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. Approximately 1% to 37% of children suffer asthma in the world. Global prevalence of asthma has increased exponentially in recent decades. 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. Inhaled corticosteroids and short-acting bronchodilators are most frequently administered to children with asthma. However, growth suppression associated with corticosteroids use remains a big concern. Persistent childhood asthma can even result in a decline in pulmonary function in young ages. Therefore, novel therapeutic approaches for pediatric asthma are unmet needs.

Complementary and alternative medicine is increasingly applied in children with asthma. Acupoint herbal patching (AHP) based on traditional Chinese Medicine (TCM) meridian theory has been widely used in China. 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.
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 | 33/33 | 6–10 | AHP + Montelukast | Montelukast | 3 | FEV1, PEF, AE |
| Wu QL 2016[18] | Remission | 51/51 | 5–14 | AHP + Montelukast | Montelukast | 9 | FEV1, PEF |
| Yin XL 2017[20] | Remission | 40/40 | 5–12 | AHP + Inhale glucocorticoid | Inhale glucocorticoid | 12 | Relapse, AE |
| Zhou F 2017[21] | Remission | 44/44 | 6–9 | AHP + Inhale budesonide | Inhale budesonide | 12 | Frequency of acute attack |
| Fu YL 2017[22] | Remission | 60/60 | 4.6–12.4 | AHP + Montelukast/seretide | Montelukast/seretide | 24 | Frequency of acute attack, FEV1, PEF |
| Shu YF 2017[23] | All stage | 40/40 | 3–11 | AHP + Inhale budesonide | Inhale budesonide | NP | FEV1, PEF |
| Zhao XB 2018[24] | 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.
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/C0 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
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."hr"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"hr"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."hr"22,31,32" AHP adding to Western medicine had additional benefits on improving pulmonary function.
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.[33] Anti-inflammatory and immunomodulatory effects of AHP may partly account for its beneficial effects.

An important concern was the skin reaction such as skin redness, itching, burning, pain, and even cause blisters. However, treatment induced blisters appeared to exhibit better therapeutic effect.[19] This phenomenon may be explained by local irritative 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 effects of the analyzed trials.

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.

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Conceptualization: Wei Li.
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References
[1] Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. Front Microbiol 2013;4:263.
[2] Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009;64:476–83.
[3] Serebrinsky D, Wiznia A. Pediatric asthma: a global epidemic. Ann Glob Health 2019;85: doi: 10.5334/aogh.2416.
[4] Ferrante G, La Grutta S. The burden of pediatric asthma. Front Pediatr 2018;6:186.
[5] Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. Front Pediatr 2019;7:247.
[6] Abrams EM, Becker AB, Szeffer SJ. Current state and future of biologic therapies in the treatment of asthma in children. Pediatr Allergy Immunol Pulmonol 2018;31:119–31.
[7] Zhang L, Lasmar LB, Castro-Rodriguez JA. The impact of asthma and its treatment on growth: an evidence-based review. J Pediatr 2019;95(Suppl 1):10–22.
[8] Tai A, Tran H, Roberts M, et al. The association between childhood asthma and adult chronic obstructive pulmonary disease. Thorax 2014;69:805–10.
[9] McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med 2016;374:1842–52.
[10] Shen J, Oraka E. Complementary and alternative medicine (CAM) use among children with current asthma. Prev Med 2012;54:27–31.
[11] Philp JC, Maselli J, Pachter LM, et al. Complementary and alternative medicine use and adherence with pediatric asthma treatment. Pediatrics 2012;129:e1148–54.
[12] Yao L, Tang J, Li HY, et al. Overview of research on acupuncture sticking therapy in treating bronchial asthma. Chin Archiv Tradit Chin Med 2015;33:2336–9.
[13] Tai CJ, Chien LI. The treatment of allergies using Sanfujiu: a method of applying Chinese herbal medicine paste to acupoints on three peak summer days. Am J Chin Med 2004;32:967–76.
[14] Deng LS, Zeng Y. Adjusting effects of Dawairenjiu Gao acupoints applicationon on pulmonary ventilation function in children with asthma. J Guangzhou Univ Tradit Chin Med 2003;20:127–30.
[15] Wu Y. Acupoint application based on Summer treatment of Winter disease in treating 86 cases of children with asthma in remission stage. Chin Med Mod Distance Edu China 2014;12:67–8.
[16] Zhao J, Zhou TT. Clinical observation of self-made traditional Chinese medicine ointment in dog days acupoint in the treatment of remission
period of the children with asthma. Clin J Tradit Chin Med 2015;27:975–6.

[17] Wang XY, Wang LB. Clinical study on bronchial asthma by dog days acupoint application. Guid J Tradit Chin Med Pharm 2016;22:73–5.

[18] Wu XQ, Peng J, Li GQ, et al. Association between skin reactions and efficacy of summer acupoint application treatment on chronic pulmonary disease: a prospective study. Chin J Integr Med 2016;22:284–92.

[19] Deng YP. Effect of Kechuanansfurie on pulmonary Function of remission stage of pediatric asthma. Hubei J TCM 2012;34:19–20.

[20] Fu YL, Li J, Dong Y, et al. Clinical study on the treatment of infantile asthma by WenYangHuayu acupoint sticking. Chin Community Doctors 2017;33:63–4.

[21] Yang XC, Yin T, Gao Q, et al. The immunomodulatory effect of acupoint application for childhood asthma: a systematic review and meta-analysis. Evid Based Complement Alternat Med 2015;2015:896247.

[22] Zhou F, Liang N, Maer M, et al. Sanfu acupoint herbal patching for stable asthma: a systematic review and meta-analysis of randomised controlled trials. Complement Ther Med 2017;30:40–53.

[23] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9, W264.

[24] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[25] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[26] Yin XL, Zhou HG, Zhou HL. Effect of acupoint application on immunoglobulin and eosinophil in children with bronchial asthma. Mod J Integr Tradit Chin Western Med 2017;26:1222–4.

[27] Zhou F, Hou CG, Fang Y, et al. Effect of acupoint application of Wenyang Quhan sticking on children with asthma in remission stage. Chin J Tradit Med Sci Technol 2017;24:791–3.

[28] Shu YF, Niu XL, Wu J. Clinical efficacy of aerosol inhalation of budesonide combined with acupoints application with Chinese herbal medicine in the treatment of pediatric asthma. J Clin Med Pract 2017;21:80–3.

[29] Zhao XB, Ma Y, Liu QA, et al. Clinical observation on 74 cases of asthma in children treated with acupoint application by the method of curing winter diseases in summer. J Pediatr TCM 2018;14:52–5.

[30] Shi LJ, Zhao Y. Clinical observation on 92 cases of childhood asthma for preventing relapse by acupoint application based on treating Winter disease on Summer. J Emerg Tradit Chin Med 2014;23:342–4.

[31] Su L, Meng L, Chen R, et al. Acupoint application for asthma therapy in adults: a systematic review and meta-analysis of randomized controlled trials. Forsch Komplementarmed 2016;23:16–21.

[32] Lee SH, Chang GT, Zhang X, et al. Acupoint herbal patching for asthma: a systematic review and meta-analysis of randomized controlled trials. Medicine 2016;95:e2439.

[33] Lau J, Ioannidis JP, Terrin N, et al. The case of the misleading funnel plot. BMJ 2006;333:597–600.