Clinical Efficacy and Safety of Chinese Herbal Medicine Auxiliary Therapy for Childhood Cough Variant Asthma: A Systematic Review and Meta-analysis of 20 Randomized Controlled Trials

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Abstract

This study aimed to evaluate the efficacy and safety of Chinese herbal medicine auxiliary therapy (CHMAT) in treating childhood cough variant asthma (CVA). A systematic literature review was conducted on RCTs that compared CHMAT, i.e., Chinese herbal medicine (CHM) plus pharmacotherapy (PT), versus the same PT alone in the treatment of CVA. All included trials were assessed for quality and risk bias and analyzed according to the criteria of the Cochrane Handbook based on the Review Manager 5.3 software program. Twenty studies were identified and the CHMAT group had a positive effect on the total effective rate and a lower recurrence rate compared with the control group. CHMAT may have positive effects on CVA, leading to better improvement in disorders of cough and asthma and less adverse effects. However, the methodology and reporting quality of current studies are generally low. Further studies should include larger sample sizes with a strict design to confirm these findings.

Key words: Chinese herbal medicine (CHM), childhood cough variant asthma (CVA), randomized controlled trials, systematic review, meta-analysis

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Introduction

Cough variant asthma (CVA) is a subtype of bronchial asthma characterized by episodes of cough, chronic cough and intractable cough, particularly at night (1, 2). CVA accounted for 24.0-33.3% of chronic cough cases, and children comprise 0.18% of the total incidence (3, 4). Pharmacotherapy (PT) consisting of glucocorticoids, antihistamine drugs or β_2 agonists is predominantly used in the treatment of CVA patients (5). However, the results are poor and considered to be largely due to contraindications, side effects or addiction. At present, Chinese herbal medicine (CHM) either used alone or integrated with conventional PT has been widely chosen for the treatment of CVA in China. In recent years, previous reports by Ge et al. (6), Zhang et al. (7), and Chen et al. (8) demonstrated systematic reviews on CHM

for childhood CVA, which compared CHM versus conventional PT alone using Jadad scores for the quality of literature evaluation and the effective rate for the clinical curative effect evaluation. Thus, previous reports have lacked a relatively objective evaluation of the quantitative indicators. Therefore, a systematic literature review was conducted in the present study using randomized control trials (RCTs) that compared CHMAT, i.e., CHM plus conventional PT, versus the same PT alone in the treatment of childhood CVA. All included trials were assessed for quality and risk bias and analyzed according to the criteria of the Cochrane Handbook. The outcome measures included the total effective rate, recurrence rate, symptom outcome improvement of traditional Chinese medicine (TCM), the levels of lung function containing the forced expiratory volume in one second (FEV_1), FEV_1 /forced vital capacity (FVC) (%), peak expiratory flow rate (PEFR), and PEFR (%). Moreover, the cough

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sensitivity LgC_s, total immunoglobulin E (T-IgE) and the levels of eosinophils (EOS) were included.

The objective of this review was to evaluate the evidence for efficacy of treatment using CHMAT versus the same PT in childhood CVA according to RCTs that used objective outcome measures and indices. Moreover, the study also aimed to assess the safety of the integrative treatments.

Methods

Criteria for study inclusion in this review

Types of studies: All RCTs without restrictions on language, blinding, or publication type were included.

Types of participants: National and international studies enrolling patients with childhood CVA as defined by the Chinese Medical Association or other well-recognized CVA diagnostic criteria were included. Patients between 0-14 years of age, of both sexes and of any ethnic group with diagnosed CVA were included. Patients with serious lung diseases, such as chronic obstructive pulmonary disease, lung cancer and tuberculosis, or mentally ill were excluded.

Types of interventions: Studies comparing oral CHMAT plus conventional PT versus the same conventional PT alone for childhood CVA, including any pharmaceutical dosage form such as decoction, capsule, particle, pill, or powder, were included.

Types of outcomes: The primary outcome was the total effective rate. Secondary outcomes included the symptom outcome improvement of TCM and the levels of lung function containing FEV₁, FEV₁/FVC (%), PEF and PEF (%). Moreover, the levels of LgC_s, T-IgE and EOS were included. The Chinese medicine (CM) efficacy standards were defined as follows (9): Efficacy index (n)=(symptom score sum before treatment - symptom score sum after treatment)/symptom score sum before treatment × 100%; ①Clinical control: n ≥ 90%; ②Markedly effective: 60% ≤ n < 90%; ③Effective: 30% ≤ n < 60%; and ④Ineffective: n < 30%. In addition, a safety evaluation was assessed using the Treatment Emergent Symptom Scale (TESS) and the incidence of treatment-effect adverse events.

Search methods for the identification of studies

We used the following electronic databases to search all relevant studies: PubMed (1966 to December 2014), the Cochrane Central Register of Controlled Trials, EMBASE (1980 to December 2014), the Chinese Biomedicine Database (CBM) (1976 to December 2014), China National Knowledge Infrastructure (CNKI) (1979 to December 2014), and VIP (1989 to December 2014). All trials included were analyzed according to the criteria of the Cochrane Handbook. The Review Manager (RevMan) 5.3 software program was used for the data analysis. The following search terms were used: “childhood cough variant asthma,” or “childhood cough type asthma” or “cough variant asthma in children” or “cough type asthma in children” AND “pharmacotherapy

or traditional Chinese herbal” or “alternative medicine” AND “randomized or controlled or clinical research/study”.

Assessment of risk of bias in the included studies

According to the recommendations in the Cochrane Handbook, the methodological qualities of trials were evaluated independently by two investigators using the assessment tool for risk of bias. The following checklists lie as follows: ① Random sequence generation; ② Allocation concealment; ③ Blinding of participants and personnel; ④ Blinding of outcome assessors; ⑤ Incomplete outcome data; and ⑥ Selective outcome reporting.

Data collection and analysis

Study selection: To verify the studies that met the inclusion criteria, we examined abstracts from the initial search independently. We telephone-interviewed the original authors of the Chinese articles to identify the randomization procedure and other methodological issues to ensure that the included studies were RCTs. If the required information was not available, then the articles were excluded.

Data extraction: The quality of studies that included randomization was assessed independently by two investigators (SP and ZLF) using a piloted data extraction form. There were no disagreements (see Table 1).

Data analysis: The Cochrane Collaboration's RevMan 5.3 software program was used for all data analyses. For dichotomous outcomes, the results were expressed as the odds risk (OR) with 95% confidence intervals (CI); for continuous outcomes, the data were expressed as the mean difference (MD) 95%CI. Heterogeneity was tested with I². The I² values of 50% or greater indicated a substantial level of heterogeneity, thus a random-effects model (REM) was used for data pooling. Otherwise, a fixed-effects model (FEM) was applied. In addition, funnel plots were conducted and checked for potential publication bias when nine or more studies reported the same outcome measure.

Results

Results of the search

An initial search identified 694 potentially relevant articles. Following the search and study selection process (Fig. 1), 20 (10-29) studies (1,590 participants) were included in this review. All studies were published in Chinese.

Assessment of risk of bias

See Table 2.

Meta-analyses of the outcomes

Comparison of the effective rate: A total of 19 trials (10-21, 23-29) reported the total effective rates with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group (OR 3.52, 95%CI 2.57-4.82, p<0.00001) (Fig. 2).

Table 1. Characteristics of the Included Studies.

References	No. of participants		Baseline	Intervention		Course of treatment (w)	Outcome measures
	Trial	Control		Trial	Control		
10	54	54	Comparability	CHMAT	PT	8	①③
11	48	48	Comparability	CHMAT	PT	4	①③④
12	40	40	Comparability	CHMAT	PT	4	①②⑧
13	58	58	Comparability	CHMAT	PT	4	①③⑧
14	27	23	Comparability	CHMAT	PT	4	①②③⑤
15	40	40	Comparability	CHMAT	PT	6	①②
16	18	18	Comparability	CHMAT	PT	4	①③
17	30	30	Comparability	CHMAT	PT	6	①⑤⑦
18	50	50	Comparability	CHMAT	PT	4	①
19	30	30	Comparability	CHMAT	PT	4	①
20	30	30	Comparability	CHMAT	PT	3	①③
21	45	45	Comparability	CHMAT	PT	4	①③
22	36	31	Comparability	CHMAT	PT	8	②③⑧
23	60	60	Comparability	CHMAT	PT	4	①②⑥⑦
24	30	30	Comparability	CHMAT	PT	4	①③⑥
25	65	50	Comparability	CHMAT	PT	4	①②③④
26	25	25	Comparability	CHMAT	PT	4	①④
27	40	40	Comparability	CHMAT	PT	3	①②③
28	40	40	Comparability	CHMAT	PT	6	①⑧
29	42	40	Comparability	CHMAT	PT	8	①③④⑧

Annotation: ①: Effective rate, ②: Recurrence rate, ③: Clinical symptom evaluation, ④: Lung function detection, ⑤: LgC_s, ⑥: IgE, ⑦: EOS, ⑧: Adverse events, CHMAT: Chinese herbal medicine adjuvant therapy, PT: Pharmacotherapy

Figure 1. Flowchart of the search and study selection process.

Table 2. Assessment of Risk of Bias for 20 Studies Based on the Cochrane Handbook.

References	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome Assessment	Incomplete outcome data	Selective outcome reporting
10	L	U	L	U	U	L
11	U	U	U	U	U	H
12	L	U	U	U	L	U
13	L	L	U	U	L	U
14	U	U	U	U	L	L
15	U	U	U	U	L	L
16	U	U	U	U	H	L
17	U	U	U	U	L	L
18	U	U	U	U	L	U
19	U	U	U	U	U	L
20	U	U	U	U	L	L
21	U	U	U	U	L	L
22	U	U	U	U	L	L
23	U	U	U	U	L	U
24	U	U	U	U	L	L
25	L	U	U	U	U	L
26	U	U	U	U	L	L
27	U	U	U	U	L	L
28	U	U	U	U	L	L
29	L	U	U	U	L	L

Annotation: Risk of bias judgments: L: Low risk, U: Unclear risk, H: High risk

Figure 2. Meta-analysis of treatment effect of CHMAT group vs. the control group on effective rate.

Publication bias: Potential publication bias was determined by a funnel plot analysis of the 19 studies comparing the effective rate of CHMAT versus PT. A significant asymmetry was observed (Fig. 3), which indicated that trials of low quality were included and the existence of potential publication bias.

Comparison of the success withdrawal rate: Seven trials (12, 14, 15, 22, 23, 25, 27) reported the success withdrawal rate, i.e., lower recurrence rate, with the fixed-effects meta-analysis demonstrating a significant difference in favor

of the CHMAT group (OR 4.18, 95%CI 2.57-6.80, $p < 0.00001$) (Fig. 4).

Comparison of the symptom outcome improvement of TCMnone

Time of cough symptom relief: A total of 9 trials (10, 11, 13, 16, 21, 22, 24, 25, 27) reported the time of cough symptom relief with the random-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-2.67, 95%CI (-3.19, -2.16), $p < 0.00001$] (Fig. 5).

Figure 3. Funnel plot. Annotation: Comparison=CHMAT group vs. the control group; outcome=effective rate.

Figure 4. Meta-analysis of treatment effect of CHMAT group vs. the control group on success with-drawal rate.

Time of cough symptom removal: Seven trials (10, 13, 16, 21, 22, 24, 25) reported the time of cough symptom removal with the random-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-2.62, 95%CI (-3.76, -1.49), $p < 0.00001$] (Fig. 5).

Time of asthma symptom removal: Two trials (10, 11) reported the time of asthma symptom removal with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-2.49, 95%CI (-2.95, -2.03)], $p < 0.00001$ (Fig. 5).

Time of disappearance of wheezing: Two trials (10, 11) reported the time of disappearance of wheezing with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-2.85, 95%CI (-3.40, -2.31), $p < 0.00001$] (Fig. 5).

Total score of CM syndrome: Three trials (14, 20, 29) reported the total score of CM syndrome with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-1.28, 95%CI (-1.55, -1.00), $p < 0.00001$] (Fig. 5).

Comparison of the levels of lung function: Regarding the levels of lung function, the CHMAT group showed better effects in the indices of FEV₁ [MD=0.25, 95%CI (0.12, 0.38), $p = 0.0002$], FEV₁/FVC (%) [MD=11.72, 95%CI (5.37, 18.08), $p = 0.0003$], PEFR [MD=1.12, 95%CI (0.69, 1.56), $p < 0.00001$], and PEFR (%) [MD=-5.00, 95%CI (-9.49, -0.52), $p = 0.03$].

Comparison of FEV₁ (L): Two trials (11, 26) reported the index of FEV₁ with the fixed-effects meta-analysis demonstrated a significant difference in favor of the CHMAT group [MD=0.25, 95%CI (0.12, 0.38), $p = 0.0002$] (Fig. 6).

Comparison of FEV₁/FVC (%): Two trials (11, 26) reported the index of FEV₁/FVC (%) with the random-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=11.72, 95%CI (5.37, 18.08), $p = 0.0003$] (Fig. 6).

Comparison of PEFR (L): Two trials (25, 26) reported the index of PEFR with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=1.12, 95%CI (0.69-1.56), $p < 0.00001$] (Fig. 6).

(A)

(B)

(C)

(D)

(E)

Figure 5. Meta-analysis of treatment effect of CHMAT group vs. the control group on symptom outcome improvement: (A) Time of cough symptom relieving. (B) Time of cough symptom removal. (C) Time of asthma symptom removal. (D) Time of disappearance of wheezing. (E) Total score of CM syndrome.

Comparison of PEFR (%): Two trials (25, 26) reported the index of PEFR (%) with the random-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-5.00, 95%CI (-9.49, -0.52), $p=0.003$] (Fig. 6).

Comparison of cough sensitivity LgCs: Two trials (14, 17) reported the levels of LgCs with the random-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=0.66, 95%CI (0.18, 1.14), $p=0.007$] (Fig. 7).

(A)

(B)

(C)

(D)

Figure 6. Meta-analysis of treatment effect of CHMAT group vs. the control group on Lung function detection changes: (A) Comparison of FEV₁ (L). (B) Comparison of FEV₁/FVC (%). (C) Comparison of PEFR (L). (D) Comparison of PEFR (%).

Figure 7. Meta-analysis of treatment effect of CHMAT group vs. the control group on cough sensitivity LgCs changes.

Comparison of T-IgE: Two trials (23, 24) reported the levels of T-IgE with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-56.67, 95%CI (-83.01, -30.34), $p < 0.0001$] (Fig. 8).

Comparison of EOS: Two trials (17, 23) reported the levels of EOS with the fixed-effects meta-analysis demonstrating a significant difference in favor of the CHMAT group [MD=-0.19, 95%CI (-0.26, -0.12), $p < 0.00001$] (Fig. 9).

Safety evaluation

Adverse events were observed in five studies (12, 13, 22, 28, 29). No studies used the TESS score, but merely reported the number of adverse reactions and specific symptoms. For the CHMAT group, one trial (12) reported that 2 cases had palpitation and 1 case had tiredness; another (13) reported that 1 case had nasopharyngeal dryness; another (28) reported that 1 case had hoarseness; and the last (29) reported that 1 case had nausea. For the PT group,

Figure 8. Meta-analysis of treatment effect of CHMAT group vs. the control group on T-IgE changes.

Figure 9. Meta-analysis of treatment effect of CHMAT group vs. the control group on EOS changes.

one trial (12) reported that 12 cases had palpitation, 14 cases had nausea and vomiting, 7 cases had hoarseness, 3 cases had tiredness and 2 cases had tremor; another (13) reported that 2 cases had tongue numbness, 1 case had dry eyes and 1 case had nasopharyngeal dryness; another (22) reported that 1 case had abdominal pain, 1 case had vomiting, 1 case had restlessness and 1 case had drowsiness; another (28) reported that 5 cases had hoarseness, 12 cases had palpitation, 11 cases had fibrillation, and 16 cases had nausea and vomiting; and the last (29) reported that 3 cases had nausea and 2 cases had palpitation.

Discussion

Summary of evidence

A total of 20 RCTs (10-29) involving 1,590 participants were included in this review and compared CHMAT with PT. The main findings of the present study were that there could be an additive benefit from CHMAT in terms of improving the indices in CVA patients. However, due to potential methodological deficits, e.g., limited number and small sample size of the included studies, the potential benefits of CHMAT in the treatment of CVA could not be fully confirmed according to the present evidence, and recommendations for clinical practice should be cautious.

The CHMAT group had a positive effect on the total effective rate compared with the control group. After treatment, the states of CVA were also improved in the CHMAT group compared with the control group in the following indices: time of cough symptom relief, time of cough symptom removal, time of asthma symptom removal, the time of disappearance of wheezing, and the total score of CM syndrome. Regarding the levels of lung function, the CHMAT group showed better effects in the indices of FEV₁, FEV₁/FVC (%), PEFR and PEFR (%). Moreover, the CHMAT

group can better improve the LgC₅ and lower the levels of T-IgE and EOS. No serious or frequently occurring adverse effects were reported between the two groups.

Limitations of the review

These promising results should be interpreted with caution for the following reasons. The methodological deficits identified in the studies included few or no details regarding the generation process for the random sequence and allocation concealment. Thus, it remained unclear whether randomization or allocation concealment was effectively conducted in the studies. Inadequate blinding also contributed to overestimation effect in the trial group. None of the studies used identical placebos for the blinding operations. Therefore, these methodological deficits may have influenced the results of the present study. In additional, language bias and overemphasizing of positive effects due to publication bias may be another limitation of this review. The studies included only those written in Chinese and all research was conducted in China. There was a high compliance from the participants, who expected benefits from CHM. Thus, bias in the performance or in the measurement may have also existed due to the abovementioned factors.

Conclusion

The meta-analysis results indicated that the oral administration of CHMAT appeared to be effective for treating childhood CVA. CHMAT may have positive effects on CVA, leading to better improvement in disorders of cough and asthma and less adverse effects. However, the methodology and reporting quality of current studies are generally low. Further studies should include larger sample sizes with a strict design to confirm these findings.

The authors state that they have no Conflict of Interest (COI).

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