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Systematic Review

Cupping therapy for patients with chronic urticaria: A systematic review and meta-analysis

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ABSTRACT

Background: Chronic urticaria (CU) is a common skin disease, which has a negative effect on quality of life. Current treatments do not fully control the symptoms of urticaria for many CU patients, thus effective and safe treatments for CU are still needed.

Objective: This review aims to evaluate the effectiveness and safety of cupping therapy in patients with CU.

Search strategy: The search strategy looked for the presence of related keywords, such as “chronic urticaria” and “cupping therapy,” in the title and abstract of research articles indexed in major databases. Randomized controlled trials (RCTs) were selected after querying nine electronic databases from their inception to May 2019 with the above search terms.

Inclusion criteria: RCTs were included if they recruited patients with CU who were intervened with dry or wet cupping. Publications could be written in Chinese or English.

Data extraction and analysis: Data were extracted, and the studies were assessed for the quality of their methodological design and risk of bias. Meta-analyses of the RCT data were conducted to assess the total effective rate of the treatment as the primary outcome. Skin disease quality of life index score, recurrence rate, and adverse events were assessed as secondary outcomes. Subgroup analyses were conducted based on different interventions.

Results: Thirteen comparisons from 12 RCTs involving 842 participants were included. There were no significant differences between wet cupping and medications in total effective rate ($n = 372$; risk ratio [RR] = 1.10, 95% confidence interval [CI] 0.97 to 1.25; $P = 0.14$) or recurrence rate ($n = 240$; RR = 0.56, 95% CI 0.23 to 1.36; $P = 0.20$). Cupping therapy, in combination with antihistamine treatment was more efficacious than antihistamines alone, with a greater total effective rate ($n = 342$; RR = 1.18, 95% CI 1.01 to 1.39; $P = 0.03$) and lower recurrence rate ($n = 342$; RR = 0.52, 95% CI 0.32 to 0.84; $P = 0.007$). Cupping therapy combined with acupuncture was more effective than acupuncture alone ($n = 156$; RR = 1.25, 95% CI 1.07 to 1.46; $P = 0.006$). No serious adverse events were reported.

Conclusion: Wet cupping may be as effective as treatment with antihistamines. When cupping therapy is used as an adjuvant therapy to antihistamines or acupuncture, it may enhance the efficacy. Results drawn from these studies should be interpreted with caution and applied with care to clinical practice, because of the poor quality among the studies that were reviewed.

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1. Introduction

Chronic urticaria (CU), with persistent outbreaks lasting at least 6 weeks, is a condition often accompanied by the development of angioedema and hives [1]. Approximately 1% of people worldwide are affected by CU [2], which can last 2 years or longer [3–6]. Recurrent urticaria is a source of anxiety, depression, irritability and social dysfunction in many patients [2,7,8]. Patients suffering from CU frequently consume medical resources [9], adding a burden to public health systems and society [2].

The second-generation H1-antihistamines are typically the first-line drugs in the treatment of CU [1], but patients continue to experience symptoms even while receiving treatment at recommended doses [10–13]. The monoclonal antibody omalizumab is also safe and effective for the treatment of CU [14–16], but its high cost is a limitation to access [17]. Because CU symptoms are not fully controlled by these primary therapies, other effective and safe treatments are needed [1].

Cupping therapy is a complementary and alternative medical technique with a long history in China [18,19]. There are two main types of cupping therapy: dry cupping and wet cupping [20]. In dry cupping, a vacuum created in the cup exerts tension on the skin and draws it into the cup. In wet cupping, a small incision is first made on the skin and then the negative pressure applied to the cup draws out a small volume of blood [21,22]. In recent years, cupping therapy has been widely used in the treatment of skin diseases [23], including CU [24–26]. Previous systematic reviews have explored the effectiveness of bloodletting therapy for CU [27], which shares some characteristics with

wet cupping. However, to date, there has been no systematic review of cupping therapy for treating CU. In this meta-analysis we evaluate the evidence for the effectiveness and safety of cupping therapy for CU.

2. Methods and analysis

The protocol for this review study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42019137451 and was also published in Medicine [28]. The review approach complied with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols and the Cochrane Handbook for Systematic Reviews of Interventions [29]. All reviewers received the same training, to ensure that they understood the background, purpose and process of the review.

2.1. Inclusion and exclusion criteria

Publications were included if: (1) the study design was a randomized controlled trial (RCT); (2) the publication language was Chinese or English; (3) the recruited patients were individuals with a confirmed diagnosis of CU [1,30]; (4) the primary intervention was dry or wet cupping, either alone or in combination with other methods; and (5) secondary interventions were given to study and control groups.

Studies were excluded if: (1) any medication was added to the cups; or (2) there was duplication of data published elsewhere.

2.2. Search strategy

Our systematic review included a literature search of PubMed, MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, China Science Journal Database (VIP), China National Knowledge Infrastructure (CNKI), Wanfang Data and China Biomedical Literature Database (CBM), from their inception to May 1, 2019. Key search terms included urticaria, nettle-rash, hives, fong-tzen-kwai, wind-rash-patch, angioedema, cupping, dry cupping, wet cupping, bloodletting, and pricking cupping (Table 1). Minor modifications to the search strategy were made for use across several databases.

2.3. Data collection and analysis

2.3.1. Selection of studies

The search results were independently screened by two of the study authors (YZS and LXZ); the initial review included the title, abstract, and keywords of each returned study. The full texts of studies appearing to meet the selection criteria were reviewed in detail. In cases where reviewers were unable to agree on inclusion/exclusion of a study, arbitration with a third party (XJX) was used to make the final decision.

2.3.2. Data extraction and management

The following information was independently extracted from the full text by two reviewers (WC and YL): participant number and general information, interventions, results, adverse events, main conclusions and other information. Any disagreement was resolved by discussion with XJX.

2.4. Assessment of risk of bias

The bias risk of each included study was independently evaluated by two authors (SYZ and QHZ) using the risk of bias tool from the Cochrane Manual V.5.1.0. The risk bias of each study was rated as low, high, or unclear, based on the following items: random sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete out-

come data, selective outcome reporting and other sources of bias. Any disagreement was resolved by discussion with the third author (YL).

2.5. Measures of treatment effect

RevMan V.5.3 statistical software was used for data analysis. A fixed-effects model was used for non-significant heterogeneity, and a random-effects model was used to analyze parameters with high heterogeneity [27]. If quantitative analysis was not appropriate, a descriptive analysis was provided. For continuous data, mean difference and 95% confidence interval (CI) were used to measure the treatment effect. For dichotomous data, risk ratio (RR) with 95% CI was used to measure the treatment effect.

2.6. Assessment of heterogeneity

Heterogeneity was measured by calculating the I^2 statistic. If the I^2 value exceeded 50%, then there was significant statistical heterogeneity, and the potential causes were explored [27]. Subgroups of the different cupping therapies and intervention forms were constructed to explore potential causes of heterogeneity. Analysis of subgroups included: (1) different methods of cupping therapy (dry cupping or wet cupping); and (2) different types of intervention forms (cupping therapy alone or combined with other active treatments).

2.7. Assessment of reporting biases

Eligible trials were assessed for reporting biases and small-study effects, using funnel plots. If at least 10 eligible studies were available, the funnel plots were assessed visually or by using Egger's test [27].

2.8. Types of outcome measures

The primary outcome used in this analysis was the total effective rate, measured according to two common standards [31,32] as cure rate + effective rate. The definition of the total effective rate of cupping therapy was derived from previous systematic reviews [27]. Secondary outcomes included the skin disease quality of life index score, recurrence rate, and occurrence of adverse events.

Table 1
Search strategy used.

No	Search items
#1	exp clinical trial/
#2	exp randomized controlled trials/
#3	(random\$ adj5 control\$ adj5 trial\$.mp.
#4	(clinic\$ adj2 trial).mp.
#5	controlled clinical trial.pt.
#6	randomi\$.mp.
#7	or/1–6
#8	(animals not (human and animals)).sh.
#9	7 not 8
#10	exp*urticaria/
#11	urticaria.ti.ab.
#12	hives.ti.ab.
#13	nettle-rash.ti.ab.
#14	ngioedema.ti.ab.
#15	fong-tzen-kwai.ti.ab.
#16	wind-rash-patch.ti.ab.
#17	or/10–16
#18	cupping.ti.ab.
#19	(dry\$ adj2 cupping).mp.
#20	(wet\$ adj2 cupping).mp.
#21	exp*bloodletting/
#22	bloodletting.ti.ab.
#23	(pricking\$ adj2 cupping).mp.
#24	or/18–23
#25	9 and 17 and 24

3. Results

3.1. Study selection

A total of 1164 citations were initially identified by searching the databases using the keywords given above; a manual search did not find additional articles. After stepwise screening, 12 RCTs with 842 participants were included in our meta-analysis [25,26,33–42]. The process of identifying trials is shown in Fig. 1.

3.2. Characteristics of included trials

The 12 trials included for meta-analysis were conducted and published in Chinese between 2006 and 2019, and two of them were unpublished theses for master's degrees [33,37]. All 12 studies were single-center randomized controlled studies. In total, there were 842 participants with CU, aged between 2 and 71 years, and the duration of disease varied from two months to seven years. One study enrolled participants younger than 12 years of age [34]. Detailed characteristics of the studies are presented in Table 2.

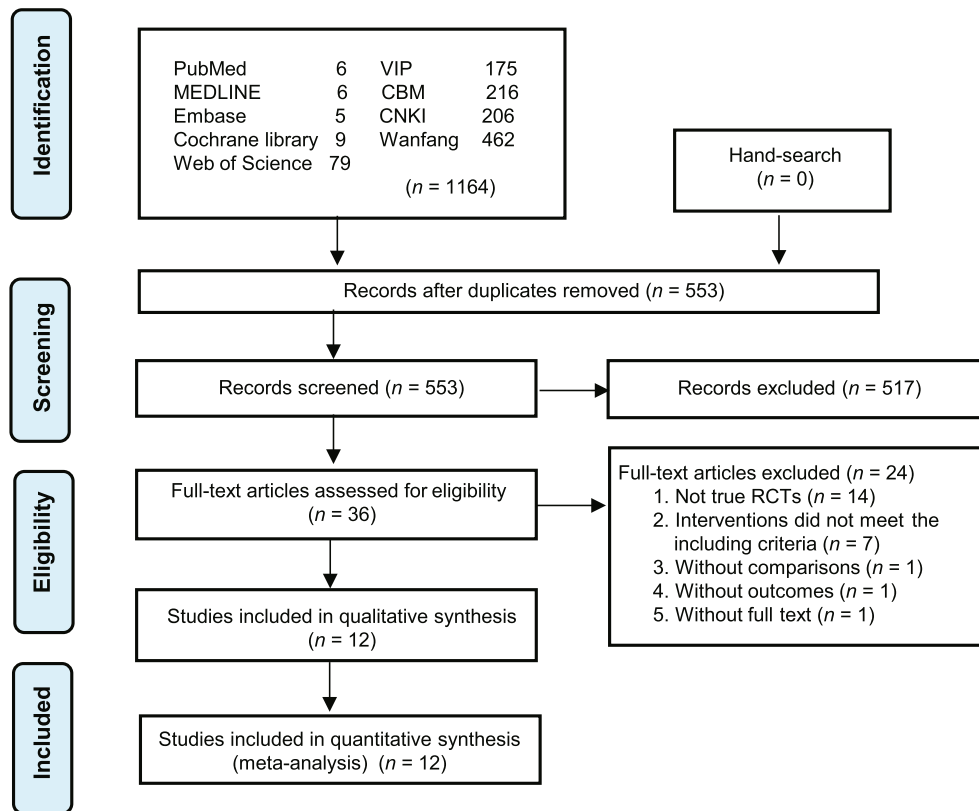


Fig. 1. Flowchart of study selection. VIP: China Science Journal Database; CNKI: China National Knowledge Infrastructure; CBM: China Biomedical Literature Database.

3.3. Cupping therapy interventions

Dry cupping was used in four studies [33–35,42]. The acupoint CV 8 was used in every study, and DU 14 and ST 36 were used in one study [42]. The total number of treatments ranged from 7 to 28 in four studies. In two studies, cupping therapy was given every other day [33,34], while in the other studies, it was applied twice weekly [35] or once daily [42]. In three of the four studies, cupping therapy was provided to patients for four weeks [33,35,42].

Eight studies used wet cupping [25,26,36–41], and six of them used the BL13 in the therapy. Other acupoints used included DU 14 (n = 5 studies), LI 11 (n = 5), SP 10 (n = 5), BL 17 (n = 2), BL 20 (n = 2), ST 36 (n = 2), BL 18 (n = 1) and LI 4 (n = 1). The total number of treatment sessions ranged from 3 to 16. The highest treatment frequency was every other day (n = 6) [26,36,37,39,41], and the longest common treatment duration was four weeks (n = 3) [26,37,38]. One study did not report the duration of treatment [36].

3.4. Control interventions

Control interventions consisted of acupuncture and antihistamine medications (Table 2). Three studies used acupuncture [25,33,35], and nine studies used antihistamines including loratadine [34,40,41], cetirizine [26,38,39], levocetirizine dihydrochloride [36], fexofenadine hydrochloride [42], ketotifen [42] and mizolastine [37]. Treatment duration was similar to cupping therapy duration.

One study used a three-parallel-arm design [37] that included wet cupping alone, wet cupping plus mizolastine and mizolastine alone. This study was divided into two comparisons for the purpose of the meta-analysis: wet cupping alone versus mizolastine

alone and wet cupping plus mizolastine versus mizolastine alone [29].

3.5. Outcome measures

All studies reported the total effective rate. Eight of 12 studies reported the recurrence rate. Seven studies reported adverse events. The skin disease quality of life index score was not reported in any study.

3.6. Risk of bias

The risk of bias assessment was conducted for each study and the results are shown in Fig. 2. Randomization of treatments was inconsistent among studies: six studies used random number tables, while the other seven studies did not mention specific randomization methods. Only one study [33] reported allocation concealment, and details of allocation were not clearly discussed in the other 11 trials. Due to the nature of cupping therapy, blinding of cupping operators was not feasible. However, none of the included trials reported blinding of the participants or researchers. Thus, we graded all 12 studies as having high risk of bias in this domain. There was also no discussion of blinding in the outcome assessments, and these were judged as “unclear” for evidence of bias. We considered 12 studies to be at low risk of bias for incomplete outcome data, according to the reports of dropouts or intention-to-treat analysis. In the selective reporting section, one study [35] was judged to have high risk of bias, because the recurrence rate of CU was not described, while the remaining 11 studies were considered to have low risk of bias. For other biases, one study [36] did not report the total time over which patients received treat-

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

Study	Sample size (male/female)		Age (years, I/ C)	Course of the disease (I/C)	Intervention (I/C)	Outcomes	Treatment frequency (period)	Follow-up time	Adverse events (I/C)	Acupoints/meridians selected by cupping
	I	C								
Lu 2006 [38]	32/30	25/23	16–60/16–60	> 6 W/> 6 W	Wet cupping + cetirizine/ cetirizine	TER; recurrence rate; adverse events	Wet cupping once a day for consecutive 4 d as a course; 3 d interval between courses (4 W)	3 M	Drowsiness: 1; dry mouth: 1/dizziness: 1; drowsiness: 1; dry mouth: 1	Dazhui (DU 14), Feishu (BL 13), Dachangshu (BL 25), Pishu (BL 20), Shenshu (BL 23)
Wu 2010 [39]	11/19	10/20	22–61/23–70	2–10 Y/1–11 Y	Wet cupping/cetirizine	TER	Wet cupping every other day (20 d)	NR	NR	Du meridian and Bladder meridian
Gao 2012 [33]	13/17	14/16	33.8 ± 9.6/ 33.4 ± 10.7	(15.8 ± 8.7) W/ (15.4 ± 9.5) W	Dry cupping + acupuncture/ acupuncture	TER; recurrence rate; adverse events	Dry cupping + acupuncture, every other day (4 W)	8 W	None	Shenque (CV 8)
Li 2013 [40]	17/19	18/18	20–52/22–47	9 M–7 Y/11 M–7 Y	Wet cupping/loratadine	TER; adverse events	Wet cupping once every 3 d (9 d)	NR	None/dry mouth: 12; headache: 5; drowsiness 10	Xuehai (SP 10), Quchi (LI 11), Weizhong (BL 40)
Zhao* 2013(A) [37]	12/18	14/16	39.92 ± 12.42/ 39.72 ± 12.44	(23.8 ± 8.88) M/ (25.13 ± 8.86) M	Wet cupping/mizolastine	TER; recurrence rate; adverse events	Wet cupping every other day (4 W)	12 W	None	Dazhui (DU 14), Feishu (BL 13), Geshu (BL 17), Ganshu (BL 18), Pishu (BL 20), Quchi (LI 11), Hegu (LI 4), Xuehai (SP 10), Zusanli (ST 36)
Zhao* 2013(B) [37]	16/14	14/16	38.57 ± 14.62/ 39.72 ± 12.44	(22.4 ± 11.04) M/ (25.13 ± 8.86) M	Wet cupping + mizolastine/ mizolastine	TER; recurrence rate; adverse events	Wet cupping every other day (4 W) + mizolastine every day (4 W)	12 W	None	Dazhui (DU 14), Feishu (BL 13), Geshu (BL 17), Ganshu (BL 18), Pishu (BL 20), Quchi (LI 11), Hegu (LI 4), Xuehai (SP 10), Zusanli (ST 36)
Teng 2014 [42]	26/30	22/34	18–67 (36 ± 6)/18–65 (37 ± 7)	(21.14 ± 10.68) M/ (20.14 ± 11.38) M	Dry cupping + fexofenadine hydrochloride + ketotifen/ fexofenadine hydrochloride + ketotifen	TER; recurrence rate	Dry cupping once a day (4 W) + fexofenadine hydrochloride and ketotifen everyday (4 W)	8 W	NR	Shenque (CV 8), Dazhui (DU 14), Zusanli (ST 36)
Li 2015 [26]	12/15	10/17	17–69/17–71	3–72 M/3–72 M	Wet cupping/cetirizine	TER; recurrence rate; adverse events	Wet cupping every other day (4 W)	6 M	None/drowsiness: 1	Dazhui (DU 14), Feishu (BL 13), Quchi (LI 11), Xuehai (SP 10)
Li 2016 [34]	12/18	13/17	2–12/2–12	> 6 W/> 6 W	Dry cupping + loratadine/ loratadine	TER; recurrence rate; adverse events	Dry cupping every other day (2 W) + loratadine everyday (2 W)	3 W	Slight skin damage around navel: 1; drowsiness: 1/ drowsiness: 2	Shenque (CV 8)
Shi 2016 [36]	NR	NR	NR	NR	Wet cupping/levocetirizine dihydrochloride	TER; recurrence rate	Wet cupping every other day (NR)	NR	NR	Feishu (BL 13), Pishu (BL 20), Xuehai (SP 10), Dazhui (DU 14), Quchi (LI 11), Zusanli (ST 36)
Wang 2017 [25]	8/10	9/9	34.06 ± 7.08/ 33.17 ± 6.96	(2.87 ± 1.54) Y/ (2.96 ± 1.48) Y	Wet cupping + acupuncture/ acupuncture	TER	Wet cupping twice a week (6 W) + acupuncture three times a week, every other day (6 W)	NR	NR	Dazhui (DU 14), Feishu (BL 13), Quchi (LI 11), Xuehai (SP 10)
Gan 2018 [41]	17/14	16/15	37.96 ± 4.32/ 35.75 ± 5.62	(2.31 ± 0.47) Y/ (2.18 ± 0.58) Y	Wet cupping/loratadine	TER; recurrence rate; adverse events	Wet cupping every other day (8 d)	1 M	Hematoma: 2/ emesis: 1; fatigue: 2; drowsiness: 1	Geshu (BL 17), Feishu (BL 13), Pishu (BL 20)
Zhang 2019 [35]	12/18	12/18	38.63 ± 12.99/ 39.03 ± 12.99	NR	Dry cupping + acupuncture/ acupuncture	TER	Dry cupping twice a week (4 W) + acupuncture five times a week (4 W)	NR	NR	Shenque (CV 8)

C: control; I: intervention; M: month; NR: not reported; TER: total effective rate; W: week; Y: year; *: Zhao 2013 (A) and Zhao 2013 (B) were the two sub-studies of Zhao 2013.

ment or the time at which treatment outcomes were evaluated, thus its risk of bias was judged to be high.

3.7. Outcomes

3.7.1. Total effective rate

3.7.1.1. Wet cupping therapy alone compared to antihistamines alone. Dry cupping was not studied as an isolated treatment, so data could not be included in the pooled analysis. Six wet cupping studies (with seven comparisons) [26,36,37,39–41] had sufficient data to be pooled for meta-analysis. There was no significant difference in total effective rate between wet cupping and control groups ($n = 372$; RR 1.10, 95% CI 0.97 to 1.25; $P = 0.14$; Fig. 3A).

3.7.1.2. Cupping therapy plus antihistamines compared to antihistamines alone. Four studies [34,37,38,42] that combined cupping therapy with antihistamines reported a total effective rate. Two studies [34,42] used dry cupping and two used wet cupping [37,38]. In this analysis, cupping therapy combined with antihistamines was associated with a higher total effective rate than antihistamines alone ($n = 342$; RR = 1.18, 95% CI 1.01 to 1.39; $P = 0.03$; Fig. 3B).

In a subgroup analysis of two dry cupping studies, pooled analysis demonstrated no significant difference between dry cupping combined with antihistamines compared to antihistamines alone ($n = 172$; RR 1.11, 95% CI 0.95 to 1.30; $P = 0.19$). In contrast, pooled analysis of two wet cupping studies showed that cupping therapy combined with antihistamines was associated with higher total effective rates than antihistamines alone ($n = 170$; RR 1.32, 95% CI 1.09 to 1.60; $P = 0.004$).

3.7.1.3. Cupping therapy combined with acupuncture compared to acupuncture alone. Three studies [25,33,35] that combined cupping

therapy with acupuncture reported their total effective rate; two of these used dry cupping [33,35]. The pooled analysis demonstrated that cupping therapy combined with acupuncture was more effective than acupuncture alone ($n = 156$; RR = 1.25, 95% CI 1.07 to 1.46; $P = 0.006$; Fig. 3C).

In subgroup analysis, dry cupping therapy combined with acupuncture was more effective than acupuncture alone ($n = 120$; RR 1.20, 95% CI 1.01 to 1.44; $P = 0.04$). The single wet cupping study reported no apparent benefit in its total effective rate when wet cupping was added to acupuncture ($n = 36$; RR 1.42, 95% CI 1.00 to 2.00; $P = 0.05$).

3.7.2. Recurrence rate

3.7.2.1. Cupping therapy alone compared to antihistamines alone. Dry cupping was not studied as a single therapy, so no pooling was possible. Four wet cupping studies [26,36,37,41] were pooled for the meta-analysis of cupping therapy compared to antihistamine therapy. There was no significant difference between the two treatments ($n = 240$; RR = 0.56, 95% CI 0.23 to 1.36; $P = 0.20$; Fig. 4A).

3.7.2.2. Cupping therapy combined with antihistamines compared to antihistamines alone. Four studies [34,37,38,42] were pooled to analyze the effects of using of cupping therapy as a co-therapy with antihistamines on the recurrence rate of CU. Of the four studies, two [34,42] used dry cupping and two [37,38] used wet cupping. The pooled analysis demonstrated that cupping therapy combined with antihistamines was more effective than antihistamines alone ($n = 342$; RR = 0.52, 95% CI 0.32 to 0.84; $P = 0.007$; Fig. 4B).

In subgroup analysis, dry cupping therapy in combination with antihistamines had a lower recurrence rate than antihistamines alone ($n = 172$; RR 0.55, 95% CI 0.28 to 0.91; $P = 0.02$). However,

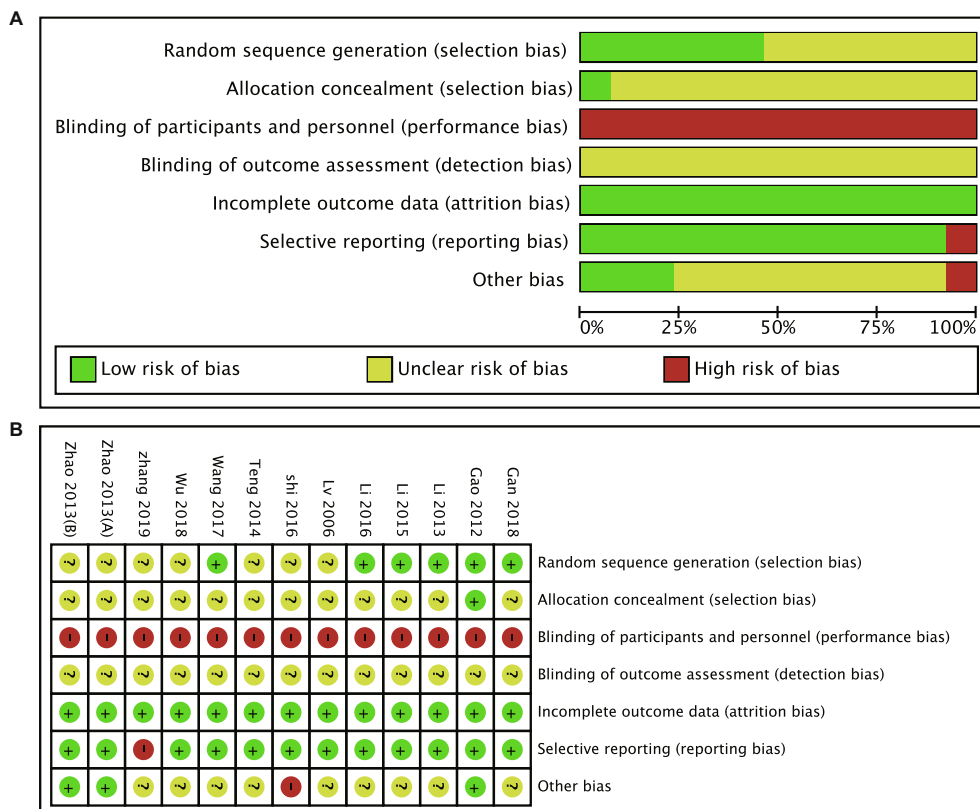


Fig. 2. Risk of bias graph and summary. A: Bias of risk graph; B: Bias of risk summary.

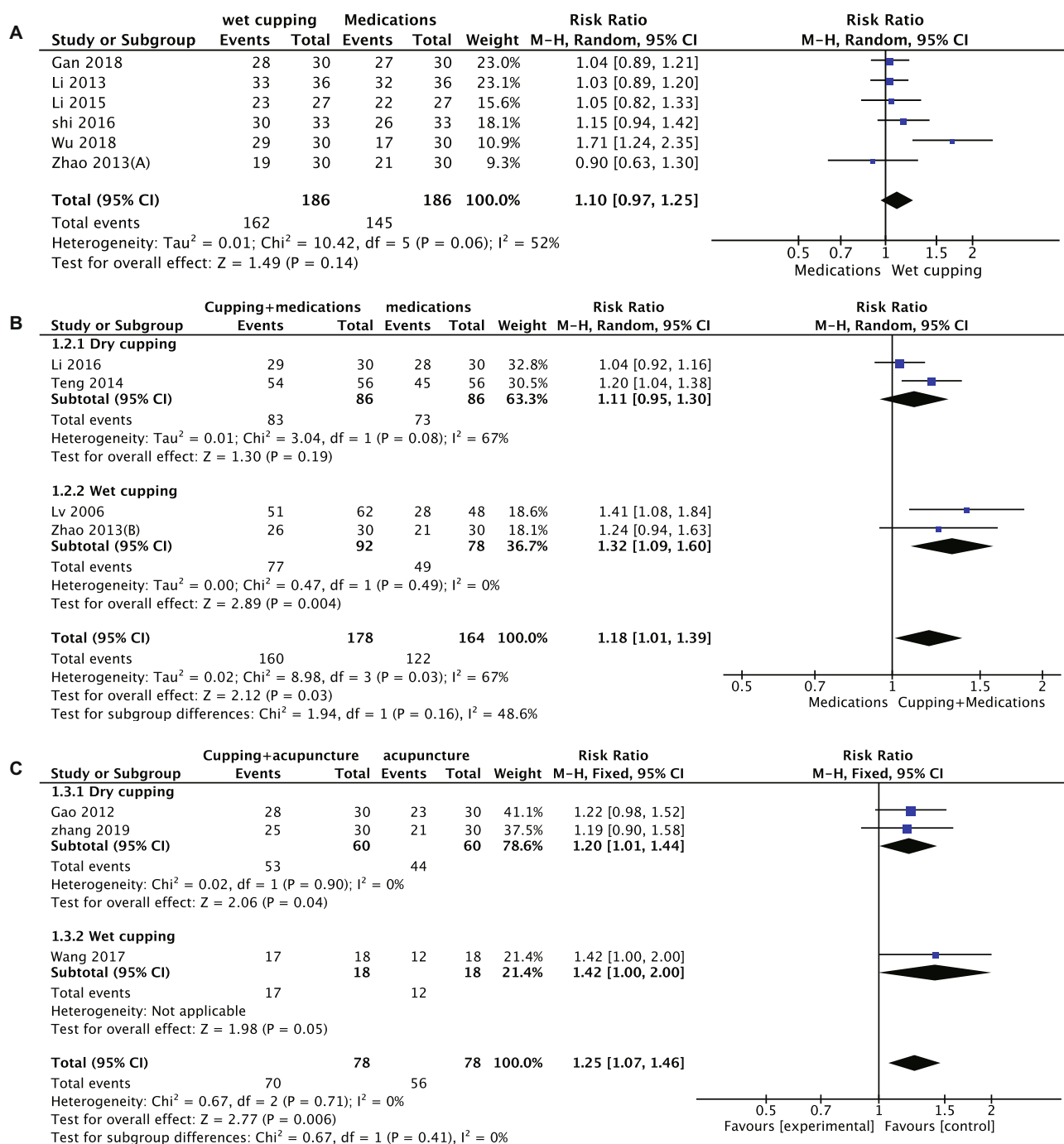


Fig. 3. Forest plot of total effective rate. A: Forest plot showing the effects of cupping therapy compared to antihistamines on total effective rate in the treatment of chronic urticaria (CU). B: Forest plot showing effects of cupping therapy combined with antihistamines compared to antihistamines alone on total effective rate in the treatment of CU. C: Forest plot showing the effects of cupping therapy combined with acupuncture compared to acupuncture alone on total effective rate in the treatment of CU.

there was no statistically significant difference between wet cupping therapy in combination with antihistamines and antihistamines alone ($n = 170$; RR = 0.55 95% CI 0.24 to 1.25; $P = 0.15$).

3.7.2.3. Cupping therapy combined with acupuncture compared to acupuncture alone. Only one study [33] reported the recurrence rate of CU when cupping therapy was used in conjunction with acupuncture. The addition of cupping therapy to acupuncture treatments did not significantly reduce the recurrence rate, com-

pared to acupuncture alone ($n = 60$; RR = 0.50, 95% CI 0.10 to 2.53; $P = 0.40$).

3.7.3. Adverse events

Adverse events were reported in seven of the 12 RCTs [26,33,34,37,38,40,41]. Two studies did not report any adverse event [33,37]. There was one case of slight skin damage around the navel and one case of drowsiness, reported in a treatment group using dry cupping plus loratadine [34]. In patients receiving wet cupping therapy alone, two cases of hematoma were reported

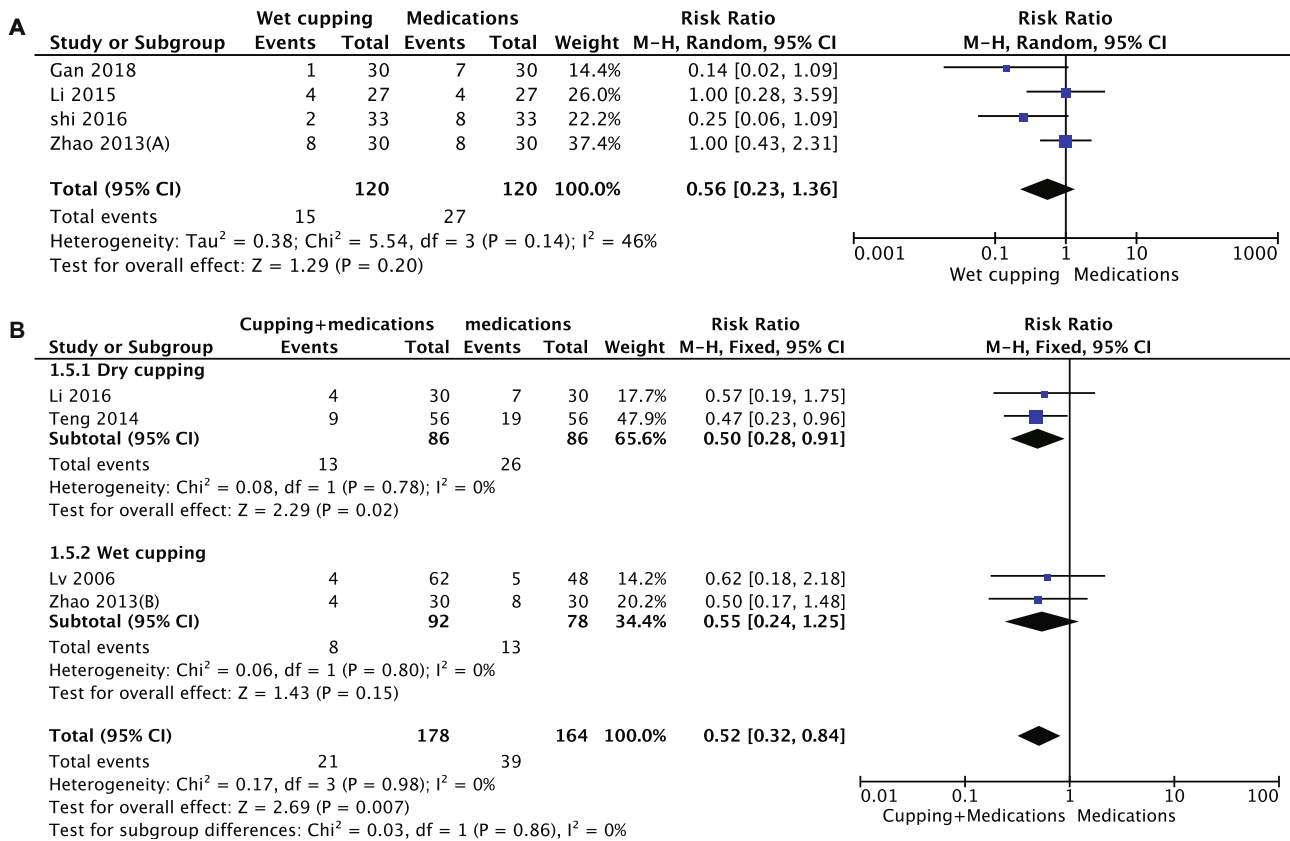


Fig. 4. Forest plot of recurrence rate. A: Forest plot showing effects of wet cupping compared to medication on recurrence rate of chronic urticaria. B: Forest plot showing effects of cupping combined with medications compared to medications on recurrence rate of chronic urticaria.

[41]. When wet cupping was combined with cetirizine, one case of drowsiness and one case of dry mouth were reported [38]. A number of expected adverse events were reported in antihistamine-only arms of several studies. The most commonly reported was drowsiness [26,34,38,40,41]. Dizziness, dry mouth, fatigue, headache and emesis were also reported across various studies.

3.7.4. Skin disease quality of life index score

None of the 12 RCTs reported the skin disease quality of life index score as a response variable.

4. Discussion

4.1. Main results

Our meta-analysis showed that treatment of CU with wet cupping or antihistamines resulted in no differences in total effective rate or recurrence rate between the therapies. Thus, wet cupping might be similarly effective to treatment with antihistamines.

The addition of cupping therapy to antihistamine treatments, led to improved total effective rates and reduced recurrence rates. However, subgroup analyses showed that wet cupping was primarily responsible for the positive changes in the total effective rate. Conversely wet cupping showed a nonsignificant trend in reducing the recurrence rate, while dry cupping significantly reduced recurrence of CU. When cupping therapy was used as an adjuvant therapy alongside acupuncture, the total effective rate was improved over acupuncture alone. There was insufficient evidence to show the same improvement in the recurrence rate. We conducted subgroup analyses based on the types of experimental

and control interventions to account for any statistical heterogeneity.

4.2. Limitations

The quality of evidence in this meta-analysis was low due to the risk of bias that was either high or unclear in many of the available studies. Our review has important limitations that should be carefully considered. First, due to the nature of cupping therapy, the blinding of cupping practitioners was not possible. This may have affected the reporting of treatment results in favor of cupping. Second, methods for random sequence generation, allocation concealment and assessment blinding were generally assessed to be poor, due to the lack of sufficient information reported in each study. Random sequence generation was reported clearly in only six studies and helped to account for their low risk of bias. Allocation of patients to study groups was adequately described in only one study out of the 12 [33]. However, assessment blinding was unclear in all 12 studies. Third, there may be a risk of publication bias due to insufficient sample size. Fourth, since there were fewer than ten studies included in the meta-analyses, the assessment of publication bias based on the funnel plots could not be carried out. Fifth, studies not indexed in Chinese or English databases may not have been identified by our search methodology.

Generalizability is a problem among these studies. Because of the lack of rigorous study design, the quality of evidence in these studies is insufficient to invite extrapolation to broader contexts. Study investigators used neither the CONSORT statement as a model for reporting their trials, nor the STRICTA criteria [43] to report the interventions. By following these guidelines, they would have provided uniform information for future systematic reviews

and meta-analyses. All the studies in this meta-analysis used the total effective rate as the primary outcome, but this is not an internationally accepted standard, particularly for CU.

4.3. Implications for practice and research

The addition of wet cupping therapy to acupuncture or antihistamine treatments was found to increase the effective rates beyond those of acupuncture or antihistamine alone. If true, this finding would provide doctors with more treatment options. From the analysis in the present review, we recommend dry cupping treatment, favoring the CV 8 acupoints, with a frequency of every other day for duration of four weeks. Similarly, for wet cupping we recommend the acupoints BL 13, DU 14, LI 11 and SP10, with a frequency of every other day for duration of four weeks.

Future studies should use patient-reported outcome measures, such as the urticaria activity score, the CU quality of life questionnaire and the urticaria control test, which would be helpful to define the effect and impact of CU on patients [1,44]. Among included studies, there was heterogeneity in frequency of treatment, the course of treatment and the follow-up period; this may reflect the fact that cupping therapy for CU does not have a consensus standard of care. Although this analysis showed that cupping therapy used as an adjuvant to drug or acupuncture therapy may have an additional benefit in CU, a well-controlled clinical trial is still needed to confirm this analysis.

Histamine and IgE play key roles in the pathogenesis of urticaria [1,45]. Cupping treatment can reduce elevated plasma IgE, thereby reducing the release of cellular transmitters and the permeability of blood vessels, which may alleviate symptoms [46]. One study speculated that cupping caused auto-hemolysis, which can then produce histamine-like substances and consequently strengthen immunity [47]. Overall, however, the mechanism for effects of cupping therapy on urticaria is unknown, and basic research is needed to supplement clinical evidence.

4.4. Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review to evaluate the effectiveness and safety of cupping for treating CU. One other systematic review, by Yao et al. [27] was performed to evaluate the efficacy of bloodletting therapy for treating CU. Yao's study [27] which was similar to the wet cupping therapies in our review only included a comparison of cupping therapy to medication therapy, while in our review, control groups receiving medication or acupuncture were included, allowing a wider range of therapies to be covered. Moreover, our study was more thorough and was able to pool more data from the included studies. Our study also considered the sources of heterogeneity and conducted subgroup analyses, where possible.

5. Conclusion

To our knowledge, this is the first meta-analysis that evaluated the efficacy of cupping therapy in the treatment of CU. Wet cupping may provide an effective treatment, especially in conjunction with antihistamines. Cupping therapy, used as adjuvant therapy with antihistamines or acupuncture, enhances the treatment efficacy compared to either method alone. In the 12 studies reviewed, cupping therapy appeared to be a safe practice. Results should be interpreted with caution and applied with care to clinical practice because of the poor methodological quality reported in these studies.

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Author contributions

Conceptualization: XJX; data curation: YZS, LXZ, WC and YL; formal analysis: CXL, XJX and SYZ; investigation: WC and ZHZ; methodology: XJX, JPY, YZS and YL; project administration: XJX and YZS; supervision: YL and QHZ; writing (original draft): XJX; writing (review and editing): MLC.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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