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Original Research Article

Effect of a combination of Tuina therapy and budesonide inhalation on asthma in children, and its influence on lung function and pro-inflammatory factors

Hanyi Li, Xinmei Zhang, Qijun Zhao, Xiang Bai, Shuying Wang*
Department of Pediatric Respiration, Gansu Provincial Maternity and Child-care Hospital, No. 143 Qilihe North Street, Lanzhou, Gansu Province, PR China

For correspondence:* ***Email:* *shuygbx265320@163.com*

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Abstract

Purpose: *To determine the effect of a combination of Tuina therapy and budesonide inhalation on pediatric asthma, and its influence on lung function and levels of inflammatory factors.*
Methods: *Eligible 100 asthmatic children admitted to Provincial Maternity and Child-care Hospital, Lanzhou, Gansu Province, from January 2019 to January 2021 were randomized either to a control group or study group (1:1). The patients in control group were treated with budesonide inhalation, while the study group was given Tuina therapy in combination with budesonide inhalation. Treatment effectiveness, levels of inflammatory factors, immune functions and number of infections were evaluated in the patients.*
Results: *The study group exhibited higher effectiveness profile versus the control group (96 vs 82 %; $p < 0.05$). After treatment, decreases were observed in the frequency of asthmatic attacks and number of respiratory infections in the two groups, with lower results in the study group than in the control group ($p < 0.05$). There were marked decreases in the levels of IgG, TNF-α and IL-8 in both groups, with the study group showing higher reductions ($p < 0.05$).*
Conclusion: *Combined treatment with Tuina and budesonide inhalation decreases the levels of inflammatory factors, regulates immune function, and improves lung function of asthmatic children. Further investigation in a larger population would be required to establish the mechanism and clinical value of this therapy.*

Keywords: *Tuina therapy, Budesonide, Pediatric asthma, Lung function, Inflammatory factors*

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INTRODUCTION

Asthma, a prevalent chronic respiratory disease in children, presents mainly as paroxysmal cough in the night or early in the morning, chest tightness, and wheezing [1]. The etiology of asthma in children is rather complicated. Airway inflammation and airway hyper responsiveness are the main pathological features, and inflammatory factors play important roles in the pathogenesis of the disease [2,3]. Pediatric asthma attacks repeatedly, and it may become more challenging without timely treatment at the early stage of the disease [4]. Glucocorticoids

are frequently-used drugs for treatment of asthma in clinical practice.

Budesonide, a new generation of glucocorticoids, exerts local anti-inflammatory effect and fast onset of action. Thus, it inhibits the production of inflammatory factors, improves the immune system, enhances airway sensitivity to β2 receptors, and promotes functional reconstruction of airway smooth muscle β2 receptors [5]. In Traditional Chinese Medicine (TCM), the pathogenesis of asthma in children is attributed to lung *qi* impairment and phlegm and *qi* stasis caused by phlegm due to external pathogens [6]. *Tuina* therapy is an important and external treatment method in TCM. It plays a crucial role in *dredging the channels and collaterals, removing evil* and strengthening the body; reconciling *yin* and *yang*, and promoting *qi* and blood [7]. Moreover, it has merits in that it is effective, non-traumatic and convenient, and there is no requirement for needles and medicines [8]. This study investigated the clinical efficacy of *Tuina* therapy plus budesonide inhalation in the treatment of children with asthma, and its effect on lung function and levels of inflammatory factors.

METHODS

Subjects

Between January 2019 and January 2021, one hundred children with asthma admitted to the Department of Pediatric Respiration, Gansu Provincial Maternity and Child-care Hospital, Lanzhou, Gansu Province, were assigned at a ratio of 1:1 either to a control group or study group via the concealed envelope method. The control group consisted of 24 male children and 26 female children aged between 2 - 8 years, averaged 5.12 ± 2.55 years. The disease course spanned from 6 months to 3 years, averaged 1.8 ± 0.4 years. The study group consisted of 23 male children and 27 female children aged 1 - 9 years old, averaged 4.9 3 ± 2.25 years, and mean disease course of 1.7 ± 0.6 years. Baseline data were balanced across the two groups of children.

Inclusion criteria and exclusion criteria

Children in the following categories were included: those who met the diagnostic criteria for asthma in children in line with the *Guidelines for the Diagnosis and Treatment of Children Chronic Cough in China*; children with no history of foreign body inhalation; children who had no chronic cough induced by other reasons, and those with no allergies to the drugs used in this study.

The following were deemed as ineligible and were excluded: Children who used glucocorticoid inhibitors one month before the study; those who recently had respiratory infections, children who had severe liver and kidney dysfunction, and those who withdrew from the study halfway as a result of poor compliance.

Ethical approval for the study was secured from the ethics committee of Provincial Maternity and Child-care Hospital, Lanzhou, Gansu Province, China (approval no. 20190230) prior to its commencement, and the patients and their families provided signed informed consent forms after being informed about the purpose and procedure of the study. The study protocol was conducted in strict accordance with the guidelines of Helsinki Declaration [9].

Treatments

Children in the control group were treated with budesonide inhalation (AstraZeneca Pharmaceutical Co. Ltd; National Medicine Standard: H20030410; specification: 200 mg/5 mL, 200 μg/spray) 100 - 200 μg at a time, 2 times/day continuously for 4 weeks. In addition to the treatment in control, studyimental group was given *Tuina* therapy which involved *clearing of the liver, lung, spleen and kidney channels*, 10 times/min and 15 min/day; *pushing the six hollow organs (inside*) and *sanguan* acupoint (outside), 150 times a day and 20 times /min; rubbing *Tiantu* acupoint 50 times a day and 10 times/min; rubbing *Neichuan* acupoint 150 times a day and 30 times/min; rubbing breast side and heel 150 times a day and 25 times/min; pushing *danzhong* acupoint 20 times at the rate of 5 times/min; rubbing the *Feishu* acupoint 150 times (25 times/min), and *Tiantu* acupoint 20 times per day (10 times/min); pushing *Kangong* 20 times per day at the rate of 10 times/min, and pushing temples 20 times a day (10 times/min), continuously for 4 weeks.

Evaluation of parameters

Clinical treatment effectiveness

Treatment was classified as *markedly effective, effective,* or *ineffective*. *Markedly effective* referred to complete relief of chest tightness, dyspnea, asthma and other clinical symptoms, and return of lung function indicators to normal range; *effective* meant that chest tightness, breathing difficulty and asthma were alleviated, and lung function indicators were improved, while

treatment was deemed *ineffective* if clinical symptoms such as chest tightness, dyspnea, and asthma were not being alleviated, and lung function indicators were not improved. Total treatment effectiveness was calculated as shown in Eq 1.

$$TTE\ (\%) = \frac{nME + nE}{TnP}\ x\ 100 \quad \ldots\ldots\ldots (1)$$

where TTE = Percentage total treatment effectiveness, nME = number of markedly effective cases, TnP is the total number of patients and nE = number of effective cases.

The number of asthma attacks and respiratory tract infections and the levels of serum tumor necrosis factor α (TNF-α), interleukin (IL-8), and interleukin (IL-4) were compared. Moreover, immunoglobulin levels in the two groups of children, including levels of IgA, IgG and IgM, were compared. Values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow percentage (PEF%) were compared between the two groups of children.

Assay methods

Three mL fasting venous blood was obtained from each patient, and the blood was centrifuged at 3000 rpm for 10 min after standing for 10 min. Serum levels of TNF-α, IL-8, IL-4, IgA, IgG and IgM levels were measured with ELISA kits (R & D Company) in accordance with the kit instructions.

Pulmonary peak flow meter and pulmonary function tester were used to evaluate the levels of FEV1, FVC and PEF % in the asthmatic children.

Statistical analysis

Data processing was done with SPSS 20.0, and the graphics visualization was conducted using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Count data are expressed as numbers and percentages (n (%)), and they were compared with chi square (λ^2) test. Measurement data are expressed mean ± SD, and they were compared using *t*-test. Statistical significance was defined at a *p-value less than* 0.05.

RESULTS

Clinical efficacy

The experimental group exhibited higher effectiveness profile versus the control group (96 vs 82 %; $p < 0.05$). (Table 1).

Asthmatic attacks and respiratory tract infections

Before treatment, the numbers of asthma attacks and respiratory infections were not remarkably different between the two groups of children ($p > 0.05$). However, the numbers of asthma attacks and respiratory infections in the two groups were decreased postoperatively, with the experimental group having markedly lower values than the control group ($p < 0.05$, Table 2).

IL-4, IL-8 and TNF-α levels

Before treatment, the IL-4, IL-8 and TNF-α levels in the two groups of children were homogenous ($p > 0.05$). Postoperatively, these parameters in the two groups of children were decreased, but there were higher degrees of reduction in the study group ($p < 0.05$; Figure 1, Figure 2 and Figure 3).

Table 1: Comparison of clinical treatment effectiveness (n = 50)

Group	Markedly effective	Effective	Ineffective	Total effectiveness
Control	17(34.00)	24(48.00)	9(18.00)	41(82.00)
Study	26(52.00)	22(44.00)	2(4.00)	48(96.00)
λ^2				5.005
P-value				<0.05

Table 2: Comparison of number of asthma attacks and number of respiratory tract infections before and after treatment (n = 50)

Group	Time	No. of asthma attacks	No. of respiratory infections
Control	Before treatment	2.57 ± 0.49	3.77 ± 0.75
	After treatment	2.14 ± 0.36*	2.65 ± 0.44*#
Study	Before treatment	2.60 ± 0.68	3.74 ± 0.71
	After treatment	1.59 ± 0.47*	1.72 ± 0.32*#

*$P < 0.05$, compared with value before treatment, #$p < 0.05$, compared with control group after treatment

From Figure 1, the TNF-α levels of children in the control group before and after treatment were 1194.20 ± 147.15 ng/L and 817.26 ± 105.14 ng/L, respectively. The levels of TNF-α in the study group before and after treatment were 1202.36 ± 169.57 ng/L and 427.23 ± 97.5 ng/L, respectively. Figure 2 shows the IL-8 levels of children in the control group before and after treatment were 86.75 ± 5.69 pg/mL and 51.33 ± 4.89 pg/mL, respectively. The IL-8 levels of children in the study group before and after treatment were 85.54 ± 6.01 pg/mL and 25.16 ± 3.74 pg/mL, respectively. On the other hand, the IL-4 levels of children in the control group before and after treatment were 121.84 ± 16.58 ng/L and 92.16 ± 13.24 ng/L, respectively. The IL-4 levels of children in the study group before and after treatment were 124.67 ± 17.11 ng/L and 47.86 ± 8.0) ng/L, respectively (Figure 3).

Levels of immunoglobulins

The levels of IgA, IgG, and IgM between the two groups of children did not statistically differ preoperatively ($p > 0.05$). However, marked decreases were observed in levels of IgA in the two groups postoperatively, with much lower level in the study group ($p < 0.5$). In contrast, there were marked increases in levels of IgG and IgM in both groups, with the study group having higher levels ($p < 0.05$, Table 3).

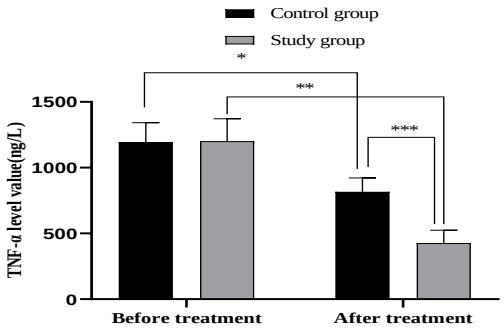

Figure 1: Comparison of TNF-α levels before and after treatment. *P < 0.001, TNF-α level before vs TNF-α level after treatment in the control group; **p < 0.001, TNF-α level before vs TNF-α level after treatment in the study group of children; ***p < 0.001, TNF-α levels in the study group vs TNF-α level in the control group

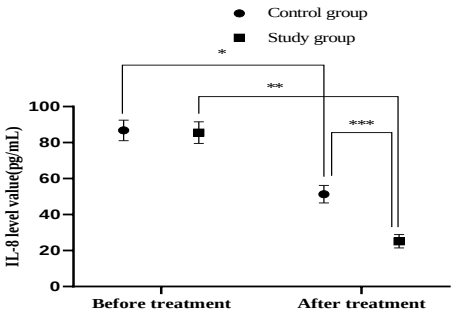

Figure 2: Comparison of IL-8 levels before and after treatment. *P < 0.001, IL-8 level before treatment vs IL-8 level after treatment in children in the control group; **p < 0.001, IL-8 level before treatment vs IL-8 level after treatment in the study group; ***p < 0.001, IL-8 level study, group vs IL-8 level in the control group

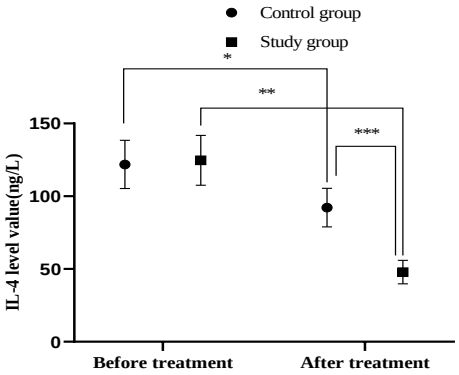

Figure 3: Comparison of IL-4 levels before and after treatment. *P < 0.001, IL-4 level before vs IL-4 level after treatment in children in the control group; **p <0.001, IL-4 level before vs IL-4 level after treatment in the study group of children; ***p < 0.001, IL-4 levels in the study group vs IL-4 levels in the control group

Changes in lung function

The FEV1, FVC, and PEF % levels in the two groups of children were comparable preoperatively. However, there were marked increases in FEV1, FVC, and PEF % levels of the two groups of children postoperatively, but the study group had higher levels of these parameters ($p < 0.05$; Table 4).

Table 3: Comparison of immunoglobulin levels (n = 50)

Group	IgA(g/L)		IgG(g/L)		IgM(g/L)	
	***Before**	***After**	***Before***	***After***	***Before***	***After***
Control	1.35 ± 0.21	0.86 ± 0.17	9.15 ± 1.34	9.98 ± 1.55	1.21 ± 0.42	1.45 ± 0.31
Study	1.33 ± 0.18	0.61 ± 0.14	9.22 ± 1.28	11.46 ± 1.61	1.20 ± 0.39	1.78 ± 0.40
λ^2	0.511	8.027	0.267	4.683	0.123	4.611
P-value	0.610	<0.001	0.790	<0.001	0.902	<0.001

*Before = before treatment; *After = after treatment

Table 4: Comparison of changes in lung function (n = 50)

Group	FEV1(L)		FVC(L)		PEF%(L/s)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	1.58 ± 0.25	2.54 ± 0.22	2.83 ± 0.39	3.31 ± 0.40	2.16 ± 0.48	2.78 ± 0.23
Study	1.60 ± 0.34	3.17 ± 0.26	2.81 ± 0.35	4.15 ± 0.44	2.11 ± 0.56	3.84 ± 0.33
λ^2	0.335	13.080	0.270	9.989	0.479	18.634
P-value	0.738	<0.001	0.788	<0.001	0.633	<0.001

DISCUSSION

Pediatric asthma is a chronic respiratory inflammation frequently seen in pediatric clinics. Genetics, environment, diet, and bacterial or viral infections are the major predisposing factors to pediatric asthma, a disease which presents clinical manifestations such as lung discomfort, wheezing, and coughing. The disease can be life-threatening in the absence of timely treatment [10]. Glucocorticoids are often used for the treatment of asthma in children. Budesonide is a glucocorticoid which suppresses the metabolism of arachidonic acid, hinders the accumulation of eosinophils, inhibits the release of various inflammatory mediators, reduces permeability of blood vessels, decreases the secretion of mucus, and prevents airway obstruction [11,12].

Traditional Chinese Medicine (TCM) believes that the mechanism underlying the pathogenesis of asthma involves an interplay of internal and external factors. The internal factors comprise dysfunctions of the kidneys, spleen, and lungs, leading to retention of phlegm which is the basis of asthma. The external factors comprise *external evils*, dietary acid-base imbalance, and exposure to foreign bodies. At the onset, the disease is dominated by *state evil: fighting this evil* achieves the purpose of treating the symptoms, while at the persistent period, *deficiency and excess* are mixed, and strengthening body resistance *clears the roots of the phlegm* [13].

Tuina therapy selects acupoints in accordance with the cause of the disease. It uses kneading, pinching, pushing and other techniques to act on acupoints on the kidney meridian, lung meridian, and spleen meridian in order to invigorate these organs, resulting in further invigoration of *qi* and *consolidation of the roots*, enhancement of blood circulation, *unblocking of the meridians*, *warming up of phlegm*, and elimination of the disease roots [14].

In this study, the experimental group exhibited superior performance with respect to total treatment effectiveness and the number of asthma attacks and number of respiratory infections in both groups. This indicates that the use of combination of *Tuina* therapy and budesonide inhalation for treatment of childhood asthma produced satisfactory outcome. It is known that IL-4, IL-8, and TNF-α are inflammatory factors synthesized and secreted by monocyte macrophages or neutrophils. These cytokines enhance lymphocyte differentiation and proliferation, and induce the release and activation of acute-phase protein. This protein induces acute-phase inflammatory response, activates inflammatory factors synthesized and secreted by T cells, induces the production of B cell antibodies, and regulates the production of compatibility complexes [15]. In this study, decreased IL-4, IL-8, and TNF-α of the two groups of children was observed postoperatively, with the experimental group having much lower values. Similarly, these findings are in line with the results reported by Becker *et al* [16]. The results suggest that combined treatment with *Tuina* therapy and budesonide inhalation therapy produces a promising result by reducing the levels of inflammatory factors in children with asthma, and by inhibiting inflammatory response.

Immunity is immensely associated with the occurrence of asthma. Immunoglobin A (IgA) is secreted by B cells, and it is an important factor in effective resistance to infection, including respiratory infections and other diseases. In addition, IgM is one of the earliest antibodies in humoral immunity, and it has the largest molecular weight. It is present in the blood, and it has a relatively potent anti-infection potential. In contrast, IgG is the main antibody component of the serum, and the only immunoglobulin that can pass through the placenta. In this study, the post-intervention IgA levels of children decreases in both groups, while the levels of IgG and IgM were increased, with the changes more pronounced in the study group.

It has been reported that combination of *Tuina* therapy and budesonide inhalation in the treatment of childhood asthma resulted in reduced IgA levels, increased levels of IgG and

IgM, mitigated immunoglobulin disorders, and regulated immune status [17,18]. Furthermore, the levels of FEV1, FVC, and PEF % in the two groups of children were increased after treatment, with the experimental group levels being significantly higher than those of the control group. This indicates that the combined use of *Tuina* therapy and budesonide inhalation therapy produced promising outcome in terms of better improvement of lung function in children with asthma, when compared with budesonide alone.

CONCLUSION

This study demonstrates that the combination of *Tuina* and budesonide inhalation improves the levels of inflammatory factors, regulates immunity, and improves lung function in asthmatic children. Therefore, the combined therapy seems to be an superior therapeutic strategy for the treatment of asthmatic children. However, further clinical trials are needed prior to application in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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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