Systematic Review and Meta-Analysis

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Acupoint herbal patching during Sanfu Days on reducing frequency of acute asthma attack in children

A systematic review and meta-analysis

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Abstract

Objective: Acupoint herbal patching (AHP) is an external therapy of Traditional Chinese Medicine. This systematic review and meta-analysis sought to evaluate whether AHP during Sanfu Days has additional benefits in children with asthma.

Methods: A comprehensively electronic literature search was performed in the Cochrane Library, PubMed, Embase, CNKI, VIP, and WanFang databases from their inception to March 2019. Randomized controlled trials that evaluated the AHP during Sanfu Days treatment for pediatric asthma were included. The main outcome measures were frequency of acute asthma attack, relapse of asthma, and pulmonary function.

Results: Eleven trials involving 882 children with asthma were identified. White mustard seed, rhizoma corydalis, and radix kansui were the most frequently used herbs. Adjunctive treatment with AHP significantly reduced the frequency of acute asthma attack (mean difference [MD] −1.62 times/year; 95% confidence intervals [CI] −2.13 to −1.11). Moreover, AHP improved the peak expiratory flow (standardized mean differences [SMD] 0.61; 95% CI 0.39–0.82) and forced expiratory volume in 1 s (SMD 0.48; 95% CI 0.31–0.66).

Conclusions: Application of AHP during Sanfu Days has additional benefits in reducing the frequency of acute attack and improving pulmonary function in children with asthma. However, the current findings should be interpreted with caution owing to the methodological flaws of the analyzed trials.

Abbreviations: AHP = acupoint herbal patching, CI = confidence intervals, FEV1 = forced expired volume in 1 s, MD = mean difference, PEF = peak expiratory flow, RCT = randomized controlled trials, RR = risk ratio, SMD = standardized mean differences, TCM = Traditional Chinese Medicine.

Keywords: acupoint sticking, asthma, children, meta-analysis, systematic review

1. Introduction

Pediatric asthma is the most prevalent chronic disease.[1] Approximately 1% to 37% of children suffer asthma in the world.[2] Global prevalence of asthma has increased exponentially in recent decades.[3,4] Asthma is also a main cause of loss of school days and hospital visits for children. Pharmacologic interventions of asthma include the use of agents for control and relief. Despite advancement in medical care, pediatric asthma still leads to death and chance of recurrence in adulthood.[5] Inhaled corticosteroids and short-acting bronchodilators are most frequently administered to children with asthma.[6] However, growth suppression associated with corticosteroids use remains a big concern.[7] Persistent childhood asthma can even result in a decline in pulmonary function in young ages.[8,9] Therefore, novel therapeutic approaches for pediatric asthma are unmet needs.

Complementary and alternative medicine is increasingly applied in children with asthma.[10,11] Acupoint herbal patching (AHP) based on traditional Chinese Medicine (TCM) meridian theory has been widely used in China.[12] This non-invasive pain-free approach can be accepted by children. "Treating Winter diseases in Summer" is a specific method of applying drugs on Sanfu Days to prevent and treat diseases attacks in winter.[13]

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This approach is firstly introduced in "Zhang's Treatise on General Medicine." Sanfu Days (each includes 10 days) is the hottest period within the year based on the lunar calendar. According to the theory of TCM, Sanfu Days are recognized as the richest time for Yang-Qi. Application of AHP during Sanfu Days generates curative effects through transdermal absorption of herbs, acupoint stimulation, and time effect. A number of clinical trials[14–18] have evaluated the additional beneficial effects of AHP during the Sanfu Days for treating pediatric asthma. However, the beneficial effects of AHP on the pulmonary function are still controversial.[19,20]

A well-designed meta-analysis[21] indicated that AHP had favorable immunomodulatory effects for pediatric asthma. However, clinical outcomes and lung function were not evaluated in this meta-analysis. Another previous meta-analysis[22] only investigated the effects of AHP during Sanfu Days for stable asthma. No previous meta-analysis has investigated the add-on effects of AHP in childhood asthma during Sanfu Days. Therefore, we performed this systematic review and meta-analysis to investigate the add-on effects of AHP during Sanfu Days on the pulmonary function and acute disease attack of childhood asthma.

2. Materials and methods

2.1. Data source and literature search

This meta-analysis strictly followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement.[23] We comprehensively searched the Cochrane Library, PubMed, Embase, CNKI, VIP, and WanFang databases from their inception to March 2019. We used the following keywords for searching in English databases: "Sanfutie" OR "acupoint" AND "asthma" AND "children" OR "childhood" OR "pediatric." For the Chinese databases, "san fu" OR "Dong bing xia zhi" OR "Tie fu" AND "xue wei" AND "xiao chuan" AND "er tong" OR "xiao er" AND "sui ji" AND "dui zhao" were applied in combination. Reference lists of eligible trials were manually scanned to identify any possible missing trials. Ethical approval was not needed due to this study only analyzed the available articles.

2.2. Study selection

Inclusion criteria were:

1. study design: randomized controlled trials (RCT);
2. study population: children (≤14 years old) with asthma;
3. interventions: AHP plus Western medicine compared with the same Western medicine alone during Sanfu Days; and
4. primary outcome was the frequency of acute asthma attack and secondary outcomes were the relapse of asthma, peak expiratory flow (PEF), forced expired volume in 1 s (FEV1), and adverse events.

Exclusion criteria were as follow:

1. participants did not restrict in children population;
2. AHP combined other Chinese herbal preparation as intervention;
3. AHP did not apply during the Sanfu Days;
4. follow-up duration <3 months for the remission stage of asthma; and
5. retrospective studies, self-controlled trial, dissertation, or duplicate publication.

2.3. Data extraction and risk of bias assessment

Two authors independently abstracted data and evaluated the methodological quality of all eligible trials. Discrepancy was resolved by consensus. We recorded the surname of the first author, publication year, sample size, age at baseline, aspects of methodological assessment, AHP intervention (including herbs, acupoint, and course of treatment),control intervention, length of follow up, and outcome measures. The Cochrane risk bias tool was used to examine the methodological quality of the included RCT. Each domain was grouped as "unclear risk of bias," "low risk of bias" or "high risk of bias."

2.4. Data analysis

Meta-analysis was conducted using RevMan 5.2 software and the STATA 12.0. Continuous data were presented as mean difference (MD) or standardized mean differences [SMD] with 95% confidence interval (CI). Dichotomous data were presented as risk ratio (RR) with 95% CI. Heterogeneity between trials was tested using the I^2 statistic and the Cochrane Q test. Due to presence of obviously clinical heterogeneity, we selected a random effect model for all the analyses. Subgroup analyses were scheduled by the stage of asthma. Publication bias assessment by the Begg's test[24] and Egger's test[25] was planned if the outcome included more than five trials. Sensitivity analyses were conducted by removal of any single trial at each turn.

3. Results

3.1. Literature search

Briefly, 539 articles were identified in our initial literature search. After removal of duplicates, 245 articles remained. Of which, 188 articles were removed after scanning the titles and abstracts. The remaining 57 articles were retrieved for full-text assessment. Forty-six articles were further removed mainly due to the lack of interesting outcomes, inappropriate intervention, acupoint application versus Western medicine or self-controlled trials. Finally, 11 trials[14–20,26–29] were included in this meta-analysis. Figure 1 shows the flow chart of trial selection process.

3.2. Study characteristics

Table 1 presents the basic characteristics of these eligible trials. The included trials were conducted in China and published between 2003 and 2018. Sample size ranged from 26 to 160, with a total of 882 children. Seven trials[15,16,18–20,26,27] enrolled the children in remission and four trials[14,17,28,29] recruited the children with all stage of asthma. Western pharmacological medications included glucocorticoid, seretide, montelukast, budesonide, and salbutamol. The length of follow-up ranged between 1 month and 2 years. AHP was administered between 3 and 9 times during a period of 30 to 40 days. Table 2 describes the details of acupoint sticking therapy.

3.3. Risk of bias

Two trials[17,22,27,30] reported the detailed method of random and others only claimed randomized controlled designs. Dropout and sample size calculation was not mentioned in the included trials. Overall, included trials had unclear risk of bias (supplemental Table S1, http://links.lww.com/MD/D702).

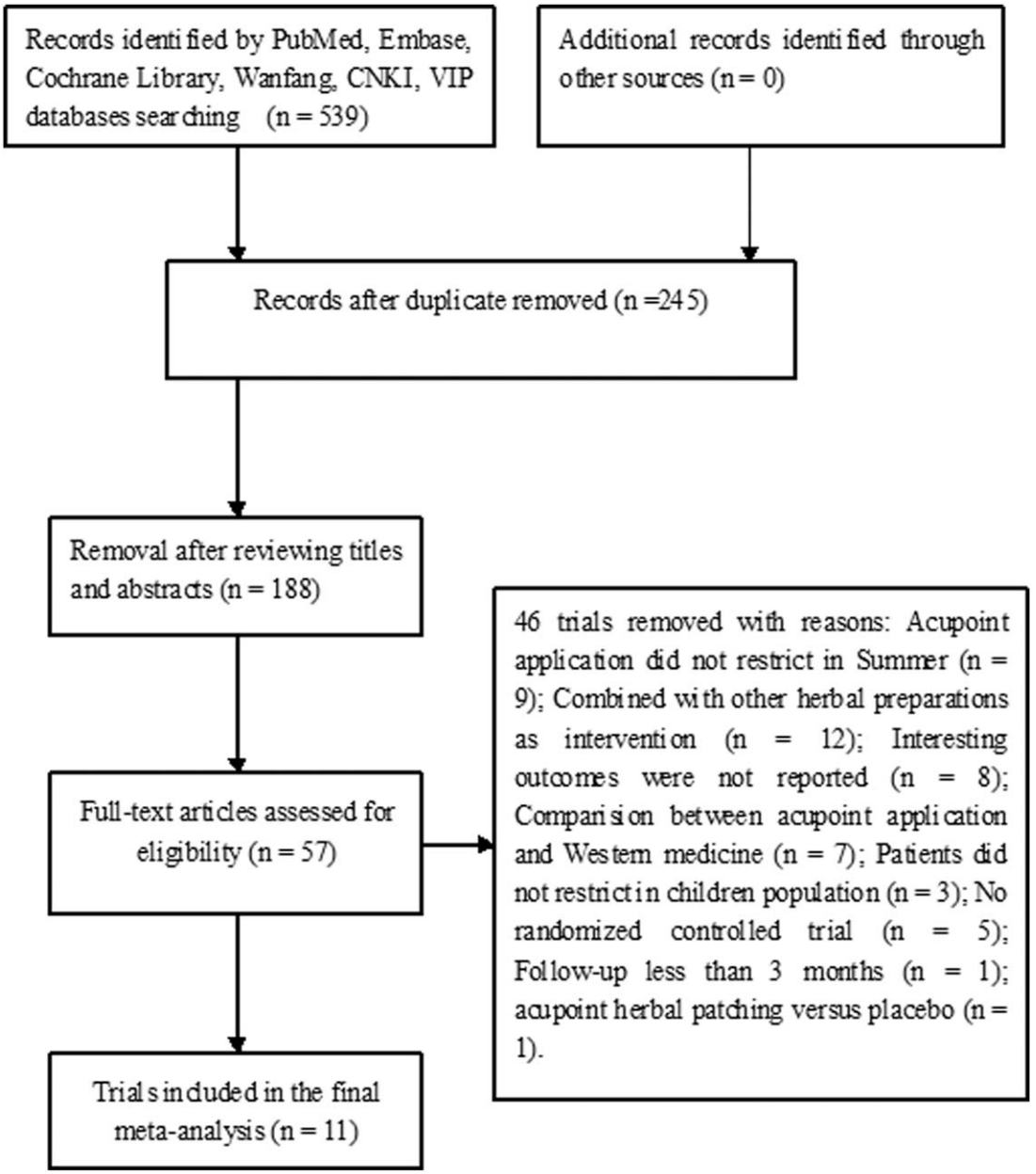

Figure 1. Flow chart of trial selection process.

Table 1

Basic characteristics of the included trials.

Author/year	Stage of disease	Sample sizes	Age (years)	AST intervention	Control intervention	Follow-up (months)	Outcome measures
Deng LS 2003[14]	All stage	13/13	4–6	AHP + inhale glucocorticoid	Inhale glucocorticoid	12	PEF
Deng YP 2012[19]	Remission	80/80	5–14	AHP + inhale seretide	Inhale seretide	12	Frequency of acute attack, FEV1
Wu Y 2014[15]	Remission	43/43	3–12	AHP + inhale glucocorticoid	Inhale glucocorticoid	12	Frequency of acute attack
Zhao J 2015[16]	Remission	20/20	2–12	AHP + inhale glucocorticoid	Inhale glucocorticoid	12	Frequency of acute attack + AE
Wang XY 2016[17]	All stage	33/31	6–10	AHP + Montelukast	Montelukast	3	FEV1, PEF, AE
Wu QL 2016[18]	Remission	31/25	5–14	AHP + Montelukast	Montelukast	9	FEV1, PEF
Yin XL 2017[26]	Remission	40/40	5–12	AHP + inhale glucocorticoid	Inhale glucocorticoid	12	Relapse, AE
Zhou F 2017[27]	Remission	44/42	6–9	AHP + inhale budesonide	Inhale budesonide	12	Frequency of acute attack
Fu YL 2017[20]	Remission	60/60	4.6–12.4	AHP + Montelukast/seretide	Montelukast/seretide	24	Frequency of acute attack,FEV1, PEF
Shu YF 2017[28]	All stage	40/40	3–11	AHP + inhale budesonide	Inhale budesonide	NP	FEV1, PEF
Zhao XB 2018[29]	All stage	74/74	2–13	AHP + Budesonide + Salbutamol	Budesonide + Salbutamol	12	Relapse, FEV1, PEF

AE = adverse events, AHP = acupoint herbal patching, FEV1 = forced expiratory volume in one second, NP = not provided, PEF = peak expiratory flow.

Table 2

Protocol of acupoint sticking therapy.

Author/year	Constituent of herb	Acupoint	Sticking methods
Deng LS 2003[14]	White Mustard Seed, Herba Asari, Moschus, Rhizoma Zingiberis Recens	Feishu (BL 13), (Ex-B1), Pishu (BL 20), Shenshu (BL23)	2 h/9 d sessions during dog days
Deng YP 2012[19]	White Mustard Seed, Rhizoma Corydalis, Radix Kansui, Herba Asari	Feishu (BL 13), Dazhui (GV 14), Dashu (BL11), Pishu (BL 20)	3–4 h/9 d sessions during dog days
Wu Y 2014[15]	White Mustard Seed, Rhizoma Corydalis, Radix Kansui, Herba Asari	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17)	2–4 h/9 d sessions before, during and after dog days
Zhao J 2015[16]	White Mustard Seed	Feishu (BL 13)	30 min–2 h/9 d sessions in dog days
Wang XY 2016[17]	White Mustard Seed, Rhizoma Corydalis, Radix Kansui, Flos Syzygii Aromatici, Fructus Amomi, Rhizoma Atractylodis	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17), Tiantu (CV22), Danzhong (CV 17), Shenque (CV 8)	3–4 h/9 d sessions during dog days
Wu QL 2016[18]	White Mustard Seed, Rhizoma Corydalis, Radix Kansui	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17), Tiantu (CV22), Danzhong (CV 17)	3–4 h/9 d sessions during dog days
Yin XL 2017[26]	White Mustard Seed, Rhizoma Corydalis, Radix Kansui, Herba Asari, Moschus, Flos Syzygii Aromatici, Fructus Amomi, Rhizoma Atractylodis, Fructus Piperis, Rhizoma Atractylodis Macrocephalae	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17), Tiantu (CV22), Danzhong (CV 17)	30 min to 2 h/7 d sessions in dog days
Zhou F 2017[27]	White Mustard Seed, Cortex Cinnamomi, Rhizoma Corydalis, Radix Kansui, Herba Asari, Rhizoma Pinelliae, Rhizoma Zingiberis	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17), Tiantu (CV22), Dingchuan (Ex-B1), Zhiyang (CV 9)	2–4 h/9 d sessions during dog days
Fu YL 2017[20]	White Mustard Seed, Herba Asari, Radix Stemonae, Radix Angelicae Dahuricae, Fructus Schisandrae, Borneolum	Feishu (BL 13), Danzhong (CV 17), Gaohuang (BL43), Dazhui (GV 14)	1–4 h/9 d sessions during dog days
Shu YF 2017[28]	White Mustard Seed, Rhizoma Corydalis, Radix Kansui, Herba Asari	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17)	1–3 h/9 sessions during dog days
Zhao XB 2018[29]	White Mustard Seed, Rhizoma Corydalis, Cortex Cinnamomi, Radix Kansui, Herba Asari, Rhizoma Pinelliae	Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17), Tiantu (CV22), (Ex-B1), Danzhong (CV 17)	2–4 h/9 d sessions during dog days

3.4. Frequency of acute attack and asthma relapse

Five trials[15,16,19,20,27] reported the effect of AHP on the frequency of acute asthma attack. Meta-analysis indicated that AHP significantly reduced the frequency of acute asthma attack (MD −1.62; times/year; 95% CI −2.13 to −1.11; $I^2=76\%$, $P=.003$) in a random effect model (Fig. 2). Two trials[22,26] reported the effect of AHP on the asthma relapse. A random effect model meta-analysis showed that AHP had no clear effect on the relapse of asthma (RR 0.25; 95% CI 0.05–1.19; $I^2=50\%$, $P=.16$; Fig. 3).

3.5. Pulmonary function indexes

Six trials[17–20,28,29] reported the effect of AHP on FEV1. As shown in Figure 4, there was no significant heterogeneity between trials ($I^2=18\%$, $P=.30$). Meta-analysis showed that AHP

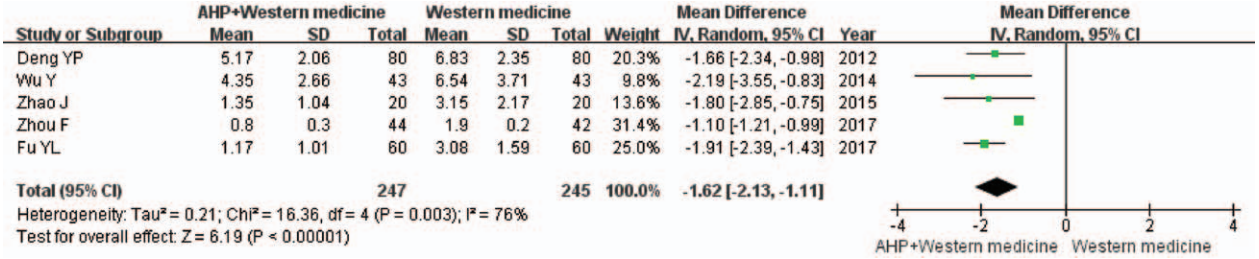

Figure 2. Forest plots showing the effect of acupoint herbal patching on frequency of acute attack.

Figure 3. Forest plots showing the effect of acupoint herbal patching on relapse of asthma.

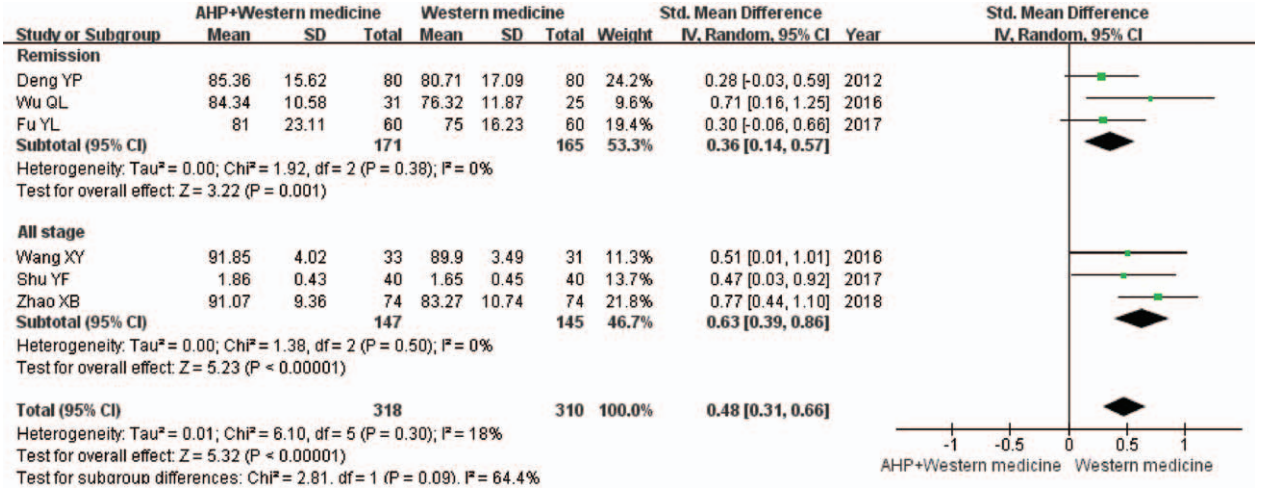

Figure 4. Forest plots showing the effect of acupoint herbal patching on forced expiratory volume in 1 s.

significantly reduced the FEV1 (SMD 0.48; 95% CI 0.31–0.66) in a random effect model (Fig. 4). Subgroup analyses showed a stronger effect of AHP on FEV1 in the all stage asthma (SMD 0.63; 95% CI 0.39–0.86) than those in remission stage (SMD 0.36; 95% CI 0.14–0.57).

The effect of AHP on PEF was reported in six trials.[14,17,18,20,28,29] Meta-analysis indicated that AHP significantly reduced the PEF (SMD 0.61; 95% CI 0.39–0.82; $I^2=24\%$, $P=.25$; Fig. 5). Also, a stronger effect of AHP on PEF was noted in the all stage asthma (SMD 0.71; 95% CI 0.47–0.95) than remission subgroup (SMD 0.45; 95% CI 0.11–0.80).

3.6. Adverse events

Three trials[16,17,26] reported the adverse events as an outcome. The most common adverse events associated with AHP were local skin redness, itching, stinging, and blistering. The incidence of total skin adverse events in the AHP group was 16.1%. Nevertheless, all the adverse events were mild and without reporting serious adverse effects.

3.7. Sensitivity analysis and publication bias

Sensitivity analysis showed that any single trial did not significantly alter the pooling effect sizes (data not shown). Results of the Begg's test ($P=.260$) and Egger's test ($P=.558$) revealed no evidence of publication bias for FEV1 outcome. Also, publication bias was not found for PEF outcome based on the results of Begg's test ($P=1.000$) and Egger's test ($P=.588$).

4. Discussion

This systematic review and meta-analysis suggest that adjunctive treatment with AHP during Sanfu Days achieves additional beneficial effects in reducing the frequency of acute attack and improving pulmonary function in terms of FEV1 and PEF in children with asthma. Local skin reactions induced by AHP were frequently developed. However, these adverse effects were generally mild and spontaneously recovered.

Our findings are consistent with those in previous systematic review and meta-analysis.[22,31,32] AHP adding to Western medicine had additional benefits on improving pulmonary

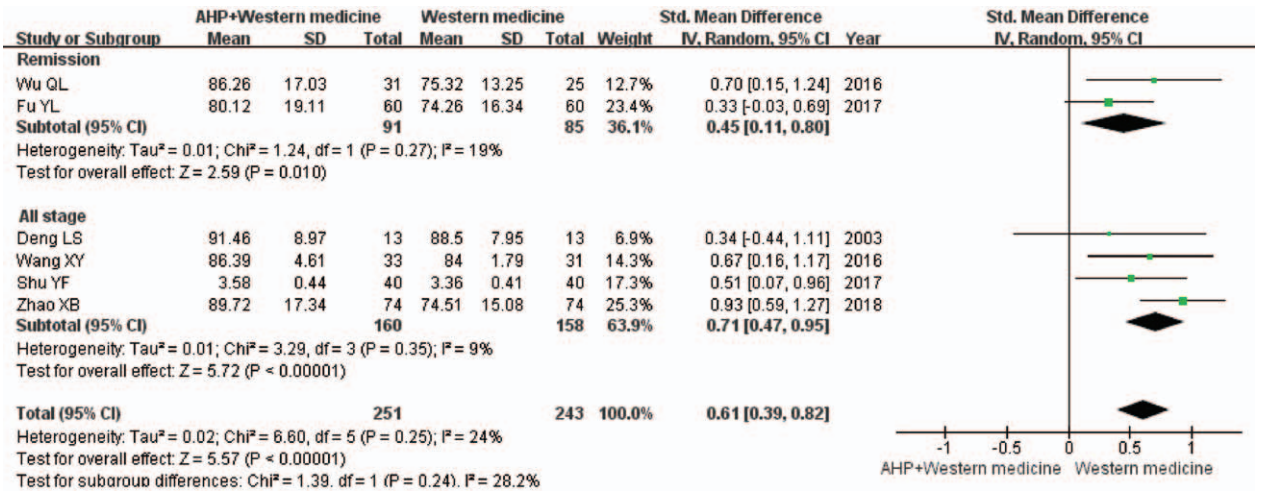

Figure 5. Forest plots showing the effect of acupoint herbal patching on peak expiratory flow.

function in patients with asthma. In pediatric asthma patients, AHP could regulate serum levels of immunoglobulin (Ig) A, Ig E, Ig G, interleukin-4, and interferon-γ.[21] However, use of AHP was not restricted to Sanfu Days and time effect of AHP was not considered.[18]

White Mustard Seed, Radix Kansui, and Rhizoma Corydalis are frequently selected herbs in the preparation of acupoint application. The Feishu (BL 13), Danzhong (CV 17), Geshu (BL 17), and Tiantu (CV22) should be considered as the key acupoints. Importantly, selection of herbs and acupoints should be considered the TCM syndrome differentiation. Future trials should focus on the comparison between different herbal preparations and various stimulating acupoints. Also, comparison between Sanfu Days and any time treatment will be a meaningful topic for future trials.

Our systematic review and meta-analysis indicated that AHP adding to Western medicine could reduce 1.62 times/year of frequency of acute attack than the Western medicine alone. AHP also regulated the serum levels of Ig A,[26,27] Ig E,[26,27] Ig G,[26] $CD4^+$ T-lymphocytes,[29] $CD8^+$ T-lymphocytes,[29] and eosinophil.[26,30] However, there was no evidence to support the beneficial effects of AHP on the relapse of asthma in our meta-analysis. This result may be explained by relatively short duration of follow-up. Asthma is a chronic inflammatory disease. Besides the immunomodulatory effects, AHP could reduce serum levels of tumor necrosis factor-α, interleukin-6, and high-sensitivity C-reactive protein.[28] Anti-inflammatory and immunomodulatory effects of AHP may partly account for its beneficial effects.

An important concern was the skin reaction such as local skin redness, itching, burning, pain, and even cause blisters. However, treatment induced blisters appeared to exhibit better therapeutic effect.[18] This phenomenon may be explained by local infiltrative effect make it easier for the body to absorb the herbs through the acupoints. Importantly, children with skin allergies or damaged skin should be treated with caution.

There are several limitations in this meta-analysis. First, main methodological flaws of the included trials were lack of description of randomization and allocation concealment method. Second, lack of TCM syndrome differentiation in recruiting patients may be another potential limitation. Third, relapse of asthma as an outcome was potentially unreliable due to the relatively short follow-up period. Future trials with longer follow-up duration are required to investigate AHP on asthma relapse. Fourth, there was highly heterogeneous I^2 in pooling the frequency of acute attack outcome. This results should be interpreted with caution due to a random-effect meta-analysis may have led to over- and under-estimate the effect of AHP. Moreover, highly clinical heterogeneity existed in the acupuncture points and constituent of herbs, which makes it difficult to determine what specific intervention component exert the noted effect. Fifth, different primary pharmacological medications are obviously clinical heterogeneity of the original trials. However, the limited number of trials in each outcome prevented us to perform the subgroup analysis by different primary pharmacological medications. Finally, results of publication bias may be unreliable due to the number of included trials was less than the recommended arbitrary number of 10.[33]

Our meta-analysis provided limited evidence for the benefits of AHP in children with asthma. For children with frequent attack of asthma, adjunctive treatment with AHP may achieve additional beneficial effects. Furthermore, AHP also exhibited promising effects in improving lung function of childhood asthma. However, an optimal AHP intervention should be determined in future trials.

5. Conclusions

AHP adding to Western medicine during Sanfu Days has additional beneficial effects in reducing the frequency of acute attack and improving pulmonary function indexes in pediatric asthma. However, the current findings should be interpreted with caution owing to the methodological flaws of the analyzed trials.

Author contributions

Conceptualization: Wei Li.
Data curation: Chunlei Wei, Xin Zhang.
Formal analysis: Chunlei Wei, Xin Zhang, Pengfei Li.
Funding acquisition: Wei Li.
Investigation: Chunlei Wei, Xin Zhang.
Methodology: Chunlei Wei, Xin Zhang.
Project administration: Wei Li.
Resources: Chunlei Wei.
Supervision: Wei Li.
Validation: Wei Li.
Writing – original draft: Pengfei Li.
Writing – review & editing: Wei Li.

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