Meta-Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(10) 4006–4018
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Efficacy of Chinese herbal medicine in treatment of allergic rhinitis in children: a meta-analysis of 19 randomized controlled trials

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Abstract

This study aimed to systematically evaluate the effect of Chinese herbal medicine (CHM) for treating allergic rhinitis in children. We reviewed relevant studies retrieved from the following databases: MEDLINE (PubMed), Embase, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, the Cqvip Database, and the Wanfang Database. The analysis was conducted by Cochrane software Revman 5.3. Nineteen randomized, controlled trials were included. Meta-analysis showed that CHM had advantages in the efficacy rate (odds ratio [OR] 3.32; 95% confidence interval [CI], 2.32–4.76), recurrence rate (OR 0.30; 95% CI, 0.18–0.49), scores of symptoms, such as sneezing (mean difference [MD] −1.24; 95% CI, −2.33 to −0.14), running nose (MD −1.32; 95% CI, −2.58 to −0.05), and nasal congestion (MD −0.70; 95% CI, −1.05 to −0.36), but not nasal itching (MD −1.37; 95% CI, −3.96 to 1.22), compared with controls. CHM could also effectively decrease immunoglobulin E levels (MD −46.01, 95% CI, −57.53 to −34.48). The current evidence suggests that CHM is more effective in treating allergic rhinitis in children compared with controls. CHM may also decrease the recurrence and level of immunoglobulin E, and improve symptoms such as sneezing, running nose, and nasal congestion, compared with controls.

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Keywords
Allergic rhinitis, children, Chinese herbal medicine, randomized controlled trial, meta-analysis, immunoglobulin E

Date received: 15 February 2018; accepted: 28 May 2018

Introduction

Allergic rhinitis (AR), which is characterized by symptoms of sneezing, rhinorrhea, nasal congestion, and nasal itching, is a type of disease of the upper respiratory tract. Studies have shown that the prevalence of AR symptoms varies from 1.5% to 24.5%.[1] In China, the mean prevalence of childhood AR ranges from 3.9% to 16.8%.[2] A higher prevalence of AR exists as a single entity in boys than in girls during childhood.[3,4] Most patients complain of symptoms of AR before 20 years old, with 40% being symptomatic before 6 years old.[5] Evidence has shown an association between AR and asthma in children.[6,7] Although AR is not a life-threatening disease, AR imposes a heavy financial burden on patients and society because of treatment and social costs.[8,9] Furthermore, AR can have a substantial negative effect on concentration and even academic performance in children.[10–12]

Effective treatment is helpful in preventing children with rhinoconjunctivitis from asthma onset later in life.[13,14] Treatment for AR includes effective symptomatic control, allergen avoidance, standardized immunotherapy, and health education of patients.[15–18] Although medications can be effective at controlling the symptoms of nasal allergies, they are associated with adverse effects, such as local epistaxis, nasal dryness, irritation from intranasal medications, and drowsiness from antihistamines.[19,20] However, growth may be hindered by use of corticosteroids.[21] AR is a manifestation of a single inflammatory process.[22] Immunoglobulin E (IgE) as identified by Immunological methods is considered as a diagnostic marker and therapeutic target on AR.[23–25]

There is a high prevalence of Chinese traditional medicine (TCM) use in the pediatric population in China. In Taiwan, parents of children with AR tend to ask for TCM treatment and Chinese herbal medicine (CHM) as the most common therapeutic approach.[26,27] Studies have shown that CHM is effective in adults.[28–30] Some clinical trials on AR in children treated with CHM have been reported.[31–49] However, to the best of our knowledge, there have been no meta-analyses for evaluating the efficacy of CHM. Therefore, this systematic review aimed to collect evidence to evaluate the effect of CHM treatment of AR in children.

Methods

Database and search strategies

The literature search was conducted by two authors (Zhipan Zheng and Zhenshuang Sun) independently. Any disagreement on the relevance of inclusion was resolved by discussion until a general consensus was reached. This study did not require ethical approval because it contained data from previously published studies.

The preliminary electronic databases that we searched were MEDLINE (PubMed), Embase, Cochrane Central Register of Controlled Trials, Chinese

National Knowledge Infrastructure (CNKI), the Cqvip Database (VIP), and the Wanfang Database up to December 2017. Key words or free-text terms that we used were as follows: "allergic rhinitis", "children", "pediatrics", "randomized, clinical trials", "traditional Chinese medicine", and "Chinese herbal medicine".

Inclusion criteria

A study was eligible for inclusion if it met the following criteria: (1) a randomized, controlled trial (RCT) was designed by the study; (2) patients were diagnosed with AR as defined by the Chinese Medical Association or other well-recognized AR diagnostic criteria were included, were of either sex, and their age not older than 18 years; and (3) patients in the treatment group were treated with CHM. All RCTs were selected with no restrictions on language, population characteristics, blinding, and publication type.

Exclusion criteria

Studies were excluded if they met any one of the following criteria: (1) duplicated publications; (2) reviews, meeting abstracts, case reports, and comments; (3) patients whose age was older than 18 years; and (4) patients in the CHM group were treated with acupuncture, external application, or massage.

Outcomes

The outcome measures were as follows: (1) total effective rate (clinical cure rate + showing effectiveness rate); (2) recurrence rate; (3) scores of the symptoms, including sneezing, running nose, nasal congestion, and nasal itching; (4) IgE levels; and (5) adverse reactions.

According to the Guiding Principle of Clinical Research on New Drugs of TCM, the clinical efficacy of TCM was classified as a clinical cure, showing an effect, and no effect. A clinical cure was defined as disappearance of symptoms and signs, and no abnormal condition as checked by rhinoscopy. An effect was defined as relief of symptoms and signs, with turbinate swelling as checked by rhinoscopy. No effect was defined as no relief of symptoms and signs. Symptoms and signs included sneezing, running nose, nasal congestion, and nasal itching. Rhinoscopy was used to detect nasal mucosa with a pale color, hyperemia, turbinate swelling, and catarrh.

Study selection and data extraction

Two reviewers independently examined abstracts in the search results to identify potential relevance, and then screened full texts for final identification. The following information was extracted: authors, date of publication, sample size, sex and age of the participants, details of the interventions, outcomes measures, and adverse reactions. All included articles were judged by a third reviewer.

Quality assessment

The methodological quality of the trials was evaluated by two coauthors independently. The Jadad score criteria were used[50]. The following three domains were assessed: method of randomization, blinding, dropouts, and withdrawals. Two points were allocated if the method of randomization was described in the study and it was appropriately conducted. One point was allocated if the method of randomization was not appropriate. Two points were allocated if the method of blinding was double-blind and the blinding method was described. One point was allocated if the method of blinding was not appropriate. One point was allocated if the study stated withdrawal or dropout. Otherwise, 0 points were allocated if the study did not describe

withdrawal and dropout. Three points or more than 3 points were considered to indicate a high-quality study. The maximum number of points was 5. Fewer than 3 points was considered to indicate a low-quality study.

Data analysis

Data were analyzed by using Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity between similar studies was evaluated by the chi-square test and I^2 statistic. If I^2 was $\leq 50\%$, then the possibility of heterogeneity between the studies was low, and a fixed-effects model was used. If I^2 was $>50\%$, there was heterogeneity between the studies, and a random-effects model was used. Enumeration data are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Measurement data are expressed as the mean difference (MD) with the 95% CI. Statistical significant difference was set as $P < 0.05$. Publication bias was examined using a funnel plot by using Review Manager 5.3 software.

Description of included studies

An initial search identified 1149 potentially relevant citations, including 351 studies from CNKI, 372 from the Wanfang Database, 373 from VIP, 27 from PubMed, 19 from Embase, and 7 from Cochrane Central Register of Controlled Trials. A total of 555 duplicated articles were excluded using EndNote X7 software (Clarivate Analytics, Boston, MA, USA). After reading the titles and abstracts, 594 articles regarding animal experiments, experience reports, and other treatments and trials carried out on adults were eliminated. Two reviewers then carefully read the full text of the remaining 40 articles; 21 studies that did not meet all of the inclusion criteria were excluded. Therefore, 19 eligible trials were chosen for the meta-analysis.[31–49] A total of 1623 participants, of which there were 832 patients in the CHM group and 791 patients in control group, were involved (Figure 1).

Methodological quality of included RCTs

Baseline information, such as interventions and outcome measurement, for the treatment and control groups is shown in Table 1. On the basis of the inclusion criteria, 19 relevant citations were included in this study. However, only six studies used the stochastic indicator method. The rest of the studies applied a randomized method, but none of them had a specific description. None of the studies had a precalculated sample size or used a double-blind method (Table 2).

Meta-analysis of curing AR in children

Efficacy rate. As is shown in Figure 2, 11 studies mentioned the efficacy rate difference between CHM and loratadine.[31,32,34,37,41–44,46–48] A total of 956 patients were included (480 patients in the CHM group, 476 patients in the control group). The fixed-effects model was applied for statistical analysis because the 11 studies did not show heterogeneity (chi-square = 4.53, $P = 0.92$, $I^2 = 0\%$). Our analysis suggested that CHM could effectively improve the efficacy rate compared with loratadine (OR 3.32; 95% CI, 2.32–4.76; $P < 0.001$) (Figure 2).

Scores of symptoms. Among all 19 studies, 2 of them selected scores of the symptoms as one of their outcome measures.[31,37] A total of 170 patients were included (85 patients in the CHM group, 85 patients in the control group). For the symptom of sneezing, there was statistical heterogeneity between these two clinical trials after testing for heterogeneity (chi-square = 24.78, $P < 0.001$,

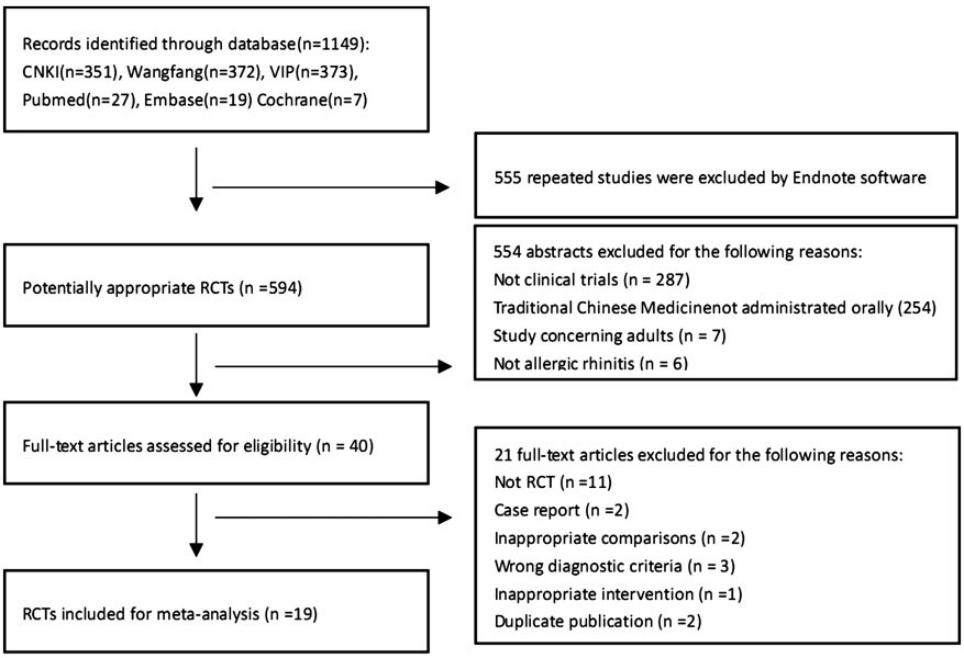

Figure 1. Flowchart of the study selection process

$I^2 = 96\%$). Therefore, the random-effects model was used, and it showed a significant difference between the CHM and control groups (MD −1.24; 95% CI, −2.33 to −0.14; $P = 0.03$) (Figure 3a). For the symptom of a running nose, there was statistical heterogeneity between these two clinical trials after testing for heterogeneity (chi-square = 22.61, $P < 0.001$, $I^2 = 96\%$). Therefore, the random-effects model was used, and it showed a significant difference between the CHM and control groups (MD −1.32; 95% CI, −2.58 to −0.05; $P = 0.04$) (Figure 3b). For the symptom of nasal congestion, there was statistical heterogeneity between these two clinical trials after testing for heterogeneity (chi-square = 4.97, $P = 0.03$, $I^2 = 80\%$). Therefore, the random-effects model was used, and it showed a significant difference between the CHM and control groups (MD −0.70; 95% CI, −1.05 to −0.36; $P < 0.001$) (Figure 3c). For the symptom of nasal itching, there was statistical heterogeneity between these two clinical trials after testing for heterogeneity (chi-square = 29.44, $P < 0.001$, $I^2 = 97\%$). Therefore, the random-effects model was used, but it showed no significant difference between the CHM and control groups (MD−1.37; 95% CI, −3.96 to 1.22, $P = 0.30$) (Figure 3d).

Recurrence rate. As shown in Figure 2, five studies described the difference in recurrence rate between CHM and loratadine.[34,36,38,41,46] A total of 405 patients were included (205 patients in the CHM group, 200 patients in the control group). The fixed-effects model was applied for statistical analysis because the five studies did not show heterogeneity (chi-square = 1.95, $P = 0.74$, $I^2 = 0\%$). The analysis showed that CHM could effectively improve the efficacy rate compared with controls (OR

Table 1. Characteristics of the eligible studies

Study	Treatment intervention	n (M/F), age (mean ± SD and range, years)	Control intervention	n (M/F), age (mean ± SD and range, years)	Course (days)	Outcome measure
Luo et al., 2017[32]	Suhuang Zhike capsules	30, NA	Loratadine tablets	30, NA	14	Efficacy, scores of the symptoms, adverse reaction
Hong et al., 2017[33]	Decoction of CHM	60 (32/28), 5.17 ± 2.50 (2–11)	Loratadine tablets	60 (29/31), 5.28 ± 2.64 (2–12)	28	Efficacy
Zhao et al., 2016[34]	Decoction of CHM	50, NA (3–12)	Montelukast sodium chewable tablets	50, NA (3–12)	28	Efficacy
Wang et al., 2016[35]	Decoction of CHM	47 (25/22), 5.28 ± 1.46 (2–13)	Loratadine syrup	47 (26/21), 5.34 ± 1.29 (2–12)	56	Efficacy, recurrence rate
Liang, 2016[36]	Bimin San	32 (28/4), 9.2 ± 1.0 (5–14)	Cetirizine dihydrochloride tablets	28 (21/7), 8.8 ± 1.2 (6–13)	56	Efficacy, adverse reaction
Hu et al., 2016[37]	Wenfei Zhiliu Dan	66 (35/31), 6.21 ± 1.44 (2–14)	Inhalebudesonideaerosol, Dermatophagoides farinae drops	66 (32/34), 6.67 ± 1.26 (3–13)	42	Efficacy, recurrence rate, adverse reaction
Liu, 2014[38]	Decoction of CHM	55 (31/24), 5.17 ± 2.50 (2–11)	Loratadine syrup	55 (34/21), 5.28 ± 2.64 (2–12)	28	Efficacy, scores of the symptoms,
Yu, 2015[39]	Decoction of CHM	48 (28/20), 6.58 ± 1.34 (4–13)	Budesonide aerosol, loratadine tablets	48 (30/18), 6.87 ± 1.35 (3–14)	56	Efficacy, recurrence rate
Zhou, 2014[40]	Decoction of CHM	60 (35/25), NA (2–15)	Biyuang Tongqiao granules	60 (31/29), NA (3–14)	14	Efficacy

(continued)

Table 1. Continued

Study	Treatment intervention	n (M/F), age (mean ± SD and range, years)	Control intervention	n (M/F), age (mean ± SD and range, years)	Course (days)	Outcome measure
Zhang, 2014[41]	Decoction of CHM	40 (23/17), NA (5–14)	Prednisone acetate tablets, ketotifen fumarate tablets, ephedrine hydrochloride and nitrofurazone nasal drops	40 (24/16), NA (6–13)	14	Efficacy
Guo et al., 2014[42]	Decoction of CHM	28 (15/13), NA (3.5–14)	Loratadine tablets	28 (14/14), NA (3.5–14)	14	Efficacy, recurrence rate
Chen, 2014[43]	Decoction of CHM	30 (16/14), 6.60 ± 2.12	Loratadine tablets	30 (17/13), 7.20 ± 1.29	28	Efficacy
Wang, 2013[44]	Decoction of CHM	50 (22/28), NA (4–14)	Loratadine tablets	50 (24/26), NA (4–12)	14	Efficacy, Scores of the symptoms
Luo, 2013[45]	Decoction of CHM	70 (42/28), NA (2–11)	Loratadine tablets	70 (41/29), NA (2–11)	21	Efficacy, adverse reaction
Wang, 2012[46]	Decoction of CHM	40 (23/17), NA (5–14)	Terfenadine tablets, prednisone acetate tablets, ephedrine hydrochloride nasal drops	20 (12/8), NA (6–14)	14	Efficacy
Yang, 2010[47]	Yupingfeng granules	25 (14/11), NA (3–14)	Loratadine tablets	21 (12/9), NA (3–14)	56	Efficacy, recurrence rate
Chen, 2010[48]	Decoction of CHM	35 (20/15), 4.86 ± 0.43 (1.5–10)	Loratadine tablets	35 (21/14), 4.76 ± 0.42 (1.8–11)	28	Efficacy
Yuan et al., 2009[49]	Bimin oral liquid	30 (16/14), 10.0 ± 3.5 (6–17)	Loratadine tablets	30 (17/13), 11.0 ± 2.9 (5–16)	20	Efficacy, IgE
Zhao et al., 2006[50]	Decoction of CHM	36 (19/16), NA (4–14)	Biyankang capsules	23 (13/10), NA (4.5–13)	10	Efficacy, IgE

M: Male; F: female; CHM: Chinese herbal medicine; NA: not available; IgE: immunoglobulin E

Table 2. Methodological quality of included randomized, controlled trials

Study	Randomized method	Blinding	Dropouts or withdrawals	Jadad score
Luo et al., 2017[32]	Claimed	Unclear	No	1
Hong et al., 2017[33]	Stochastic indicator method	Unclear	No	2
Zhao et al., 2016[34]	Claimed	Unclear	No	1
Wang et al., 2016[35]	Stochastic indicator method	Unclear	No	2
Liang, 2016[36]	Claimed	Unclear	No	1
Hu et al., 2016[37]	Stochastic indicator method	Unclear	No	2
Liu, 2014[38]	Stochastic indicator method	Unclear	No	2
Yu, 2015[39]	Claimed	Unclear	No	1
Zhou, 2014[40]	Claimed	Unclear	No	1
Zhang, 2014[41]	Claimed	Unclear	No	1
Guo et al., 2014[42]	Claimed	Unclear	No	1
Chen, 2014[43]	Stochastic indicator method	Unclear	No	2
Wang, 2013[44]	Claimed	Unclear	No	1
Luo, 2013[45]	Claimed	Unclear	No	1
Wang, 2012[46]	Stochastic indicator method	Unclear	No	2
Yang, 2010[47]	Claimed	Unclear	No	1
Chen, 2010[48]	Claimed	Unclear	No	1
Yuan et al., 2009[49]	Claimed	Unclear	No	1
Zhao et al., 2006[50]	Claimed	Unclear	No	1

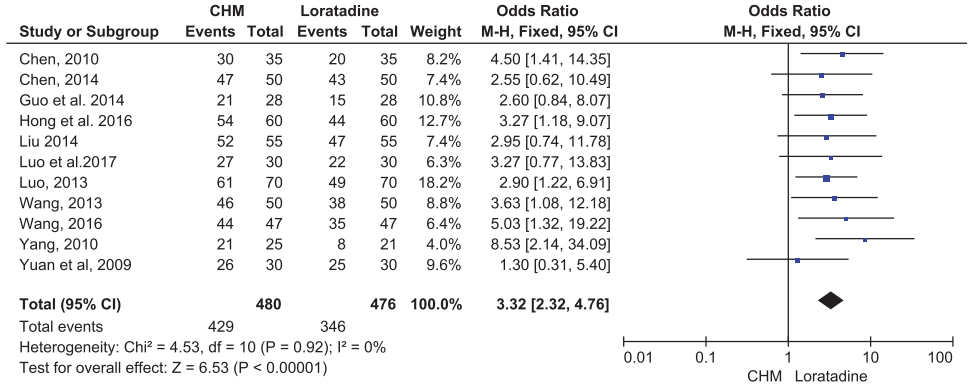

Figure 2. Efficacy rate using CHM versus loratadine. CHM: Chinese herbal medicine

0.30; 95% CI, 0.18 to 0.49; $P < 0.001$) (Figure 4).

IgE. Among the 19 studies, two of them selected IgE as one of their outcome measures.[33,48] A total of 118 patients were included (65 patients in the CHM group, 53 patients in the control group). The fixed-effects model was applied for statistical analysis because the two studies did not show heterogeneity (chi-square = 1.02, $P = 0.31$, $I^2 = 2\%$). The analysis showed that CHM could effectively decrease IgE levels compared with the control group (MD −46.01; 95% CI, −57.53 to −34.48; $P < 0.001$) (Figure 5).

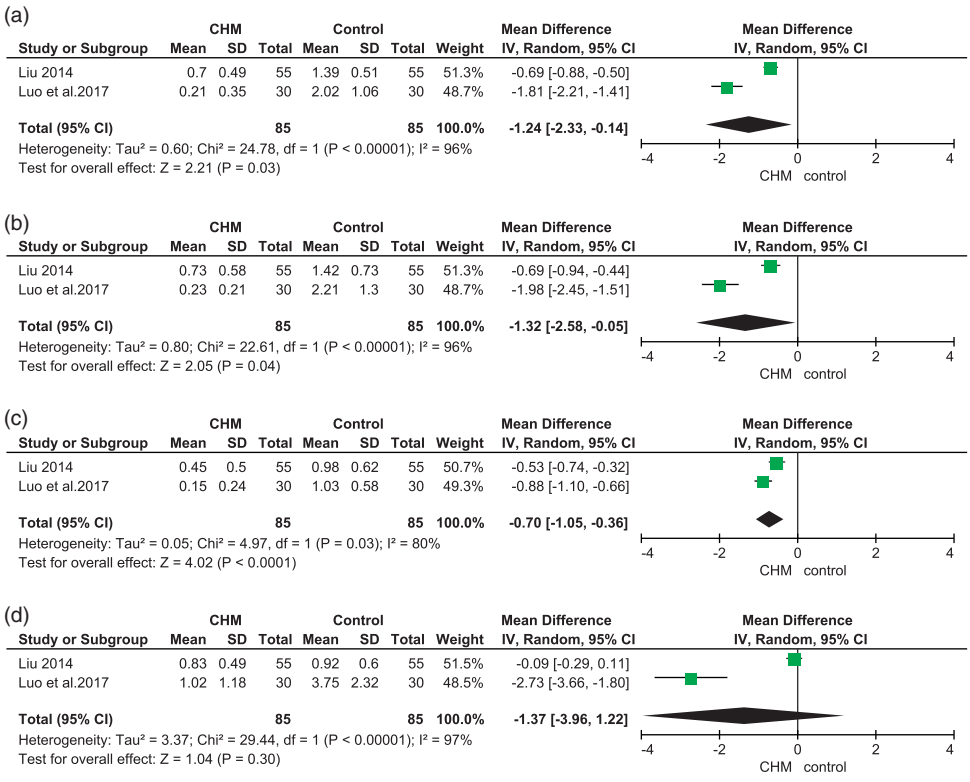

Figure 3. Scores of the symptoms using CHM versus controls. (a) Sneezing. (b) Running nose. (c) Nasal congestion. (d) Nasal itching.
CHM: Chinese herbal medicine

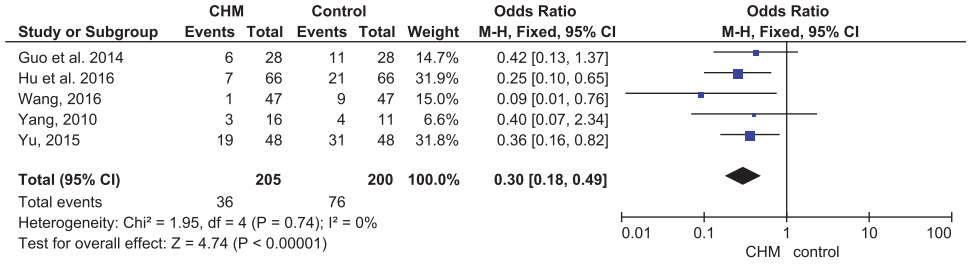

Figure 4. Recurrence rate using CHM versus controls.
CHM: Chinese herbal medicine

Publication bias. An "inverted funnel" pattern analysis was used to confirm publication bias. The asymmetrical figure indicated potential publication bias that might affect the results (Figure 6).

Adverse reactions. Four patients experienced skin rash in the CHM group who were treated with Wenfei Zhiliu Dan,[36] and no other adverse reactions were reported. Adverse reactions in the control group

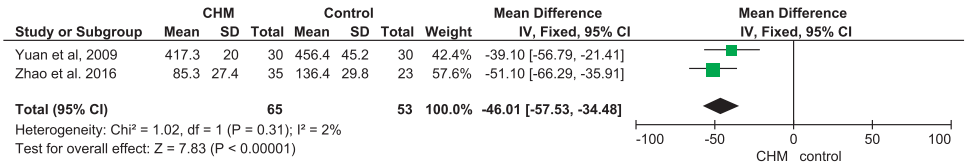

Figure 5. IgE levels using CHM versus controls.
CHM: Chinese herbal medicine

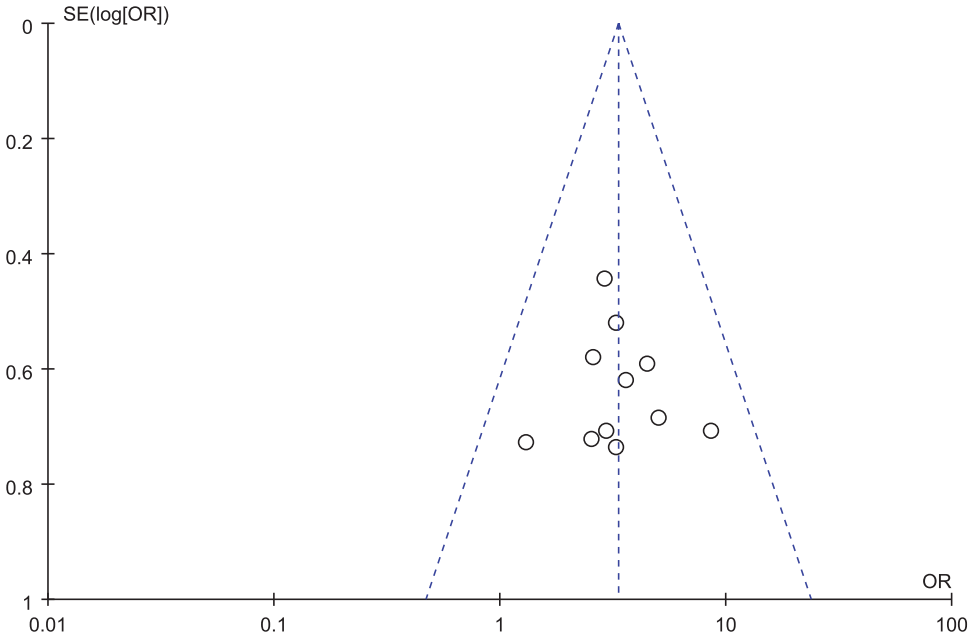

Figure 6. Funnel plot. Annotations: comparison = CHM group versus the control group; outcome = effective rate.
CHM: Chinese herbal medicine

included drowsiness, nosebleed, fever, thirst, skin rash, and fatigue. However, calculating the incidence of adverse reactions was difficult because of insufficient adverse events reported.

Discussion

In this study, we systematically evaluated and analyzed previous literature on RCTs regarding the efficacy of CHM in clinical treatment of AR in children. We found that CHM could effectively improve the efficacy rate compared with loratadine. CHM may have advantages in terms of the recurrence rate and the scores of symptoms, such as sneezing, running nose, and nasal congestion, but not nasal itching. CHM may also reduce IgE levels compared with controls.

According to the TCM theory, the nose is the orifice of the lung. The pathogeny of AR as "Feng Xie" leads to obstruction of lung-qi, which triggers symptoms, including sneezing, running nose, nasal congestion, and nasal itching. Therefore, therapeutic

methods are focused on dispelling the Feng Xie and relaxing the depressed lung-qi. This type of theory is the foundation for CHM formula on AR. The mechanism of CHM on AR may include controlling the balance of T helper 1/T helper 2, suppressing eosinophilic activity, reducing IgE levels, regulating allergenic cell degranulation, and antihistamines.[51–55]

There are some limitations concerning this study. First, the RCTs that were included in this study were limited and the sample sizes were small. Therefore, ruling out the influence of contingency factors is difficult. Second, the overall methodological quality of the included RCTs was not high. Although all of 19 studies stated that they used the random method, only 6 of them elaborated on the details of the stochastic method.[32,34,36,37,42,45] No studies claimed a double-blind method. There was no withdrawal or dropout described. In fact, there was a high possibility of selection bias and measurement bias. Third, publication bias cannot be fully excluded without sufficient studies. In this review, an inverted funnel plot (Figure 6) showed that the publication bias might have affected the results. Some results of our study showed high heterogeneity (Figure 3). There was a high possibility of measurement bias. Finally, the intervention duration in the included articles ranged from 10 to 56 days. However, unfortunately, there is no relevant standard for the time of intervention.

Therefore, ensuring that the trials were properly conducted is difficult. Consequently, we are unable to make confirmative conclusions. High-quality, large-sample, RCTs still need to be performed in the future.

Declaration of conflicting interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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