at 0.1. $P < 0.1$ was considered to be statistically significant. Heterogeneity was measured using the I^2 statistic [19], and any P greater than 0.1 and I^2 smaller than 50% were considered to show that the studies were statistically homogeneous. We used a fixed-effects model to combine effect sizes [20]. On the other hand, any P smaller than 0.1 and I^2 greater than 50% but smaller than 75% were considered to have statistical heterogeneity. In order to deal with this heterogeneity, we used subgroup analysis or sensitivity analysis.

While combining the effect sizes, we calculated relative risk (RR) with 95% confidence interval (CI) for dichotomous data and the mean difference (MD) with 95% CI for continuous data.

3. Results

3.1. Study selection

We identified 1467 studies from the electronic databases using search strategy and data collection described above. We assessed 154 studies from PubMed, 146 from MEDLINE, 2 from Cochrane, 557 from CNKI, 303 from CQVIP and 305 from Wanfang Data. After eliminating duplicates, 854 studies were included. After reading through the titles and abstracts, 618 citations that included patients with migraine with aura or other types of headaches were excluded. The remaining 236 documents were evaluated in more detail. Full text review eliminated another 222 of these documents, leaving 14 RCTs [13,21–33] that met all inclusion criteria and data quality standards. See Fig. 1 for study flow.

3.2. Study characteristics

Of the 1155 participants with MWoA in the 14 RCTs [13,21–33], 567 participants received acupuncture, of which 72 also had ear acupuncture, and 30 also had blood-letting therapy, and 28 participants received electro-acupuncture, in the treatment groups. In the control groups, 426 received medications and 134 received sham acupuncture. In the medication groups, 30 took propranolol, 85 took ibuprofen, 223 took flunarizine and 88 took nimodipine as prophylactic drugs. Twelve trials originated from China, one from Italy and one from Iran. The characteristics of each RCT are shown in Table 2.

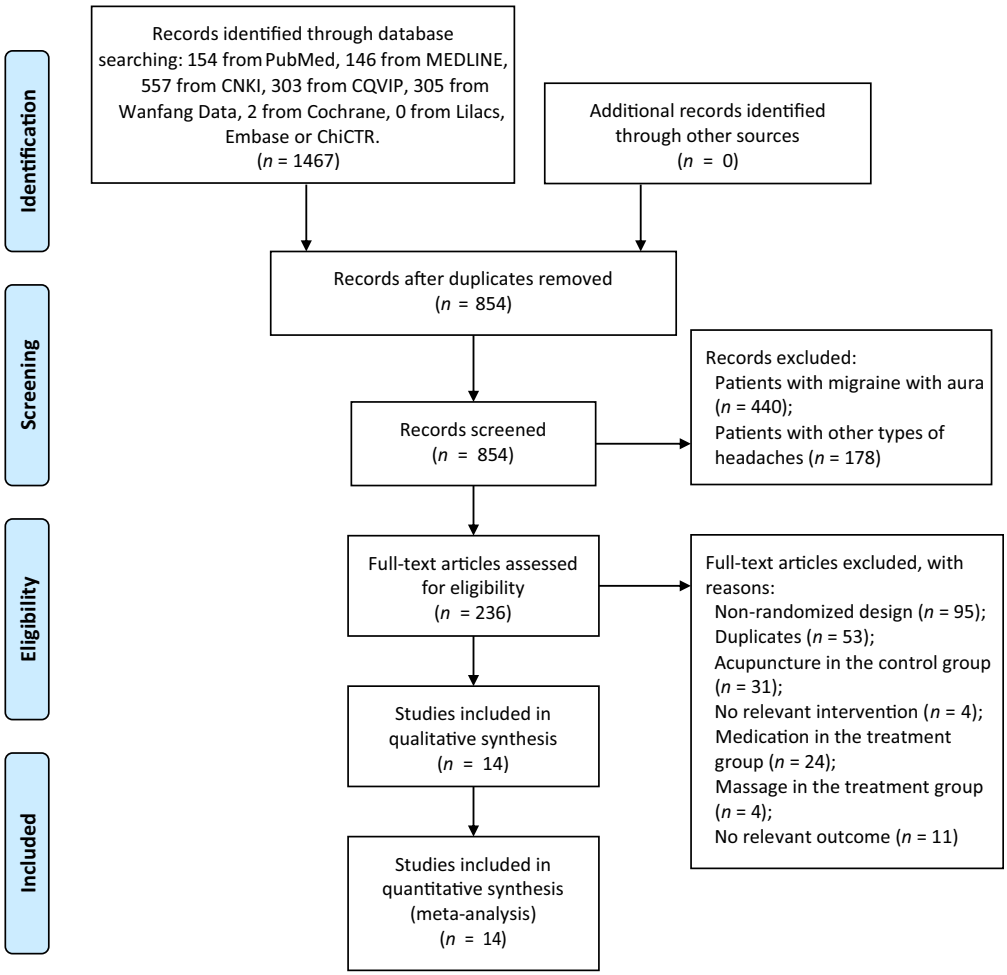

Fig.1. PRISMA flow chart of study selection in this review. CNKI: China National Knowledge Infrastructure; CQVIP: Chongqing VIP; ChiCTR: Chinese Clinical Trial Registry.

Table 2
Characteristics of the included studies in the meta-analysis.

Study	Country	Patients (T *vs* C)	Dropout (T *vs* C)	Treatment group	Control group (mg/d)	Duration of treatment group	Headache measure	Follow-up	Adverse events (T *vs* C)
Han (2016) [30]	China	30 *vs* 30	0	Acupuncture	Ergotamine 6 & propranolol 20–120	2 weeks	ER	NA	1 *vs* 7
Meng (2015) [24]	China	30 *vs* 30	0	Acupuncture	Sham acupuncture	4 weeks	FM, VAS	4 weeks	NA
Song (2012) [13]	China	30 *vs* 30	0	Acupuncture	Ibuprofen 600	8 weeks	ER	1 month	NA
Li (2011) [29]	China	72 *vs* 38	0	Acupuncture & ear acupuncture	Ergotamine 6 & flunarizine 10	4 weeks	VAS	6 months	NA
Ren (2012) [28]	China	56 *vs* 55	0	Acupuncture	Ibuprofen 300	Once	VAS	1 week	NA
Wan (2013) [27]	China	14 *vs* 14	0	Acupuncture	Sham acupuncture	2 weeks	VAS	3 months	NA
Wang (2016) [31]	China	30 *vs* 30	0	Acupuncture & blood-letting	Nimodipine 60	4 weeks	ER	1 month	NA
Wu (2011) [32]	China	30 *vs* 30	0	Acupuncture	Flunarizine 10	4 weeks	ER, SF-36	NA	NA
Ye (2009) [33]	China	28 *vs* 28	0	Electro-acupuncture	Nimodipine 120	4 weeks	ER	8 weeks	NA
Zhang (2013) [26]	China	30 *vs* 30	0	Acupuncture	Nimodipine 90	3 weeks	FM, ER	NA	NA
Allais (2002) [25]	Italy	80 *vs* 80	3 *vs* 7	Acupuncture	Flunarizine 10	2 months	FM	4 months	10 *vs* 29
Zhao (2014) [21]	China	40 *vs* 40	2 *vs* 5	Acupuncture	Sham acupuncture	8 weeks	FM, NM, VAS, HIT-6	NA	3 *vs* 2
Foroughipour (2014) [22]	Iran	50 *vs* 50	NA	Acupuncture	Sham acupuncture	4 weeks	FM	3 months	1
Wang (2011) [23]	China	75 *vs* 75	9 *vs* 11	Acupuncture	Flunarizine 10	4 weeks	NM, VAS, SF-36	3 months	5 *vs* 7

T *vs* C: treatment group *vs* control group; NA: not reported; ER: effective rate; FM: frequency of migraine; NM: number of migraine days; VAS: visual analogue scale; SF-36: the MOS 36-item short-form health survey; HIT-6: headache impact test.

3.3. Risk of bias in included studies

Most of the trials are either at unclear or high risk of bias (Fig. 2). In particular the two blinding criteria show high risk in performance bias and detection bias, except for in three studies [21–23].

3.3.1. Comparison with sham acupuncture

Three trials [21,24,27] reported adequate methods for allocation, sequence generation and concealment of allocation. One trial [22] used adequate concealment of allocation but did not report any details on randomization. The patients were blinded to the treatment type in two trials [21,24]. Another two trials [22,27] did not mention the blinding, and we could not assess additional information. Therefore, bias cannot be ruled out. One trial [22] reported that some patients did not complete the treatment and were replaced without a record of the number or reasons for dropout, resulting in unclear attribution bias. One trial [21] reported dropouts. The other two trials [24,27] reported no dropouts. One trial [21] had been registered in the Chinese Clinical Trial Registry. We were not able to obtain any registration information or protocols in three of the trials [22,24,27], thus reporting bias and other bias could not be ruled out.

3.3.2. Comparison with medication therapy

Three trials [23,30,33] reported adequate methods for random sequence generation and allocation concealment. Two trials [25,32] used adequate methods for sequence generation, but did not mention the details on concealment of allocation. Four trials [26,28,29,31] mentioned randomization without details and whether the allocation was concealed or not was unclear. One trial [13] allocated the patients according to priority, so that selection bias could not be ruled out. One trial [23] used a double-dummy technique to rule out performance bias. The other nine trials [13,25,26,28–33] did not mention blinding. Two trials [23,25] reported dropouts, and the other eight trials [13,26,28–33] reported no dropouts. No trials were registered, and the risk of bias was unclear.

3.4. Results of individual studies

3.4.1. Critical and important outcomes

3.4.1.1. FM. Three trials [21,22,24], with a total of 240 participants, included FM as an outcome, comparing it with sham acupuncture. In the figures we generated to represent the quantitative meta-analysis, the combined effect is located on the left side of the forest plot. This heterogeneity was significant ($P = 0.03$; $I^2 = 72\%$). Pooled analysis showed that FM reduced more greatly in acupuncture treatment groups than in sham acupuncture groups (MD = −1.05; 95% CI: −1.75 to −0.34; $P < 0.01$; Fig. 3).

A comparison of FM between patients receiving medication therapy and acupuncture therapy was conducted in two trials [25,26] with a total of 220 participants. It showed that the reduction in FM was greater in the acupuncture group than in the medication group (MD = −1.50; 95% CI: −2.32 to −0.68; $P < 0.01$; Fig. 3). However, the heterogeneity was significant ($P = 0.02$; $I^2 = 81\%$).

3.4.1.2. NM. Only one trial [21], with 80 participants, comparing acupuncture with sham acupuncture, included NM as an outcome. We did not conduct meta-analysis for this single study, as the analysis requires at least two independent studies.

Only one trial [23], with 140 participants, compared acupuncture with medication therapy, and included NM as an outcome. Similarly, it was not included in the meta-analysis.

3.4.2. Important but not critical outcome

3.4.2.1. VAS score. Three trials [21,24,27], with 168 participants, reported VAS score as an outcome in the comparison between acupuncture and sham acupuncture. The heterogeneity was not significant ($P = 0.63$; $I^2 = 0\%$). Pooled analysis showed that VAS score was more greatly reduced in the acupuncture group than in the sham acupuncture group (MD = −1.19; 95% CI: −1.75 to −0.63; $P < 0.01$; Fig. 3).

Three trials [23,28,29], with 361 participants, reported differences from baseline of VAS when comparing acupuncture therapy and medication therapy. The heterogeneity was not significant in the meta-analysis ($P = 0.24$; $I^2 = 29\%$). Pooled analysis showed that VAS score reduced more greatly in the acupuncture group than in the medication group (MD = 0.97; 95% CI: 0.63 to 1.31; $P < 0.01$; Fig. 3).

3.4.2.2. ER. Six trials [13,26,30–33], with 356 participants, reported ER as an outcome, when comparing acupuncture therapy to medication therapy. All six trials were measured according to *Guiding Principles of Clinical Research on New Drugs of TCM* in China [13]. In this quantitative meta-analysis, a fixed-effects model was used,

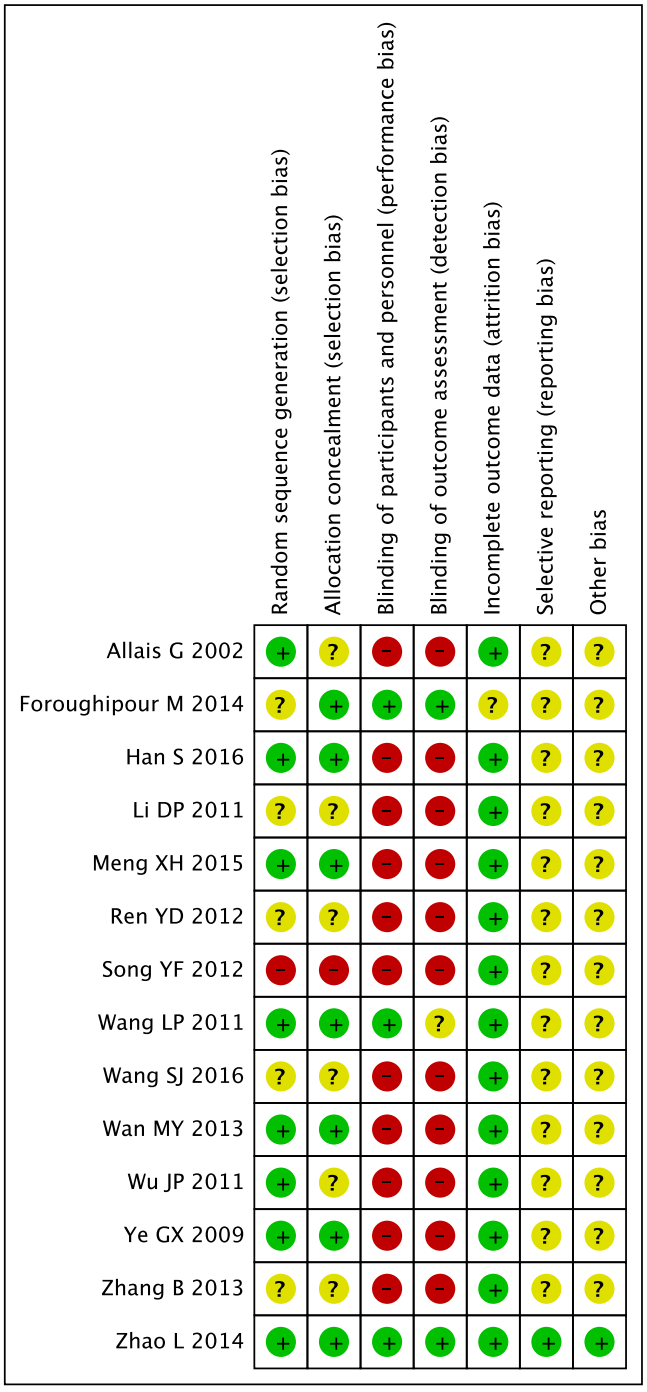

Fig. 2. Risk of bias summary of every included study. +: low risk; −: high risk; ?: unclear.

since the heterogeneity was not significant ($P = 0.25$; $I^2 = 25\%$). These six RCTs reported that for 156 out of 178 (87.6%) participants, treatments were more effective in the acupuncture group than in the medication group, with 120 out of 178 (67.4%) patients having positive results. The meta-analysis results favored acupuncture therapy ($RR = 1.30$; 95% CI: 1.16 to 1.45; $P < 0.01$; Fig. 3). Of the 14 RCTs, none included ER as an outcome compared with sham acupuncture.

3.4.3. Safety

Five trials [21–23,25,30] reported adverse effects. Out of 595 participants, 18 adverse effects (3.0%) were reported in acupuncture therapy groups; out of 351, 36 were reported (10.3%) in the medication therapy groups. In the acupuncture groups, one patient [22] complained of periorbital ecchymosis, two [21,30] suffered fainting during treatment, five [21,23] had minor hemorrhage at the needling site and ten patients [25] complained of local pain. In the medication groups, one trial [30] with propranolol reported abdominal pain, diarrhoea, distal numbness and dullness of mind; one study [25] with flunarizine reported drowsiness, weight gain and depression. Therefore, acupuncture was more tolerated than medication because of fewer adverse events ($RR = 0.29$; 95% CI: 0.17–0.51; $P < 0.01$).

3.5. Quality assessment by using GRADE

The assessment of quality using GRADE is shown in Tables 3 and 4. The evidence supporting the differences between acupuncture and sham acupuncture for FM, NM and VAS score was very low. Comparing acupuncture therapy to medication therapy, evidence supporting differences in FM was very low, while evidence for NM, ER and VAS score was low. Quality of evidence supporting the main outcome was low (to very low) for the risk of bias, inconsistency and imprecision.

4. Discussion

4.1. Summary of main results

In this meta-analysis, compared with sham acupuncture, acupuncture might have had a greater effect in the reduction of FM and VAS score, but considering the small sample size and sources of bias, the evidence was not strong. None of the trials reported ER.

Compared with medication therapy, several trials, using quite variable prophylactic drug treatments, consistently showed that acupuncture seemed to be more effective in reducing FM and VAS score; however, study results were statistically heterogeneous for FM, contributing to the low quality of evidence. The trend supporting a higher ER for acupuncture was consistent, but undermined by the quality of the research in the available trials. However, results from five trials reporting adverse events suggested that acupuncture therapy was safer than medication therapy, due to lower frequency of adverse events.

4.2. Possible explanations of the findings

The interventions tested in 14 RCTs included acupuncture, ear acupuncture, electro-acupuncture and blood-letting therapy. We regarded these acupuncture therapies as a holistic therapy and did not separate the difference in point selection and manipulation. Acupuncture is a general term, and includes many specific kinds of interventions, such as scalp acupuncture, electro-acupuncture, body acupuncture, warm acupuncture, auricular point sticking and elongated needle. This review concentrated on acupuncture interventions without other cotreatments. Interventions like cupping and acupressure were excluded in our review, for they are different branches of acupuncture therapy. Laser acupuncture is commonly used in studies, but it was also excluded, as it does not belong to traditional TCM acupuncture therapy.

Similarly, the medication control group utilized different prophylactic drugs, including β-blocking agents (propranolol), calcium channel antagonists (flunarizine and nimodipine) and analgesics and anti-inflammatory drugs (ibuprofen and ergotamine). However, drug dose was not consistent across studies, and three trials [26,31,33] took different dosages of nimodipine. Our review concentrated on the efficacy of acupuncture therapy as a nondrug therapy, compared with drug therapy. Thus, due to the small

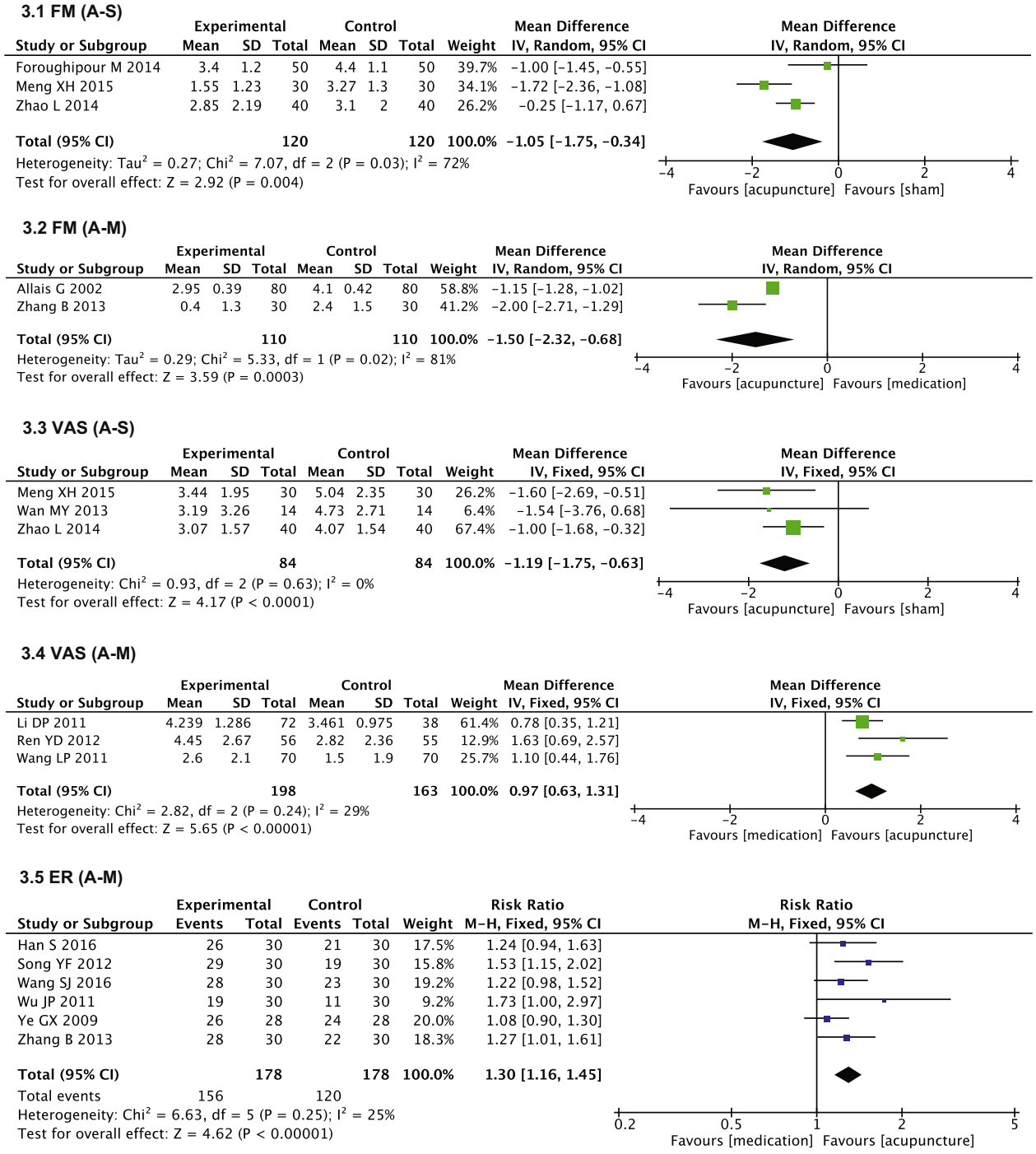

Fig. 3. Forest plots of treatment outcomes. The squares and horizontal lines correspond to the study-specific risk ratio and 95% CI. The area of the squares reflects the weight (Mantel-Haenszel). The diamond represents the summary risk ratio and 95% CI. FM: frequency of migraine; VAS: visual analogue scale; ER: effective rate; SD: standard deviation; CI: confidence interval. A-S: acupuncture *vs* sham; A-M: acupuncture *vs* medication.

sample size, we were not able to analyse these three kinds of drugs and their dosages separately. However, these variables may contribute to the statistical heterogeneity of the samples.

4.3. Quality of the evidence

The methodological quality of the included RCTs was generally low (Fig. 2). Among these 14 RCTs, few articles were sufficiently rigorous. The total sample size of 14 RCTs was small, given the variation in methods and outcomes. The quality of the evidence was either low or very low mainly because of risk of bias, inconsistency and imprecision.

In the evaluation of the risk of bias, random sequence generation and allocation concealment were the main factors. Of the 14 studies, 5 [22,26,28,29,31] mentioned randomization without providing details and in one trial [13] the randomization was considered to be of high risk for bias because of using visiting order. Of the 14 studies, 6 [25,26,28,29,31,32] inadequately described blinding of group allocation, and one trial [13] was considered to be of high risk for bias. While only three RCTs [21–23] specifically

Table 3
Assessment of study quality using GRADE (acupuncture compared to medication therapy for migraine without aura).

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk (medication)	Corresponding risk (acupuncture)			
Frequency of migraine at 4-month follow-up	The mean frequency of migraine ranged across control groups from 2.4 to 4.1 days	The mean frequency of migraine in the intervention groups was 1.50 lower (2.3–0.68)		220 (2 studies)	⊕⊖⊖⊖ Very low[1,2,3,4,5]
Effective rate at 6-week follow-up	Study population 674 per 1000 Moderate 717 per 1000	876 per 1000 (78–978) 932 per 1000 (83–1000)	RR 1.30 (1.16 to 1.45)	356 (6 studies)	⊕⊕⊖⊖ Low[1,2,3]
VAS at 4-month follow-up	The mean VAS ranged across control groups from 1.50 to 3.46	The mean VAS in the intervention groups was 0.97 (0.63–1.31)		361 (3 studies)	⊕⊕⊖⊖ Low[1,2,3]

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided according to GRADE Working Group grading quality of evidence. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; GRADE: grading of recommendations assessment, development and evaluation; VAS: visual analogue scale.
[1] The methods of random sequence generation and allocation concealment were not clear.
[2] Lack of blinding.
[3] Loss of follow-up.
[4] Great heterogeneity will exist.
[5] The sample size failed to meet the optimal information size criteria.

Table 4
Assessment of study quality using GRADE (acupuncture compared to sham acupuncture for migraine without aura).

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk (sham)	Corresponding risk (acupuncture)		
Frequency of migraine at 3-month follow-up	The mean frequency of migraine ranged across control groups from 3.1 to 4.4 days	The mean frequency of migraine in the intervention groups was 1.05 lower (1.75–0.34)	240 (3 studies)	⊕⊖⊖⊖ Very low[1,2,3,4,5]
VAS at 3-month follow-up	The mean VAS ranged across control groups from 4.07 to 5.04	The mean VAS in the intervention groups was 1.19 lower (1.75–0.63)	168 (3 studies)	⊕⊕⊖⊖ Low[2,3,5]

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided according to GRADE Working Group grading quality of evidence. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; GRADE: grading of recommendations assessment, development and evaluation; VAS: visual analogue scale.
[1] The methods of random sequence generation and allocation concealment were not clear.
[2] Lack of blinding.
[3] Loss of follow-up.
[4] I^2 = 72%.
[5] The sample size failed to meet the optimal information size criteria.

mentioned that they were single-blinded, it was impossible to blind both doctors and patients to acupuncture treatments. Even so, lack of blinding was considered to be a relatively low risk factor for decreasing quality of evidence. Finally, three RCTs [21,23,25] reported the numbers and reasons for patient withdrawals, which may overstate the effect.

We believe that the sample size of the included studies did not meet the highest standards for precision. All the sample sizes from included studies were < 200. The small sample size reduces statistical power and limits the reliability of results, so reducing confidence in study results. The low statistical power would reduce the quality of evidence from the RCTs.

For their outcome variables, five studies [21,22,24–26] selected FM, two studies [21,23] selected NM, and six studies [21,23,24,27–29] used VAS score. These objective clinical symptom scores could increase the reliability of acupuncture effectiveness scores. Six studies [13,26,30–33] selected ER, which was an outcome according to relevant standards in China, and used exclusively in Chinese studies. This may cause a risk of bias and increase the limitations of the conclusions. Furthermore, only one study [21] reported the HIT-6 questionnaire to assess the severity and impact of headache on a patient's life; it showed no significant differences between the two groups. At the same time, two articles [23,32] mentioned the MOS 36-item short-form health survey (SF-36). Together, the two scales could reflect the quality of life and be used as a tool to observe curative effect [5]. Since they were not widely used, they were included in this analysis. However, of the 14 RCTs, only one study [29] followed long-term efficacy after six months of acupuncture treatment and only three RCTs [21,23,25] reported the numbers and reasons for cases of patient withdrawal. Therefore, we could not determine the long-term efficacy of acupuncture. Thus, the available evidence was insufficient to judge the efficacy of acupuncture compared with medication therapy and sham therapy for the long-term management of patients with MWoA.

4.4. Potential biases

Although we searched nine databases, trial registries and conference proceedings and extended the search to related studies found in the references of the included papers, with no language restrictions, there might still be a publication bias. On the other hand, there was no extremely uniform standard among the inclusion and exclusion criteria and the included acupuncture therapies had differences. Moreover, the measurements of main outcomes, such as FM and NM, were mainly recorded by the patients themselves, which may affect the precision of the results. At the same time, the determination of ER followed guidance employed exclusively in China. Therefore, we could only conduct quantitative meta-analysis through relevant and available data.

4.5. Agreements and disagreements with other findings

There were few meta-analyses focusing on acupuncture for MWoA alone. One meta-analysis by Linde et al. [34] found that acupuncture was more effective than sham acupuncture and might had similar effectiveness as prophylactic therapy. It was an update

to their previous reviews [35,36], suggesting that acupuncture could provide an option for migraine treatment by reducing the frequency of headaches. Our study focused on MWoA alone, which can be considered a subset of the data considered in these reviews. Although data quality weakens confidence in the patterns we observed, we found that acupuncture may be more effective than medication therapy. More high-quality trials that undertake the comparison of acupuncture with medication therapy are urgently needed to eliminate the limitations of currently available clinical studies.

4.6. Implications for practice

Acupuncture is commonly used to treat MWoA. Our meta-analysis of the available data finds that its effectiveness is uncertain, as the quality of the included studies is low. However, the study may provide hope to patients with MWoA who take medicine frequently, since our results from five trials that reported adverse events found that acupuncture therapy was safer than medication therapy, due to the lower frequency of adverse events. Additional adequately powered RCTs are required to prove its analgesic effect for acute pain during the acute phase of migraines and its ability to reduce migraine frequency during remission stage.

4.7. Implications for research

In systematic reviews, the objectivity and accuracy of conclusions depend on RCTs of high quality. The low (to very low) evidence limits the interpretation of our results. This emphasizes the urgency that the design of future RCTs adhere to recommendations from the CONSORT statement of 2010 [37]: RCTs should report the details of random sequence, allocation concealment and blinding; the sample size must be large enough to reflect a significant difference between the study group and the control group; a placebo treatment should be used in the control group, such as well-designed sham acupuncture; the flow chart of the study should report the details of cases that dropped out; RCTs should report the results completely, including follow-up with details; analysis could be by intention to treat. Additional well-designed and powered RCTs are needed for clinical practice.

TCM is characterized by individualized treatment based on syndrome and meridian differentiation. While evaluating the efficacy of acupuncture, researchers need to consider the abundant intervention methods and multiple biological effect indices. The difficulty to quantize parameters of treatment design makes it hard to evaluate traditional Chinese literature according to evidence-based medicine. Our results could only indicate a trend in the pattern of efficacy, but could not draw a definite conclusion. Therefore, in the future, either pluralistic statistical analysis methods or multivariate regression models could be used to quantize the complex efficacy evaluation system, for the sake of objective evaluation, to reflect the characteristics of TCM.

Our findings indicated that acupuncture therapy, for its relative safety and nontoxicity, could be an effective method to treat patients with MWoA. Considering that most available TCM studies mainly focused on point selection treatment based on syndrome or meridian differentiation, without a uniform intervention or clear standard of manipulation, larger RCTs of high quality are urgently needed.

5. Conclusions

Our meta-analysis shows that the effectiveness of acupuncture is still uncertain, but it might be safer than medication therapy in the treatment and prophylaxis of MWoA. Considering the low (to very low) quality of evidence, more high-quality, large sample and multicenter RCTs are needed to clarify the relationship.

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Conflicts of interest

The authors declare no financial or other conflicts of interest.

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