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Original Article

Oral administration versus iontophoresis of Sang-Su decoction (a formula for dispersing lung to calm panting and resolve phlegm and for dredging collateral) in the treatment of acute bronchial asthma: a comparative study on their efficacy and impacts on the prognosis

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Abstract: Objective: To investigate the efficacy of oral administration versus traditional Chinese medicine (TCM) iontophoresis of Sang-Su decoction (SSD) in the treatment of acute bronchial asthma (ABA) and their impacts on the clinical prognosis. Methods: One hundred patients with ABA were randomly and equally divided into two groups: A and B. In group A, patients were given the oral administration of SSD, a self-made formula for dispersing lung to calm panting and resolve phlegm as well as dredging collateral (mulberry leaf 10 g, perilla leaf 10 g, pericarpium citri reticulatae 10 g, rhizoma pinelliae 10 g, tuckahoe 10 g, radix glycyrrhizae preparata 6 g, thunberg fritillary bulb 10 g, bombyx batryticatus 10 g, trichosanthes kirilowii maxim 15 g, herba schizonepetae 10 g, houttuynia cordata thunb 15 g, scutellaria baicalensis 10 g), while in group B, patients received TCM iontophoresis of SSD. After 4 weeks of treatment (4 weeks), the comprehensive therapeutic efficacy in both groups was assessed (rate of reduction in TCM syndrome score). Meanwhile, the following variables before and after treatment were evaluated and compared in two groups: scores of asthma control test (ACT), pulmonary function (forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) 25%-75%, both of which were expressed as a percentage of their predicted values), eosinophil (EOS) counts in the peripheral blood, and serum immunoglobulin E (IgE) levels. The frequency of acute asthma attacks within half a year after the treatment was also compared between two groups. Results: After treatment, significant clinical effects of the TCM therapy were observed in both groups, however, the efficacy in group B was even greater ($P<0.05$). The ACT scores in both groups rose significantly after treatment, while the score in group B was higher than that in group A ($P<0.05$). The value of FEVI and PEF 25%-75% were improved similarly in two groups ($P>0.05$). EOS counts in the peripheral blood and serum IgE levels all decreased after treatment, and the decreases in group B were greater (both $P<0.05$). There was no intergroup difference in the frequency of attacks within half a year after treatment (both $P>0.05$). Conclusion: In comparison with the treatment method using SSD only, the method using the combination of SSD and TCM iontophoresis can achieve more significant efficacy in treating ABA without improvement on the prognosis.

Keywords: Asthma, Sang-Su decoction, traditional Chinese medicine iontophoresis

Introduction

Bronchial asthma (BA), or simply called asthma, is defined as a chronic inflammatory disorder of the airways, which involves various cells (such as mastocyte, eosinophil, neutrophil, T lymphocyte, airway epithelial cell) and cell components. It is characterized by airway hyperreactivity (AHR), with common symptoms of reversible and changeable airflow limitation. Main symptoms include wheezing, dyspnea, chest distress, and cough. Most of them can remit spontaneously or by medications and treatment [1]. The acute bronchial asthma (ABA), as one of the diseases with high incidence worldwide, can severely affect the pulmonary function of the patients and their quality of life [2]. At present, there are about at least 300 million patients with asthma, and every 1 out of 250 patients would die of this disease [3]. In addition, the high expenses incurred by the treatment have become an increasing

financial burden for patients and the whole society [4].

Currently, medicines for treating asthma mainly consist of two categories: bronchodilator and anti-inflammatory drug [5]. The bronchodilator include β2-agonist (such as short-acting drug terbutaline, salbutamol and long-acting drug salmeterol), theophylline, and anticholinergic agents; while anti-inflammatory drugs mainly include glucocorticoid (inhalation is its most common mode of administration in clinic, which can make the drug enter into the respiratory tract directly, leading to fast onset of action and high local drug concentration, with low required dosage), leukotriene modifiers (such as montelukast and zafirlukast, that can alleviate airway inflammation and slow down airway remodeling), and antihistamine drugs (loratadine) [6]. These medicines can control the frequency of the acute asthma attacks within a short period of time, but cannot fundamentally solve the problem. Since there are still many unexplainable areas with respect to the pathogenesis of asthma, and the current treatment methods cannot achieve an ideal effect in controlling its acute attacks, and can incur high costs and severe side effects, it is of great importance to find out a new method that can treat this disease effectively.

Currently, there are still some limitations of the western medicine therapy in treating ABA, thus we considered using the traditional Chinese medicine (TCM) therapy to relieve the symptoms of asthma during acute attacks. As we all know, TCM emphasizes on holism, and according to the theory, it can treat ABA's core syndrome (retention of phlegm-heat) through a holistic approach and can effectively improve pulmonary function and reduce mortality, with advantages of less side effects, more durable therapeutic effects, and good tolerance. All these features bring TCM excellent prospect for its clinical application. In western countries, TCM is now playing a more and more important role in the modern medicine, with many studies demonstrating that it can achieve unique efficacy in relieving the symptoms of ABA [7-9]. Iontophoresis is a type of non-invasive method that can improve the absorption rate of TCM. It applies electric current on the skin to generate a directional force on the medicine ions, making drug's effective components pass through the mucous membrane more deeply and effectively, enter into the human body rapidly, and go straight to the lesion. By this means, the drug can be absorbed and achieve its efficacy in a better way [10]. This treatment method has been gaining recognition by patients and the whole society, and its effectiveness and safety have been proved by various studies [11-13].

In TCM, asthma belongs to the category of "Xiao Zheng". The theory believes that the principal pathogenic factor of asthma is the long-retained phlegm in the lung, which can be induced by things like exogenous pathogenic factors, improper diet, emotional disturbance, overstrain, and other factors. This can make the accumulated phlegm move upwards with Qi, obstruct the airway, and impair the proper diffusing and descending of lung Qi, thus bringing about wheezing cough with phlegm. "Xiao Zheng" is manifested as deficiency of healthy Qi, and as evil excess during the acute attacks. Through years of clinical practice, we have found that the retention of phlegm-heat in the lung is the most common syndrome among ABA patients. Li Zhongzi once said "phlegm is a type of internal heat in visible form, while internal heat is a type of phlegm in invisible form". Therefore, we proposed the idea of clearing heat, resolving phlegm, and dispersing lung to calm panting as the therapy, and established the fundamental treatment method of "dispersing lung to resolve phlegm and dredging collateral". In the self-made prescription of Sang-Su decoction (SSD), the houttuynia cordata thunb and scutellaria baicalensis were used as the monarch drug to clear lung heat; the thunberg fritillary bulb and trichosanthes kirilowii maxim were used as the minister drug to clear heat and resolve phlegm, which worked together with rhizoma pinelliae (processed with ginger) and pericarpium citri reticulatae to regulate Qi and resolve phlegm; the mulberry leaf, perilla leaf and herba schizonepetae were used to disperse lung; radix glycyrrhizae preparata and tuckahoe were used to invigorate spleen and harmonize the spleen and stomach as the guiding drug. Through TCM iontophoresis, the active ingredients entered from the body surface into the meridian and collateral, by which they were then transported further down to the viscera to target the lung, where the phlegm was retained. This can avoid the first-pass effect in the liver and the intervention and degradation by the gastrointestinal tract.

In sum, we used SSD, a formula for dispersing lung to calm panting and resolve phlegm and

Table 1. Comparison of patients' characteristics

Group	Case	Gender (male/female)	Age (year, $\bar{x} \pm sd$)	BMI (kg/m^2, $\bar{x} \pm sd$)
A	50	28/22	37±16	22.9±2.7
B	50	29/21	40±14	21.8±2.9

Note: Group A, oral administration of SSD; group B, TCM iontophoresis of SSD; BMI, body mass index; TCM, traditional Chinese medicine; SSD, Sang-Su decoction.

for dredging collateral, through oral administration or TCM iontophoresis in the treatment of ABA with retained phlegm-heat in the lung. The clinical efficacy following the treatment and their impacts on the prognosis was observed in both groups, with the aim of finding new TCM approaches for treating this disease.

Materials and methods

Patients

A total of 100 patients with ABA who were treated in our hospital from Mar. 1st 2016 to Aug. 31th 2016 were selected as subjects. The study was approved by the Ethics Committee of the hospital and informed consents were obtained by patients or their families.

Based on the diagnostic standards in the guidelines for BA prevention proposed by the Asthma Group of Respiratory Disease Branch of Chinese Medical Association in 2008, the diagnostic criteria were as follows: 1) repeated wheezing, shortness of breath, chest distress or coughing, which were often brought on by exposure to allergen, cold air, physical or chemical stimulation, or caused by viral upper respiratory tract infection, sports or other factors; 2) presence of expiratory phase wheezing sound distributed in two lungs, and the expiratory phase was prolonged; 3) the aforementioned symptoms could remit spontaneously or by medications and treatment; 4) symptoms of wheezing, shortness of breath, chest distress and cough triggered by other diseases were excluded; 5) if patient's clinical symptoms were atypical (for example, no noticeable asthma or physical sign), then at least one of the following clinical test results should be positive: a. bronchial provocation test or exercise test; b. bronchodilator reversibility test (the value of forced expiratory volume in one second (FEV1) was increased by more than 15% and the increased absolute value of FEV1>200 ml); c. the diurnal variation of peak expiratory flow (PEF) or its variation rate between day and night ≥20%.

Inclusion criteria: 1) Patients who met the diagnostic criteria; 2) Patients aged between 18-60 years; 3) Patients with body mass index (BMI) at 18-25 kg/m^2.

Exclusion criteria: 1) Patients who didn't meet the diagnostic criteria; 2) Patients who were in the remitting stage of asthma or were critically ill during the attacks; 3) Patients with severe lung diseases, such as chronic obstructive pulmonary disease, lung cancer, pulmonary tuberculosis; 4) Patients who were aged above 60 years or under 18 years, or women in pregnancy or lactation; 5) Patients who had severe primary diseases such as cardiovascular, liver, and kidney diseases; 6) Psychiatric patients; 7) Patients who had histories of being allergic to TCM components.

Grouping and treatment

According to the random number table, 100 patients were divided into 2 groups with 50 cases in each group: in group A, patients received oral administration of SSD, a self-made therapy for dispersing lung to calm panting and resolve phlegm as well as dredging collateral (mulberry leaf 10 g, perilla leaf 10 g, pericarpium citri reticulatae 10 g, rhizoma pinelliae 10 g, tuckahoe 10 g, radix glycyrrhizae preparata 6 g, thunberg fritillary bulb 10 g, bombyx batryticatus 10 g, trichosanthes kirilowii maxim 15 g, herba schizonepetae 10 g, houttuynia cordata thunb 15 g, scutellaria baicalensis 10 g), while in group B, patients received TCM iontophoresis of SSD. Both groups underwent one course of treatment (4 weeks, all medicines were in the same batch).

Outcome measures

Main outcome measures: clinical efficacy after the treatment (measured by the rate of reduction in TCM syndrome score, a score ≥95% meant that the asthma was controlled clinically; a score ≥70% and <95% meant that the treatment was markedly effective; a score ≥30% and <70% meant that the treatment was effective; a score <30% meant that the treatment was ineffective), score of asthma control test (ACT score, a value >25 represented that the symptoms were controlled completely; 20-24 meant that the symptoms were partially controlled; <20 meant that the symptoms were not controlled), pulmonary function test (FEV1/predicted value *100%, PEF 25%-75%/predicted value *100%), eosinophils (EOS) count in

Table 2. Comparison of comprehensive therapeutic efficacy between two groups

Group	Case	Clinical efficacy ($\bar{x}$ ± sd)
A	50	69.37±1.89%
B	50	87.52±2.32%[a]

Note: [a]P<0.001 versus group A; group A, oral administration of SSD; group B, TCM iontophoresis of SSD; TCM, traditional Chinese medicine; SSD, Sang-Su decoction.

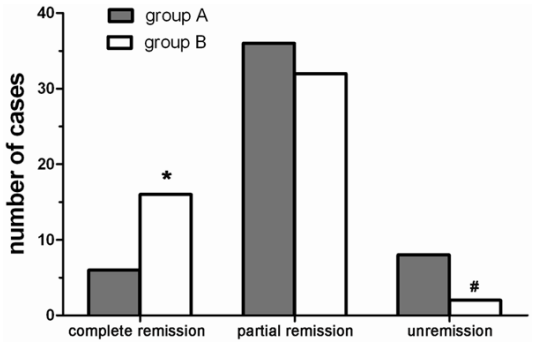

Figure 1. Symptom relief in two groups. *P<0.05 versus group A in terms of complete remission, #P<0.05 versus group A in terms of non-remission.

the peripheral blood, serum immunoglobulin E (IgE) level, frequency of asthma attacks within half a year after the treatment. Secondary outcome measures include age, BMI, and sex ratio.

Statistical analysis

SPSS 21.0 was applied for the statistical analysis. The measurement data were presented as mean ± standard deviation ($\bar{x}$ ± sd); independent t test was used for comparison between groups; the count data were presented as rate and compared by χ^2 test. A value of $P<0.05$ was considered as statistically significant.

Results

Patients' characteristics

There was no intergroup difference in terms of gender, age, BMI, and the severity of the asthma (P>0.05, **Table 1**).

Comprehensive therapeutic efficacies in both groups after treatment

Compared with the condition before the treatment, there were noticeable comprehensive therapeutic efficacies in both groups after one treatment course. The TCM syndrome score decreased evidently. The efficacy in group B was greater than that in group A (P<0.001, **Table 2**).

Table 3. Comparison of PEF 25%-75% percentage of the predicted value before and after the treatment between two groups

Group	Case	Before treatment ($\bar{x}$ ± sd)	After treatment ($\bar{x}$ ± sd)
A	50	77.2±26.8%	91.9±23.7%[a]
B	50	77.8±27.1%	94.9±26.6%[b, c]

Note: [a]P=0.021 versus group A before treatment; [b]P=0.017 versus group B before treatment; [c]P=0.631 versus group A after treatment; group A, oral administration of SSD; group B, TCM iontophoresis of SSD; PEF, peak expiratory flow; TCM, traditional Chinese medicine; SSD, Sang-Su decoction.

Table 4. Comparison of FEV1 percentage of the predicted value before and after treatment between two groups

Group	Case	Before treatment ($\bar{x}$ ± sd)	After treatment ($\bar{x}$ ± sd)
A	50	62.5±18.8%	89.7±19.3%[a]
B	50	59.8±19.6%	91.1±18.6%[b, c]

Note: [a]P<0.001 versus group A before treatment; [b]P<0.001 versus group B before treatment; [c]P=0.856 versus group A after treatment; group A, oral administration of SSD; group B, TCM iontophoresis of SSD; FEV1, forced expiratory volume in onesecond; TCM, traditional Chinese medicine; SSD, Sang-Su decoction.

ACT scores in both groups after treatment

According to ACT scoring system, the symptoms of most patients in two groups were partially controlled, and the symptoms of few patients were completely controlled after one course of treatment, as compared with their conditions before the treatment. **Figure 1** shows that the symptoms in group B were better controlled than those in group A (P<0.05).

Pulmonary function before and after treatment in both groups

After one course of treatment, both FEV1 and PEF 25%-75% increased significantly in two groups, with no intergroup difference (P>0.05, **Tables 3** and **4**).

Table 5. Comparison of EOS count in the peripheral blood and serum IgE level before and after treatment between two groups

Group	Case	EOS count (*10^6/L)		IgE level (IU/L)	
		Before treatment	After treatment	Before treatment	After treatment
A	50	116.03±2.21	77.33±1.98[a]	731.04±8.01	279.02±3.35[c]
B	50	118.09±2.15	60.12±1.68[b,e]	742.03±7.67	145.17±3.77[d,f]

Note: [a]P<0.001 versus EOS count before treatment in group A; [b]P<0.01 versus EOS count before treatment in group B; [e]P<0.001 versus EOS count after treatment in group A; [c]P<0.001 versus IgE level before treatment in group A; [d]P<0.01 versus IgE level before treatment in group B; [f]P<0.001 versus IgE level after treatment in group A; group A, oral administration of SSD; group B, TCM iontophoresis of SSD; EOS, eosinophil; TCM, traditional Chinese medicine; SSD, Sang-Su decoction.

Table 6. Comparison of frequency of asthma attacks within half a year after treatment between two groups

Group	Case	No. of people who underwent asthma attacks within half a year	Average No. of asthma attacks per person within half a year
A	50	12	2.92
B	50	11	3

Note: Group A, oral administration of SSD; group B, TCM iontophoresis of SSD; TCM, traditional Chinese medicine; SSD, Sang-Su decoction; TCM, traditional Chinese medicine; SSD, Sang-Su decoction.

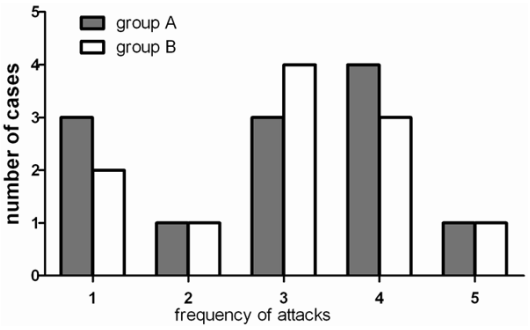

Figure 2. Frequency of attacks within half a year after treatment in both groups.

EOS count in the peripheral blood and serum IgE level

After one course of treatment, the EOS counts in the peripheral blood and serum IgE levels both decreased in two groups (P<0.05, P<0.01, **Table 5**), while the reductions in group B were more significant than those in group A (P<0.001, **Table 5**).

Frequency of attacks within half a year after treatment

A half year follow-up was conducted for all the participants after treatment. Some patients experienced several attacks, and there was no intergroup difference in this area (**Table 6**, **Figure 2**).

Discussion

In modern medicine, the chronic inflammation of the airway is believed to be the root cause for BA. The main basis for this is that the infiltration of huge amounts of inflammatory cells can be found in airway mucosa, such as EOS, mastocyte, neutrophil, and basophile [14]. These inflammatory cells can release and synthesize various inflammatory mediums, including leukotriene, histamine, prostaglandin, and platelet activating factor, which can all bring about airway inflammation. The type I allergic reaction mediated by IgE plays a key role in the asthma attack, and the EOS count as well as IgE level serve as the most important indicators for the allergic diseases. IgE can achieve synergistic effect with allergen, enforce the function and activity of T lymphocyte, leading to the reactive inflammation of the airway. Serum IgE level can indicate severity of inflammatory reaction. Therefore, measuring the total serum IgE level and EOS count during the attacks can help determine the severity of BA [15, 16]. The present study demonstrated that the two treatment methods (oral administration of SSD and TCM iontophoresis of SSD) can both reduce the serum total IgE level and EOS count in the peripheral blood significantly, however, the efficacy achieved by the latter one was even greater.

AHR, as the most major pathogenic basis of BA, is the main characteristic and diagnostic criteria for asthma. Evaluation of AHR serves as the main method for determining the severity of AHR in patients with asthma. The value of FEV1 and PEF 25%-75% percentage of their predicted values are two important indicators for the severity of AHR [17], which are playing essential roles in the diagnosis of BA and the assessment of the therapeutic effect. It can be seen

from our study that both treatment methods can improve these two indicators.

ABA can cause great harm to the human body. It can not only disturb people's normal daily life, but can also inflict psychological burdens, making patients mentally and physically exhausted, and bring about emotional distress. Many researchers have found that for most patients with asthma, the influence of dyspnea on their quality of life is the main reason for them to seek treatment [18, 19]. Due to the development of the medical mode in which biological, psychological and social factors are integrated, the modern medicine is now paying more attention to patients' psychological discomfort in the treatment. According to TCM theory, emotional disorder is one of the key pathogenic factors. Although disease itself can cause emotional disorder, emotional disorder at the same time can also generate, aggravate a disease and delay the recovery. Emotional changes can either contribute to the recovery of a disease, or worsen the disease and even lead to death. Since ACT has been recognized worldwide as a questionnaire that can evaluate the impacts of asthma on the quality of life [20], we adopted the ACT scoring system and TCM syndrome score as important indices to evaluate the efficacy of SSD with or without TCM iontophoresis in treating patients with syndromes of retention of the phlegm-heat in the lung during the acute attacks of BA. It can be seen from the study results that the SSD could achieve marked effects in controlling ABA, while SSD in combination with TCM iontophoresis could increase patients' ACT score and improve their quality of life even more significantly.

Currently, there have been many studies proving that TCM can achieve unique effects in relieving the symptoms of ABA. Besides SSD, we have also incorporated TCM iontophoresis into the treatment, which could be a feature in the present study. The results showed that both methods, oral administration of SSD and TCM iontophoresis of SSD, could achieve great comprehensive therapeutic effects, significantly control the asthma, bring evident recovery of the lung function, and greatly reduce the key inflammatory factors in the peripheral blood during the acute asthma attacks.

However, there were still some limitations in the study. For example, the number of cases chosen was quite limited, with only 50 patients in each group. This small sample size made the results impossible to present statistical significance of each effect with 100% accuracy. Meanwhile, due to the limited time period, the follow-up for the evaluation of patients' prognosis only lasted for half a year following the treatment, and no significant difference in the frequency of attacks within this time period had been found in two groups. Therefore, we cannot determine whether TCM iontophoresis of SSD can achieve more positive effects on patients' prognosis than oral administration of SSD.

In conclusion, both oral administration and TCM iontophoresis of SSD (the formula for dispersing lung to calm panting and resolve phlegm and for dredging collateral) can achieve significant efficacy in controlling ABA, which may provide some useful information in the clinical practice. However, the impacts of these two methods on the long-term prognosis of asthma still remain unclear, and further investigation would be necessary for our future studies.

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Disclosure of conflict of interest

None.

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