Tropical Journal of Pharmaceutical Research February 2022; 21 (2): 367-374
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i2.20

Original Research Article

Effectiveness of Zhixiao Decoction in children with bronchial asthma, and its effect on serum levels of IL-13, IL-6, and IL-17

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Sent for review: 13 August 2021 *Revised accepted: 20 January 2022*

Abstract

Purpose: *To probe into the efficiency of Zhixiao Decoction in treating children with bronchial asthma, and its effect on serum levels of interleukin (IL)-13, IL-6, and IL-17.*
Methods: *140 children with bronchial asthma who were treated in the Affiliated Hospital of Shandong University of traditional Chinese medicine from February 2018 to October 2020, were included as the study group, while 70 children at the same period of physical examination served as the control group. Using the random number table, the study group was equally subdivided into regular group given Asthma-relief Oral Liquid, and treatment group given Zhixiao Decoction. Serum levels of IL-13, IL-6, and IL-17, and effectiveness and safety of Zhixiao Decoction, were measured.*
Results: *Zhixiao Decoction showed higher levels of IL-13, IL-6, and IL-17 and greater treatment effectiveness in patients compared with Asthma-relief Oral Liquid ($p < 0.05$). IL-13, IL-6, and IL-17 levels exhibited negative correlation with FEV1 and PEF. The treatment group had lower post-treatment traditional Chinese medicine syndrome scores, serum levels of IL-13, IL-6, IL-17; fractional exhaled nitric oxide, and eosinophil counts. The treatment group also demonstrated higher scores in asthma control test, mini-asthma-related quality of life, and better lung function than the regular group ($p < 0.05$).*
Conclusion: *Zhixiao Decoction mitigates clinical symptoms of bronchial asthma children, improves lung function and clinical efficacy, and down-regulates levels of inflammatory cytokines. Thus, this therapeutic approach has potentials in the management of pediatric asthma.*

Keywords: *Bronchial asthma, Lung function, Inflammatory factors, TCM syndrome score*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Bronchial asthma is a chronic disease of the respiratory tract in children. The disease manifests in unrelenting cough, shortness of breath, wheezing, and chest tightness due to restriction of expiratory airflow, which seriously affects children's health. Aggravated air pollution has resulted in a rise in the incidence of bronchial asthma in children. If the patients are not given timely treatment, bronchial asthma may result in symptoms such as respiratory failure

and heart failure which may persist into adulthood [1-3]. In Western medicine, it is believed that bronchial asthma is attributed to allergies, airway remodeling, and chronic airway inflammation, which are given inhaled corticosteroids and oral leukotriene receptor antagonists [4,5]. However, the efficacy of western medicine is compromised by non-compliance with medications and high risks of relapse [6].

Traditional Chinese medicine (TCM) practitioners are veterans in the prevention and treatment of childhood asthma and are of the view that the pathogenesis of bronchial asthma is due to *qi stagnation, blood stasis,* and *phlegm obstruction.* Thus, TCM advocates the use of strategies with an enhancement of blood circulation and removal of *blood stasis* for treatment of asthma [7,8]. This study examined the clinical effectiveness of *Zhixiao Decoction* in the treatment of children with bronchial asthma.

METHODS

General profile of patients

Totally140 children with bronchial asthma enrolled in the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from February 2018 to October 2020 were included as the study group, while 70 age- and sex-matched children at the same period of physical examination served as the control group. The study group was randomly sub-divided into a regular group and a treatment group, with 70 children in each group. The two groups had similar baseline data ($p > 0.05$). This study was reviewed and ratified by the medical ethics committee of our hospital.

Inclusion and exclusion criteria

Inclusion criteria

Patients in the following categories were recruited in the study: (1) patients in the age range of 6 - 18 years; (2) those who met the diagnostic criteria of traditional Chinese and Western medicine for bronchial asthma, as well as the TCM classification of heat asthma (onset period); (3) who signed informed consent form, or had the form signed by their guardians as an indication of their willingness to cooperate in the research and to accept telephone calls and outpatient follow-up; and (4) who complied very well during this trial.

Exclusion criteria

The following groups of patients were excluded: (1) patients with other primary diseases of the lung; (2) patients with severe primary diseases in the heart, liver, kidney, and hematopoietic system; (3) those with psychological problems; (4) patients who used anti-asthma medications 2 weeks before the screening; and (4) patients who were participants in clinical trials involving other drugs.

Ethical approval

This trial protocol was reviewed and approved by the ethic committee of People's Hospital of Jiyang District (license no. 2017.24.21). The protocol followed the Declaration of Helsinki guidelines for human studies [9].

Treatments

The regular group was treated with *Asthma-relief Oral Liquid for Children* (Rongchang Pharmaceutical Co. Ltd.; National Medical Product Administration of China Approval Number: Z20010138), thrice daily at a dose of 15 mL after meals (for children aged 6 to 10) or 20 mL (for children over 10 years of age). The treatment group was given *Zhixiao Decoction*. The prescription included 20 g of perilla seeds, 20 g of earthworm, 20 g of radix peucedani, 2 g of chuanxiong, 5 g of fried bitter almond, 20 g of rhizoma belamcandae, 20 g of radix scutellariae, 20 g of celandine, and 20 g of cortex dictamni radicis. These components were decocted twice with water. The decoction was administered at a dose of 120 mL for children aged 6 to 10 years, and at a dose of 150 mL for those aged over 10 years.

Table 1: Baseline data of patients

Variable	Regular group (n = 70)	Treatment group (n = 70)	t/χ^2	*P*-value
Gender			0.265	0.867
Male	46	37		
Female	24	33		
Mean age (years)	14.65 ±3.04	13.94±3.83	5.664	0.734
Mean body mass index (kg/m^2)	18.45±2.37	17.19±3.04	9.751	0.662

The drug was given 3 times a day, 20 min before meals, or 30 min after meals. Four consecutive days constituted a full course of treatment.

Assessment of parameters

Serum levels of inflammatory factors

Fasting venous blood (5 mL) was obtained from all eligible children in the control group and study group (treatment group and routine group) on the day of physical examination and from the study group one day after admission and after treatment. The serum levels IL-13, IL-6, and IL-17 were determined with ELISA. The TCM syndrome score and clinical effectiveness were determined in line with the *Guiding Principles for Clinical Research of New Chinese Medicine* [10]. The major symptoms of gasping, cough, expectoration, chest tightness and wheezing were scored before and after treatment, and were classified as follows: 0 points (none), 2 points (mild), 4 points (moderate), and 6 points (severe). The score was proportional to the severity of the symptoms. Clinical effectiveness was evaluated as per the clinical symptoms and reduction in TCM syndrome scores, and it was categorized as *clinically controlled*, *markedly effective*, *effective*, or *ineffective*. Asthma was regarded as *clinically controlled* if there was≥75 % relief from symptoms. Treatment outcome was *markedly effective* if ≥50 % relief of asthma symptoms was produced, while ≥ 25 % relief of symptoms meant that the treatment was *effective.* However, if the symptoms were not in any way alleviated, or even became worsened, the treatment outcome was regarded as *ineffective*. Total treatment effectiveness (TTE) was calculated as in Eq 1.

TTE = {*(CC + ME + E)/TNC}100* ……. (1)

where *CC = clinically controlled, ME = markedly effective, E = effective, and TNC =_total number of cases.*

The ACT score and mini AQLQ score were determined as outlined earlier [11]. Usually, the ACT score is used for the assessment of asthma control in patients after 4 weeks. It has a score of 24 points: a higher score indicates better asthma control. The mini-AQLQ scale involves 15 questions, each of which is usually scored from 1 to 7 points. On this scale, the total score ranges from 15 to 105 points: the score is proportional to the quality of life of patients.

The values of FeNO and eosinophil counts were determined using the procedures described earlier [12]. The FeNO and peripheral blood eosinophil counts were measured before and after treatment. A NO meter (Beijing Baisai United Technology Co. Ltd) was used for the measurement of NO. The patients were instructed to exhale as much as possible, wrap their lips around the mouthpiece, inhale deeply for 5 seconds, and then smoothly exhale for 10 seconds. After 90 s, the NO value was determined. The FeNO level was expressed in volume fraction. An automatic blood cell analyzer was used to determine eosinophil counts in peripheral blood.

Statistical analysis

The SPSS 23.0 software was employed for data processing and analyses, while GraphPad Prism 8.0 software was used for graphics plotting. Measurement data and count data are expressed as mean ± standard deviation (SD) and numbers and percentages [n (%)], respectively. Statistical analyses were performed using *t*-test and chi-square test. Pearson correlation analysis was used to analyze the correlation between lung function and levels of IL-13, IL-6, and IL-17. $P < 0.05$ indicated a statistically significant difference.

RESULTS

Serum levels of IL-13, IL-6, and IL-17

The study group had lower serum levels of IL-13, IL-6, and IL-17 versus the control group ($p < 0.05$).

Table 2: Serum levels of IL-13, IL-6, and IL-17 in the study group and the control group (ng/L, mean ± SD)

Group	IL-13	IL-6	IL-17
Study (n=140)	35.29±8.23	84.33±15.67	89.22±12.02
Control (n=70)	23.02±5.30	42.35±9.02	62.35±8.18
t	11.35	20.75	16.84
P-value	<0.001	<0.001	<0.001

Correlation between lung function and levels of IL-13, IL-6, and IL-17 in the study group

The levels of IL-13, IL-6 and IL-17 were negatively correlated with % FEV1 (r = -0.573, $p = 0.004$; r = -0.473, $p = 0.017$; and r = -0.528, $p = 0.001$, respectively). Similar negative correlations were observed between % PEF and levels of IL-6 and IL-17 (r = -0.432, $p = 0.022$; r = -0.403, $p = 0.011$, respectively). There was no significant correlation between IL-13 and PEF (%). These results are presented in Table 3, Table 4 and Table 5.

Table 3: Correlation between IL-13 and lung function in the study group

Variable	IL-13	
	r	*P*--value
FEV1 (%)	-0.573	0.004
PEF (%)	-0.387	0.072

Table 4: Correlation between IL-6 and lung function in the study group

Variable	IL-6	
	r	*P*--value
FEV1 (%)	-0.473	0.017
PEF (%)	-0.432	0.022

Table 5: Correlation between IL-17 and lung function in the study group

Variable	IL-17	
	r	*P*-value
FEV1 (%)	-0.528	0.001
PEF (%)	-0.403	0.011

Clinical effectiveness

The treatment group had higher total effectiveness of 87.14% (61/70) than the regular group which had total effectiveness of 67.14% (47/70) (p = 0.005), as shown in Table 6.

TCM syndrome scores

Table 7 shows no great disparities between the two groups regarding scores for TCM syndromes such as gasping, coughing, expectoration, chest tightness and wheezing, before treatment (p > 0.05). However, after treatment, the TCM syndrome scores were decreased, with lower values in the treatment group versus the regular group (p < 0.05).

Serum levels of IL-13, IL-6, and IL-17

Prior to treatment, both groups had similar levels of IL-13, IL-6, and IL-17 (p > 0.05). In contrast, post-treatment serum levels of IL-13, IL-6, and IL-17 were reduced, with lower values in the treatment group versus the regular group (p < 0.05) (Table 8).

Table 6: Comparison of treatment effectiveness between the treatment and regular groups {n (%), N = 70}

Group	Control	Markedly effective	Effective	Ineffective	Total effectiveness
Treatment	18（25.71）	25（35.72）	18（25.71）	9（12.86）	61（87.14）
Regular	12（17.14）	20（28.57）	15（21.43）	23（32.86）	47（67.14）
χ^2					7.94
P-value					0.005

Table 7: Comparison of TCM syndrome scores between the treatment group and the regular group before and after treatment (mean ± SD)

Variable		Treatment group (n=70)	Regular group (n=70)	*t*	*P*--value
Gasping	Before treatment	3.67±0.82	3.53±0.64	1.126	0.262
	After treatment	0.61±0.17	1.02±0.31	9.702	<0.001
Coughing	Before treatment	4.38±0.73	4.41±0.62	0.2621	0.794
	After treatment	0.82±0.22	1.27±0.31	9.904	<0.001
Expectoration	Before treatment	1.88±0.31	1.90±0.27	0.407	0.685
	After treatment	1.24±0.24	1.45±0.18	5.857	<0.001
Chest tightness	Before treatment	3.11±0.46	3.22±0.52	1.326	0.187
	After treatment	0.83±0.19	1.45±0.27	15.71	<0.001
Wheezing	Before treatment	3.28±0.45	3.32±0.28	0.6314	0.529
	After treatment	0.82±0.18	1.35±0.24	14.78	<0.001
Total scores	Before treatment	14.56±2.44	15.02±1.83	1.262	0.209
	After treatment	5.03±1.28	7.89±1.72	11.16	<0.001

Table 8: Comparison of serum levels of IL-13, IL-6, and IL-17 (ng/L) in the treatment group and the regular group, before and after treatment

Variable		Treatment group (n=70)	Regular group (n=70)	*t*	*P*-value
IL-13	Before treatment	37.24±9.53	34.56±7.35	1.863	0.065
	After treatment	25.67±4.53	29.35±5.03	4.548	<0.001
IL-6	Before treatment	86.35±12.46	83.46±14.30	1.275	0.205
	After treatment	47.25±7.92	56.36±9.22	6.271	<0.001
IL-17	Before treatment	91.35±13.45	88.25±11.36	1.473	0.143
	After treatment	67.46±10.24	75.67±9.35	4.954	<0.001

ACT and mini-AQLQ scores

As shown in Figure 1 and Figure 2, the two groups had no marked disparities in ACT and AQLQ scores before treatment *(p* > 0.05). However, after treatment, there were marked increases in the values of these indexes, but higher scores were seen in the treatment group than in the regular group *(p* < 0.05).

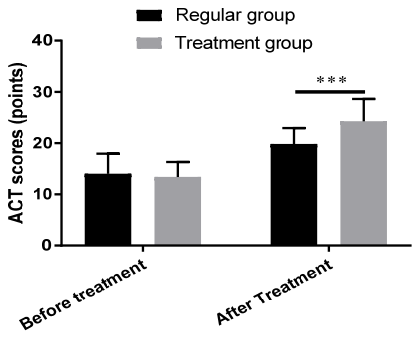

Figure 1: Comparison of ACT scores between the treatment group and the regular group, before and after treatment. ***P < 0.001

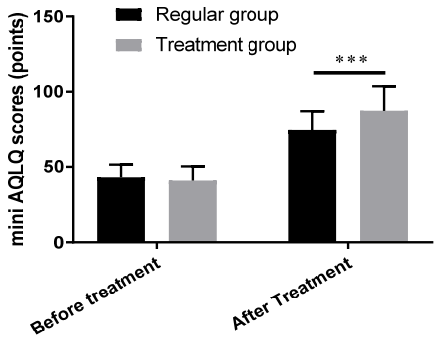

Figure 2: Comparison of mini-AQLQ scores between the treatment group and the regular group, before and after treatment. ***P < 0.001

FeNO and eosinophil counts

There were no noticeable disparities in pre-treatment FeNO and eosinophil counts between the two groups (p > 0.05). After treatment, there were decreases in the values of the two indexes, but lower counts were seen in the treatment group versus the regular group (p < 0.05). (Figure 3 & Figure 4).

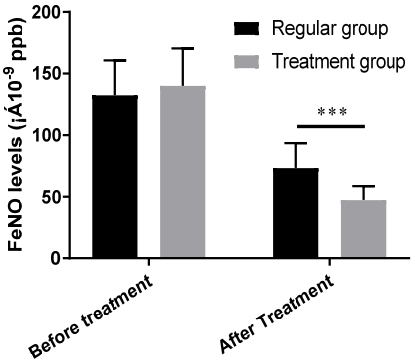

Figure 3: Comparison of FeNO between the treatment group and the regular group, before and after treatment. ***P < 0.001

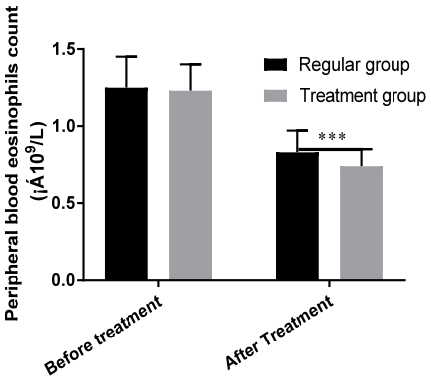

Figure 4: Comparison of eosinophil counts between the treatment group and the regular group, before and after treatment. ***P < 0.001

Lung function

Results in Table 9 demonstrate similar pre-treatment lung function indicators (PEF, FEV1, and FEV1/FVC) between the two groups *(p* > 0.05). However, there were increases in the post-treatment values of these parameters, with markedly higher values in patients from the treatment group versus those from the regular group (p < 0.05).

Table 9: Comparison of lung function before and after treatment between the treatment group and the conventional group (mean ± SD, n = 70))

Variable		Treatment group	Regular group	*t*	*P*-value
PEF (L/s)	Before treatment	4.24±0.52	4.33±0.56	0.985	0.326
	After treatment	6.03±1.32	5.12±0.91	4.749	<0.001
FEV1 (L)	Before treatment	49.35±11.27	52.01±12.93	1.298	0.197
	After treatment	67.28±14.52	76.18±16.41	3.398	<0.001
FEV1/FVC（%）	Before treatment	47.89±8.24	45.68±9.93	1.433	0.154
	After treatment	64.36±14.57	51.39±8.83	6.369	<0.001

DISCUSSION

The main clinical manifestations of bronchial asthma in children are recurrent shortness of breath and wheezing. Severe cases may result in the inability to lie down, as well as cyanotic lips, which seriously compromises the quality of life of the patient. Delayed treatment may even lead to respiratory failure and heart failure [13]. In Western medicine, it is accepted that bronchial asthma is triggered by chronic airway inflammation, airway hyperresponsiveness, and increased airway sensitivity. Therefore, the clinically preferred treatments for asthma involve the use of bronchodilators and glucocorticoids for rapid relief of the symptoms [14].

However, the effect of western medicine is undermined by the high incidence of relapse due to long-term aerosol inhalation [15]. In TCM, it is believed that *healthy qi* keeps *pathogenic qi* away. Thus, bronchial asthma in children is associated with the *deficiency of lung, spleen and kidney; imbalance in body fluids, and invasion of pathogenic qi of phlegm* for which the TCM treatment of bronchial asthma relies on the strengthening *healthy qi* and removing the pathogenic factors. Therefore, children with bronchial asthma require strengthening of *healthy qi* as the mainstay of treatment, while treatment for adults is based on the removal of the pathogenic factors [16].

The inflammatory response in the immune system is a major factor in the pathogenesis of bronchial asthma. However, this has not yet been fully understood. It is known that the important inflammatory factors in bronchial asthma i.e., IL-13, IL-6, and IL-17 which are strongly associated with neutrophil chemotaxis, enhance airway sensitization [17]. In specific terms, IL-13 induces the synthesis of Th2 in cells, leading to an imbalance in Th2/Th1 ratio, and it is also an important cytokine that induces IgE synthesis [18]. Moreover, IL-6 is a key factor in the Th2-type immune response that activates T lymphocytes and IL-1. It also accelerates local proliferation and infiltration of neutrophils in the airways, thereby aggravating inflammation. It is also known that IL-17, a pro-inflammatory cytokine secreted by Th17 cells, is involved in allergy-related diseases, autoimmune diseases, and inflammatory reactions. Here, the levels of IL-13, IL-6, and IL-17 in the study group were markedly higher than the corresponding levels in the blank group. The levels of IL-13, IL-6, and IL-17 were negatively correlated with FEV1, while IL-6 and IL-17 were negatively correlated with PEF (%). Similar results were also found in previous findings [16].

The results demonstrated that the treatment group had better clinical effectiveness than the regular group. The TCM syndrome scores, FeNO level, and eosinophil counts were lower in the treatment group, and the treatment group had higher ACT scores, Mini-AQLQ scores, and superior lung function than the regular group.

In TCM, the aim of *Zhixiao Decoction* treatment is to "detoxify and relieve stuffy lungs, abate asthma, promote blood circulation and remove blood stasis". Perilla seed, earthworm, and chuanxiong in the *Zhixiao Decoction* reduce *qi* and abate asthma, relieve stuffiness in lungs and spasms, enhance blood circulation, and *activate collaterals*. Perilla seed relieves cough and asthma, decreases *qi,* and reduces phlegm. Earthworm *clears heat* and *relieves wind*, and mitigates asthma by *dredging collaterals*. Chuanqiong promotes blood circulation, removes *qi*, and dispels wind. In addition, radix peucedani, bitter almonds, and rhizoma belamcandae are medicines which *clear the lungs and heat*, expel phlegm and relieve asthma. The use of a combination of these ‘drugs’ yields promising results in children with bronchial asthma [19-21].

Traditional Chinese medicine (TCM) possesses unique advantages in the treatment of bronchial asthma in children. The treatment is sequential, and the prescription is adjusted per symptoms manifested, so as to effectively relieve the symptoms and improve lung function. The treatment group had lower serum levels of IL-13, IL-6, and IL-17 than the conventional group, indicating that *Zhixiao Decoction* yielded effectively diminished inflammatory response associated with asthma.

However, most studies on TCM are still empirical-based and difficult to popularize because of the lack of standardized drugs and dosage forms. Nonetheless, the effect of *Zhixiao Decoction* has been confirmed in this study. During asthmatic attacks, the relatively slow anti-asthmatic effect of Chinese medicine is unable to offer a positive effect in patients with a severe condition. Furthermore, the mechanism involved in the association between asthma and serum levels of IL-13, IL-6, and IL-17 requires further exploration.

CONCLUSION

The use of *Zhixiao Decoction* in the treatment of children with bronchial asthma significantly reduces the clinical symptoms of the disease, improves lung function, and down-regulates serum levels of inflammatory cytokines, thereby resulting in significant clinical treatment effectiveness. Therefore, this therapeutic approach has potentials in the management of pediatric asthma.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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