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STUDY PROTOCOL

The Effectiveness and Safety of Cupping Therapy on CV8 Shenque for Urticaria; a Protocol for Systematic Review and Meta-Analysis

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Purpose: Urticaria is a common mast-cell-driven disease that poses a great burden on patients and society. Suggested therapeutic methods include avoidance of triggers and the use of medications, such as H1-antihistamines; however, limitations remain regarding efficacy, dealing with comorbidities, and adverse events. Cupping therapy (CT) at CV8 Shenque has been used in traditional Chinese medicine for the treatment of various dermatological diseases, including urticaria. The efficacy of the treatment has been revealed by previous clinical trials and case reports. This study was performed to provide a protocol for a systematic review and meta-analysis to analyze the effectiveness and safety of CT at CV8 Shenque for urticaria patients.

Patients and Methods: Searches of electronic databases using manual searches and contact with the corresponding authors will be performed using predefined criteria for all randomized controlled trials on CT at CV8 Shenque for urticaria patients. Every part of the process will be conducted by two independent researchers, with conflicts being solved by a third author. The primary outcomes will be symptom scores, quality of life, and effective rate. Secondary outcomes will be adverse events and diagnostic test results. RevMan 5.4 software will be used to perform the meta-analysis. The Cochrane Collaboration "Risk of bias" tool will be used for risk of bias judgments.

Results: Our study will evaluate the effectiveness and safety of CT at CV8 Shenque as a treatment option for urticaria.

Conclusion: This systematic review is the first to investigate the effect of CT at CV8 Shenque for urticaria patients. Our study will provide objective evidence of an alternative approach to urticaria for clinicians and patients.

Study Registration: PROSPERO (Registration number: CRD42023434913).

Keywords: urticaria, Shenque, cupping therapy, systematic review, meta-analysis

Introduction

Urticaria is a common condition that is specified by the appearance of wheals, skin lesions and central swelling of variable size associated with itching or burning sensation that disappears within 24 hours, and angioedema, which sometimes causes pain and can take up to 72 hours to disappears, or both.[1] The updated European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), and European guidelines (EuroGuiDerm) alongside the Asia Pacific Association of Allergy and Asthma and Clinical Immunology (APAAACI) guidelines classify different types of urticaria based on duration, such as whether they are acute (6 weeks or less) or chronic (more than 6 weeks), and the existence of definite triggers, such as being either inducible or spontaneous.[2] The global lifetime prevalence for acute urticaria (AU) is 20%,[2] while it is 1% for chronic urticaria (CU).[3] Although the pathogenesis is not clear, it is known to be a mast cell-driven disease that is related to the release of mediators from activated skin mast cells.[1] The diagnosis of urticaria is mostly based on anamnesis and physical examinations, while for chronic urticaria, diagnostic tests, such as differential blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin G (IgG), anti-Thyroperoxidase (anti-TPO), and total immunoglobulin E (IgE) may be

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consulted.[2] The evaluation of disease activity is performed by using scales, including the urticaria activity score (UAS) and chronic urticaria quality of life questionnaire (CU-Q2oL), as suggested by the EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines.[2] Currently, the therapeutic approach aims to identify and eliminate the underlying causes and reduce the signs and symptoms, until they are completely relieved. The use of second-generation H1-antihistamines represents the first-line therapy for urticaria. However, if no significant benefits are observed, even following an increase in dosage (up to four-fold), then, omalizumab is added as the second-line therapy. Additionally, if the second-line therapy also fails, the immunosuppressive medicine ciclosporin can be used as the third-line therapy, although ciclosporin is used off-label for urticaria and its use presents higher incidences of adverse effects.[2] Therefore, the current therapeutic approaches for urticaria are limited and the elimination of its underlying causes remains impossible in most cases since they also remain unknown. Thus, pharmacological treatment should be continued until the symptoms are completely resolved. However, more than 25% of patients are resistant to H1-antihistamines, while using omalizumab and ciclosporin can only control symptoms in two-thirds of H1-antihistamine-resistant patients.[2] Psychiatric comorbidities should also be considered in urticaria patients, especially for CU, where patients present a high prevalence of 35% to 60%.[4] Anxiety disorders are the most common comorbidity followed by depression and somatoform disorders.[5] Urticaria symptoms disturb daily life, through the constant itching and unpredictable occurrence of wheals, ultimately leading to withdrawal from society.[4] Quality of life (QoL) impairment is also imposed by treatment through concern about health triggered by poor responses to medication and fatigue induced by antihistamines.[4,6,7] Previous studies have shown a positive correlation between psychological symptoms and physical symptoms (UAS and visual analog scale (VAS)).[7] The current hypothesis suggests that CU is induced by the immune and nervous systems or that CU occurs due to a stress-related mechanism involving cortisol.[7] Thus, there is a need for effective, safe, and cost-effective novel therapies that can improve symptoms and QoL.

External treatments including traditional Chinese medicine (TCM), such as cupping therapy (CT), are garnering clinical attention as new treatment approaches to urticaria.[8] External treatment methods can directly reach the skin, thereby offering local and overall therapeutic effects, alongside being simple in operation, flexible in method, less irritating, and providing remarkable curative effects.[8] CT is a TCM external therapy that has been used clinically to treat various dermatological conditions, including urticaria.[9] It is performed by creating a sub-atmospheric pressure at selected skin places, either through heat or suction.[10] In a modern perspective, cupping promotes an increase in blood flow to the skin, changes the skin's biomechanical properties, increases pain thresholds, improves local anaerobic metabolism, reduces inflammation, and modulates the cellular immune system.[11] A randomized controlled trial revealed that cupping therapy combined with autohemotherapy significantly downregulated the stimulant and mediator levels in mast cells, including serum interleukin 4 (IL-4) and Ig E, in patients with CU.[12] CT at CV8 Shenque is a major external treatment for urticaria.[8] According to a meta-analysis on cupping therapy for CU, CV8 Shenque was one of the most frequently selected acupoints (in 4 out of 13 included studies), while it was used in all the studies that used the dry cupping method.[13] CV8 Shenque, which is located at the umbilicus, is characterized by abundant microcirculation and an effect on the microvascular endothelial cells, which derives from its unique vascular biology.[14] There have been many case reports on the effectiveness of CT occurring at CV8 Shenque, which has relieved the symptoms of both AU and CU.[15,16] Indeed, in a RCT, which included 82 patients with chronic urticaria, performing cupping at CV8 Shenque combined with medicinal vesiculation had a superior effect on reducing IgE and IL-4 levels, compared to conventional medications.[17] Moreover, CV8 Shenque is also known for its sedative effect, whereby it is used as one of the important acupoints for insomnia.[18] In TCM theory, CV8 Shenque relieves Yang deficiency, which is associated with depression and fatigue.[19] According to previous studies, treatments at CV8 Shenque effectively relieved anxiety, depression, and sleep disorders,[18,20,21] which suggests that CT at CV8 Shenque has a unique therapeutic benefit in both physical and psychological aspects. In our knowledge, a systematic review (SR) on the use of CT on CU has been previously conducted;[13] however, this SR focuses on the effect of applying CT to a specific acupoint, which has not previously been conducted. Thus, in this meta-analysis, we aimed to evaluate the effectiveness and safety of performing CT at CV8 Shenque for urticaria.

Materials and Methods

Study Registration

SR and meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement.[22] It has also been registered on PROSPERO (Registration number: CRD42023434913).

Data Sources and Search Strategies

Researchers will independently perform the search according to the predefined search strategy using combinations of keywords, such as "cupping", "Shenque", "CV8", and "urticaria" in each database's language. The full search strategy is described in Table 1. We will search the following databases: MEDLINE, PubMed, Cochrane Library, China National Knowledge Infrastructure, China Science Journal Database, KoreaMed, Wanfang Data, CiNii, J-STAGE, Korean Medical Database, Korean Studies Information Service System, National Digital Science Library, Korea Institute of Science and Technology Information, and Oriental Medicine Advanced Searching Integrated System from their inception to October 30, 2023. Other literature resources, such as conference articles and registers of clinical trials will also be browsed for potential information. If insufficient information is provided, the relevant authors will be contacted.

Eligibility Criteria

Types of Studies

The SR will only include randomized clinical trials (RCTs) that assessed the efficacy of Shenque cupping on urticaria. Other research, such as non-clinical trials, non-RCTs, reviews, case series, and animal studies will be excluded.

Participants

Patients diagnosed with both AU and CU will be included. The diagnosis could have been performed according to the authoritative guidelines of Chinese medicine or Western medicine. The EAACI/GA²LEN/EuroGuiDerm/APAAACI

Table 1 Search Strategy

No.	Search Terms
#1	Randomized controlled trial
#2	Controlled clinical trial
#3	Random OR randomly
#4	Placebo
#5	OR #1–4
#6	Cupping OR cupping therapy
#7	Shenque OR Shenque acupoint
#8	CV8
#9	Umbilicus
#10	OR #7–9
#11	Urticaria
#12	Chronic urticaria
#13	Acute urticaria
#14	OR #11–13
#15	#5 AND #6 AND #10 AND #14

Note: Search strategy will be modified according to device.

guidelines suggest that diagnosis be based on the anamnesis and expression of characteristic symptoms for AU, with additional provocation tests conducted for subtypes of chronic inducible urticaria (CindU). Historical, physical expression, and results on basic testing (ESR, CRP, IgG, anti-TPO, and IgE) were considered in the diagnosis of chronic spontaneous urticaria (CSU) and in distinguishing between its subtypes.[2] Gender, age, etiology, ethnic groups, and severity will not be regarded. Patients with other complications and dermatological conditions, or taking medicine will be excluded.

Interventions

Studies will be included if the intervention group was treated with CT at CV8 Shenque. There will be no restrictions on the methods used, such as dry cupping, wet cupping, moving cupping, or on the materials, such as glass, porcelain, and plastic. Any other treatment or co-treatment applied to CV8 Shenque, including medication or moxibustion, will be excluded. Co-interventions, such as conventional medicine or other TCM methods will be allowed when the same method was used in both groups.

Comparisons

The control group will be treated with any other treatment, such as conventional medication and TCM methods, including acupuncture and herbal medicine. Comparisons between CT and other treatments on CV8 Shenque will not be conducted, thus, the application of these treatments on CV8 Shenque will be excluded.

Outcomes

The effect sizes in the outcome were extracted at the first time point after the intervention finished. Symptom severity and QoL are factors most commonly used in the assessment of urticaria with various scales, such as urticaria activity score (UAS), VAS, and CU-Q2oL.[2,23] We expect to identify significant improvements in both aspects following CT at CV8 Shenque. Thus, our primary outcomes will be symptom scores such as wheal score (WS) and pruritus score (PS) included in UAS, QoL, and effective rate (ER). Secondary outcomes will be adverse events and diagnostic test results, including ESR, CRP, and IgE. Outcomes in any measure will be primarily collected and converted to the same measure, if possible. If not, they will either be analyzed separately or only as outcomes with sufficient number of studies collected.

Study Selection

Two researchers (CSY and PSS) will independently select the studies based on predefined criteria. Initially, duplicates will be deleted before the title and abstract were screened for eligibility. The full text of the remaining articles will be read for further assessment. Any disagreement during the process will be solved through discussion or consultation with the third author (SWS). The selection procedure will be reported using the PRISMA flowchart, as shown in Figure 1.

Data Extraction and Management

Two researchers will independently extract the following information: basic information on studies (title, author information, publication, type of study, etc.), participants (sample size, gender, age, type of urticaria, and duration of disease), interventions and controls (method, frequency, and time), outcomes, study design, and other controversial details. Conflicts will be solved through discussion or submitted to a third author for evaluation. Corresponding authors will be contacted for additional information if there is any ambiguous or missing data. Then, if impossible, the analysis will be conducted with whatever complete data obtained. EndNote X20 software will be used throughout the review for data management.

Data Synthesis and Analysis

A wide variety of study settings is expected, thus the meta-analysis of studies will be conducted using comparable intervention and outcome. The changes from the baseline of the trial to the end of the intervention will be synthesized. Data analysis will be conducted using RevMan 5.4 software from the Cochrane Collaboration. The effect sizes will be presented by a forest plot for each outcome. For continuous outcomes, the treatment effect will be evaluated by mean differences (MD) for the same outcome measures, or standardized MD for different outcome measures, with 95%

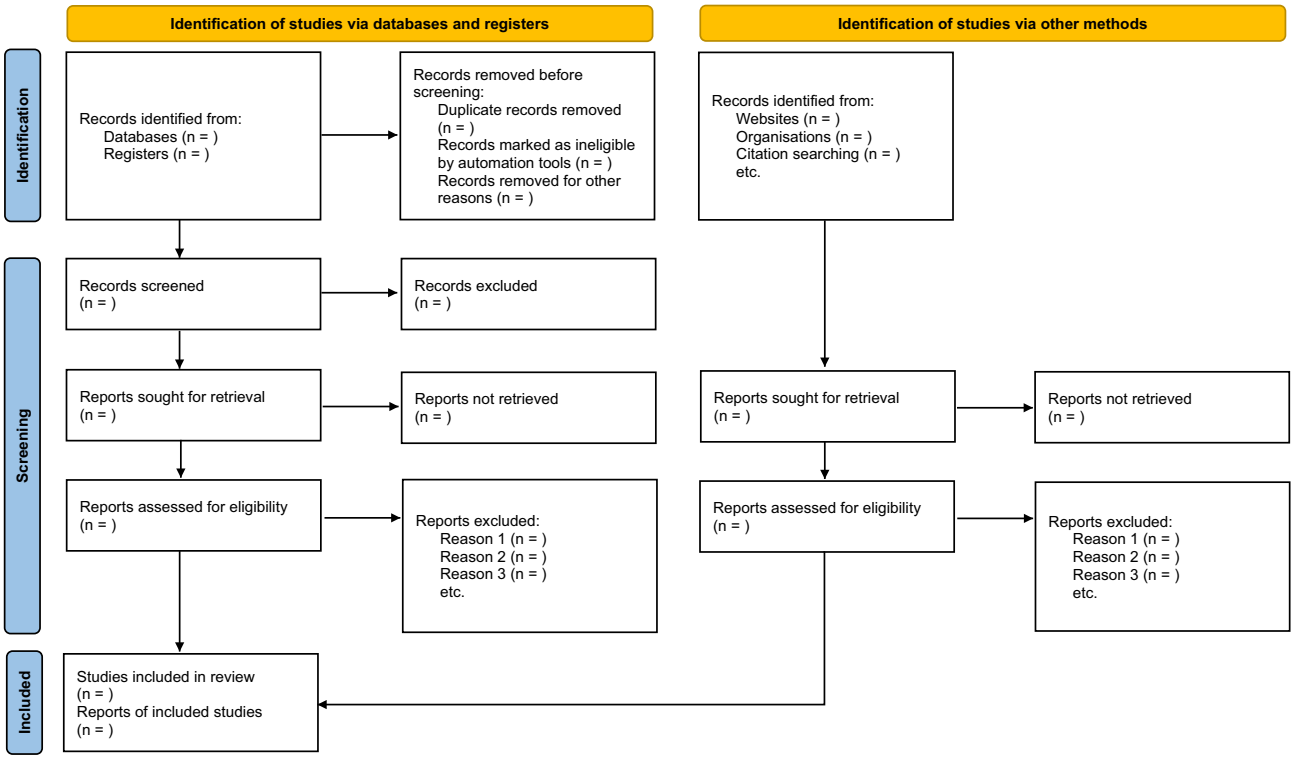

Figure 1 PRISMA 2020 flowchart for systematic review.

confidence intervals (CIs). Moreover, for the dichotomous outcome, the risk ratio or odds ratio will be calculated with 95% CIs. In the presence of significant heterogeneity, a random-effects model will be used, and if not, a fixed-effect model will be used.[24] Heterogeneity will be examined by Chi-squared and I^2 tests; if $P > 0.1$ or $I^2 < 50\%$, it will be assumed that the no heterogeneity was evident. Subgroup analysis will be conducted, if possible, in consideration of the possible influence of factors, such as different methods, interventions, and patient groups. The robustness of the outcome will be assessed by sensitivity analysis. Regarding publication bias, if more than 10 studies are included, the assessment will be performed through visual inspection using funnel plots. In all analyses, p-value < 0.05 will represent statistical significance. The quality of evidence will be rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as high, moderate, low, and very low.[25]

Risk of Bias Assessment

Two independent reviewers (CSY and PSS) will use the Cochrane Risk of Bias Tool to assess the risk of bias in the selected studies.[26] Then, the risk of bias will be rated as low, high, or unclear for each of the following seven domains: random sequence generation, allocation concealment, blinding methods (participants/outcomes) incomplete outcome data, selective reporting, and other biases. Discussions will be conducted on any disagreements between the reviewers, and if a conclusion cannot be reached, the third author (SWS) will make the final decision.

Ethics

This study will not require the personal information of the patient, thus, no ethical approval will be required.

Discussion

As a disease with a long duration, an average duration of 11.5±10.8 years for CU, urticaria causes a substantial burden to patients and society.[3] Unpredictable occurrence of symptoms and common comorbidities, including anxiety and depression, thereby interfering with the daily lives of patients. The burden from treatment costs is also notable, with the global direct costs ranging

from around 900 to 2400 purchasing power parity dollars (PPP$) per patient per year, and indirect costs mainly from work productivity loss ranging from PPP$ 6.550 to PPP$ 15.550.[3] Although medication, such as H1-antihistamines and omalizumab are suggested in the guidelines, they still have limitations regarding efficacy, dealing with psychological comorbidities, and adverse events.[27] Therefore, the search for effective and safer treatments for urticaria is in progress. Previous studies have demonstrated that TCM external therapies, such as CT at acupoint CV8 Shenque, present a significant effect in relieving the symptoms and improvement of QoL. According to the literature on ancient Chinese medicine "Medical Primitives", CV8 Shenque is said to be closely related to all meridians (twelve meridians, eight extra meridians) and distributes five internal organs, thereby describing its ability to regulate body functions.[28] In a modern perspective, CV8 Shenque possesses abundant microcirculation, endothelial cells, microvascular endothelial cells, transient receptor potential vanilloid family channels, and neuropeptides secreted by endothelial cells.[18] The exact mechanism for how CT at CV8 Shenque affects urticaria remains unclear and needs to be researched further, although considering previous RCTs and case reports, we believe that CT at CV8 Shenque provides benefits as an alternative treatment for urticaria. Our SR will provide evidence for clinicians, patients, and researchers.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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