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Review Article

Montelukast sodium in decreasing inflammatory cytokines and improving immunity in children with bronchial asthma

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Abstract: Objective: To investigate the effects of montelukast sodium in decreasing inflammatory cytokines and improving immunity in children with bronchial asthma. Methods: Totally 147 cases of children with bronchial asthma admitted to our hospital were elected as research subjects. Among them, 77 children treated with montelukast sodium were included in the research group (RG), and 70 children treated with ketotifen monotherapy were enrolled in the control group (CG). The therapeutic effect and adverse effects in both groups were observed. Expression of interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), and changes of CD3+, CD4+ and CD4+/CD8+ in T cell lymphocyte subsets were compared. The improvement of pulmonary function and the scores of asthma symptoms of children were observed and compared. Results: There was no difference in the therapeutic effect and the incidence of adverse effects between the two groups (P>0.05). Four weeks after treatment, IL-1, IL-6, IL-8 and TNF-α expression in the RG were lower than those in the CG (P<0.05), while CD3+, CD4+ and CD4+/CD8+ expression in the RG were higher than those in the CG (P<0.05). The improvement of pulmonary function in the RG was better than that in the CG (P<0.05). After treatment, daytime asthma symptoms and nighttime asthma symptoms scores of the RG were lower than those of the CG (P<0.05). Conclusion: In the treatment of bronchial asthma, montelukast sodium has significant efficacy, high safety, and can effectively reduce inflammatory cytokines in children and improve the immune function, which has extremely high clinical application value.

Keywords: Montelukast sodium, bronchial asthma, inflammatory cytokines, immunity

Introduction

Bronchial asthma is a kind of heterogeneous disease characterized by chronic airway inflammation involving various cells (such as eosinophils, neutrophils, T lymphocytes) and cytokines. It is a chronic inflammation associated with bronchial hyperresponsiveness [1, 2]. Most cases of bronchial asthma occur in childhood [3], usually accompanied by extensive and variable limitation of reversible expiratory airflow, resulting in repeated attacks of wheezing, shortness of breath, chest tightness, cough, etc. The symptoms become worse with the lengthening of time, which seriously affects the normal development of children [4, 5]. Irreversible airway constriction and airway remodeling can occur due to the prolongation of the course of disease [6]. In recent years, with the rapid development of industrialization and the serious decline of air quality in China, the living environment has become an important factor aggravating the incidence of bronchial asthma [7]. Data showed that the incidence of bronchial asthma increased significantly in large cities in China [8]. Therefore, while reducing environmental pollution, effective therapeutic measures must be taken to treat children's bronchial asthma and reduce its incidence.

Montelukast sodium is a class A drug for medical insurance, which is generally well tolerated

and has minor side effects. It is not usually discontinued in clinical treatment, so it has a high clinical utilization rate [9]. Montelukast sodium is an effective selective leukotriene receptor antagonist, which can specifically inhibit cysteinyl leukotriene receptor, suppressing the proinflammatory mediator [10]. Team of Sun and Liu [11] pointed out that minimally invasive catgut embedding combined with montelukast sodium had a significant effect on the treatment of cough-variant asthma in children. Wei [12] et al. also demonstrated that montelukast sodium had better efficacy and safety in preventing bronchopulmonary dysplasia. However, at present, there are few studies on montelukast sodium single drug therapy for bronchial asthma in children, and most previous studies were limited to the clinical effect of montelukast sodium on bronchial asthma. No studies have shown the effects of montelukast sodium on immune function in children. Etiological treatment and symptomatic treatment are treatment principles of bronchial asthma, and antibiotic treatment is required for respiratory tract infections. If patients suffer from wheezing, they should be relieved from asthma. If their breathing is difficult, the airway should be kept open, and oxygen can be inhaled or even mechanical ventilation should be given. Ketotifen is one of the most common asthma drugs in clinical practice, and one of the first choice drugs for children with asthma. Its efficacy has been clinically recognized. Montelukast sodium is also an effective asthma treatment drug, which has been found to have higher safety than ketotifen in previous studies. At present, the research on the treatment of asthma with montelukast sodium is not thorough. Therefore, this study conducted a comparative analysis of montelukast sodium and ketotifen to verify the treatment effect of montelukast sodium in bronchial asthma, and to observe the changes of inflammatory cytokines in children and its effects on immune function, so as to provide a new therapeutic idea and method for the clinical treatment of children bronchial asthma in the future.

Materials and methods

Clinical data collection

Totally 147 cases of bronchial asthma children admitted to Affiliated Hospital of Hebei University of Engineering from March 2016 to March 2018 were elected as research subjects for prospective analysis, aged from 2-9 years, with an average age of 5.2±4.1 years. Among them, 77 children receiving treatment of montelukast sodium were included in the RG (RG), and 70 children receiving treatment of ketotifen monotherapy were enrolled in the CG (CG). This experiment has been approved by the Ethics Committee of Affiliated Hospital of Hebei University of Engineering, and all subjects involved in the study have signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: Children diagnosed with bronchial asthma after a series of examinations in Affiliated Hospital of Hebei University of Engineering [13]; Children who was less than 13 years old; Children received treatment in Affiliated Hospital of Hebei University of Engineering after diagnosis; Children with complete case data; Children agreed to cooperate with and participate in the arrangement of medical staff of our hospital; Children whose immediate family signed the informed consent.

Exclusion criteria: Children comorbid with multiple chronic diseases; Children combined with cancer; Children with other cardiovascular and cerebrovascular diseases; Children who received treatment of immunomodulator before admission; Children with dysfunction of vital organs; Children with drug allergy; Children with mental illness; Children with systemic dysfunction.

Methods

Patients in the RG were treated with montelukast sodium (Merck & Co., Inc., Hangzhou, SFDA approval number: J20120072) orally, 10 mg/d, once/d, and took it before bed for 4-6 weeks. Patients in the CG were treated with ketotifen (Changzhou Pharmaceutical Factory Co., Ltd., SFDA approval number: H32024643) orally, 1 tablet/time, 2 times/d, for 4-6 weeks. Fasting venous blood (5 mL) was extracted from patients in both groups before treatment, two weeks after treatment, and four weeks after treatment. Changes of IL-1 (Shanghai Gudo Biotechnology Co., Ltd., GD-G10246), IL-6 (Shanghai Hengfei Biotechnology Co., Ltd.,

Table 1. Clinical efficacy

Therapeutic effect	
Markedly effect	The wheezing symptoms completely disappeared, and wheezing sound significantly decreased or disappeared during auscultation, and the breathing was stable and strong.
Effective	After treatment, the wheezing symptoms of the children were alleviated, and the wheezing sound was alleviated during auscultation, and the breathing was basically stable.
Ineffective	The wheezing symptoms did not change or worsen after treatment, and the wheezing sound did not decrease during auscultation.

SEB815Hu-1), IL-8 (Shanghai Xiyuan Bio Co., Ltd., XY-70R-35386), TNF-α (Shanghai Jingkang Bioengineering Co., Ltd., JK-(a)-0016), and T lymphocyte subsets (Beckman CytoFLEX flow cytometer) in peripheral blood were detected.

Detection methods

Serum concentrations were determined with the help of enzyme-linked immunosorbent assay (ELISA). Blank wells, standard wells, and sample wells to be tested were set separately. The S0 standard with a concentration of 0 was put into the blank wells. The standard wells were added with 50 μL of standards of different concentrations. Sample to be tested (10 μL) was first added to the sample well, followed by 40 μL sample diluent, with nothing being added to the blank well. In addition to the blank wells, horse radish peroxidase (HRP, 100 μL) labeled detection antibody was put into each well of the standard and sample wells. The reaction wells were blocked with a sealing plate membrane and incubated at 37°C in a water bath for 65 min. 50 μL of each of substrates A and B were put into each well and incubated at 37°C in the dark for 10 min. Each well was added with 50 μL of stop solution, and the OD value of each well was determined at 450 nm within 15 min.

Flow cytometry method: Ethylene diamine tetraacetic acid (EDTA) anticoagulant was added for full blending. Lymphocytes were labeled with fluorescent antibody CD3-phycoerythrin cyanin 5 (PeCy5) and CD4-phycoerythrin (PE) (BD, USA). The erythrocytes were dissolved with hemolysis agent and centrifuged. The supernatant was discarded, and then washed with phosphate buffer saline (PBS) for 2 times. Flow cytometry (BD FACS Calibur) was used for detection. Kaluza analysis software (Beckman Coulter, USA) was used to analyze the percentages of CD3+ T cells and CD4+ T cells in the total T cells (CD3% and CD4%), and the CD4/CD8 ratio was calculated.

Outcome measures

Main outcome measures: The therapeutic effect of the two groups of children was observed, and it was divided into markedly effective, effective and ineffective. Total efficacy = markedly effective + effective. As shown in **Table 1**. The incidence of adverse effects of children in both groups was observed. Changes of inflammatory factors and immune function in the two groups were observed.

Secondary outcome measures: The improvement of pulmonary function forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow (PEF) and asthma symptom scores of children in the two groups were observed.

Statistical methods

SPS22.0 statistical software was applied to analyze the data. Graphpad7 was used for image rendering of the data. The counting data were represented by rate. Chi-square test was utilized for comparison between groups. The measurement data were represented as mean ± standard deviation and t test was adopted for inter-group comparison. Repeated measures variance analysis and Bonferroni post hoc. testing were used for comparison among multiple time points. When $P<0.05$, the difference was considered statistically significant.

Results

General data

There was no difference in age, BMI, gender, living condition, family medical history, respiratory history, nationality, and inflammatory phenotype ($P>0.05$). More details were shown in **Table 2**.

Table 2. Comparison of general data of patients in the two groups [(%)]

	RG (n=77)	CG (n=70)	t or X^2	P
Age (years)	5.2±4.1	5.8±3.2	0.982	0.328
BMI (kg/cm^2)	20.41±1.18	20.67±1.16	1.345	0.181
Gender			1.251	0.270
Male	40 (51.59)	30 (42.86)		
Female	37 (48.05)	40 (57.14)		
Living environment			0.821	0.365
Cities	60 (77.92)	50 (71.43)		
Countrysides	17 (22.08)	20 (28.57)		
Family medical history			0.143	0.705
with	35 (45.45)	34 (48.57)		
without	42 (54.55)	36 (51.43)		
Respiratory history			1.279	0.258
with	24 (31.17)	16 (22.86)		
without	53 (68.83)	54 (77.14)		
Nationality			0.186	0.667
Han Chinese	70 (90.91)	65 (92.86)		
Minority	7 (9.09)	5 (7.14)		
Inflammatory phenotype			0.036	0.998
Eosinophils	32 (41.56)	30 (42.86)		
Neutrophils	22 (28.57)	20 (28.57)		
Mixed granulocytosis	15 (19.48)	13 (18.57)		
Low granulocytes	8 (10.39)	7 (10.00)		

Changes of IL-1, IL-6, IL-8, TNF-α

The test results revealed that there was no remarkable difference in the levels of IL-1, IL-6, IL-8, and TNF-α before treatment between children in the RG and the CG (P>0.05). After two weeks of treatment, the levels of IL-1, IL-6, IL-8 and TNF-α in the two groups were lower than those before treatment, and the RG was notably lower than the CG (P<0.05). After four weeks of treatment, the levels of IL-1, IL-6, IL-8, and TNF-α in both groups were lower than those two weeks ago, and the RG was notably lower than the CG (P<0.05). See **Figure 1**.

Changes of CD3+, CD4+, CD4+/CD8+

The test results indicated that there was no notable difference in the expression of CD3+, CD4+, CD4+/CD8+ before treatment between the RG and the CG (P>0.05). After two weeks of treatment, the expression levels of CD3+, CD4+, CD4+/CD8+ in the two groups were higher than those before treatment, and the RG was remarkably higher than the CG (P<0.05). After four weeks of treatment, the expression of CD3+, CD4+, CD4+/CD8+ in both groups were higher than those two weeks ago, and the RG was remarkably higher than the CG (P<0.05). **Figure 2**.

Improvement of pulmonary function in children

The observation results exhibited that there was no remarkable difference in FVC, FEV1 and PEF between the RG and the CG before treatment (P>0.05). After treatment, FVC, FEV1 and PEF% in both groups were all higher than those before treatment, and the RG was significantly higher than the CG, with statistically significant differences (P< 0.05). As shown in **Figure 3**.

Asthma symptom scores in children

The observation results exhibited that there was no statistically remarkably difference in the scores of daytime asthma symptoms and nighttime asthma symptoms in the two groups of children before treatment (P>0.05). After treatment, the scores of daytime asthma symptoms and nighttime asthma symptoms in both groups were lower than before treatment, and both daytime asthma symptoms and nighttime asthma symptoms scores were remarkably lower in the RG than in the CG. (P<0.05). See **Figure 4**.

Clinical efficacy

In the RG, 79.22% were markedly effective patients (61 cases), 16.88% were effective patients (13 cases), and 3.90% were ineffective patients (3 cases), and the rate of effective treatment was 96.10%. In the CG, 74.29% were markedly effective patients (52 cases), 21.43% were effective patients (15 cases), 4.29% were ineffective patients (3 cases), and the rate of effective treatment was 95.72%. There was no remarkable difference in effective treatment rates between the patients in the RG and the CG (P<0.05). See **Table 3**.

Comparison of adverse effects

In the RG, there were 3.90% (3 cases) of headache, 1.30% (1 case) of fever, 2.60% (2 cases)

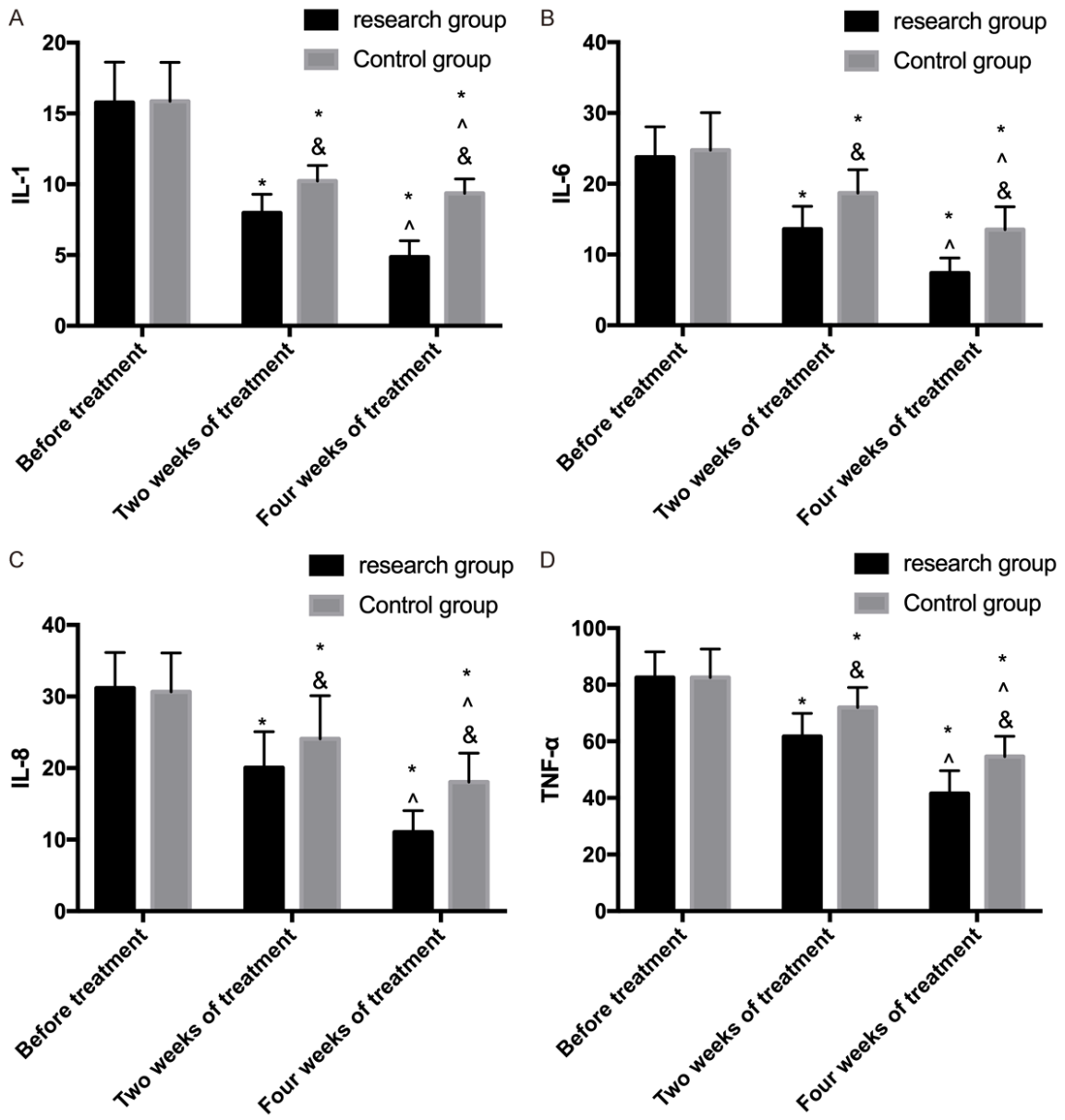

Figure 1. Inflammatory cell changes of IL-1, IL-6, IL-8, and TNF-α. A. Changes of IL-1. B. Changes of IL-6. C. Changes of IL-8. D. Changes of TNF-α. Notes: * indicates comparison with before treatment, & indicates comparison with RG, ^ indicates comparison with after two weeks of treatment.

of energielos, 1.30% (1 case) of skin allergy, no nausea and vomiting, 1.30% (1 case) of oral bacterial infection, and the incidence of adverse effects was 10.40%. In the CG, there were 2.86% (2 cases) of headache, 1.43% (1 case) of fever, 2.86% (2 cases) of energielos, 2.86% (2 cases) of skin allergy, 1.43% (1 case) of nausea and vomiting, and no oral bacterial infection, and the incidence of adverse effects was 11.44%. There was no remarkable difference in the incidence of adverse effects between the RG and the CG (P=0.840). As shown in **Table 4**.

Discussion

Bronchial asthma is a disease mainly characterized by allergic inflammation and bronchial hyperresponsiveness involving eosinophils and mast cells [14], which is also the most common chronic respiratory disease in children [15]. The disease has a long course

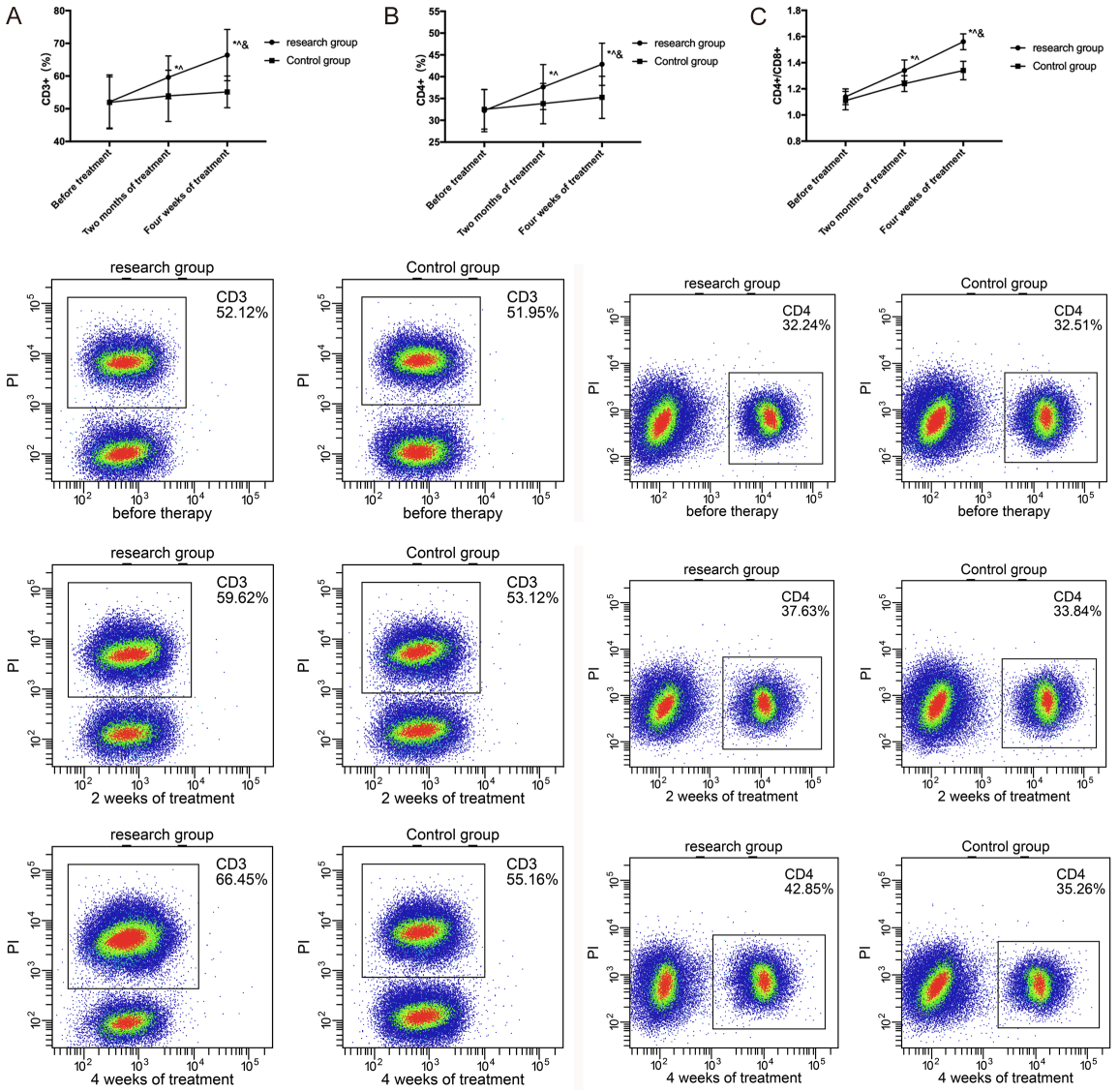

Figure 2. Changes of CD3+, CD4+, CD4+/CD8+. A. Changes of CD3+. B. Changes of CD4+. C. Changes of CD4+/CD8+. Notes: * indicates comparison with before treatment, ^ indicates comparison with RG, & indicates comparison with after two weeks of treatment.

and is prone to recurrent attacks. When the disease is severe, respiratory failure occurs, which seriously threatens the physical and mental health of the children, and also brings a heavy mental and economic burden to the families and society [16]. At present, the overall level of children's asthma control in China is not ideal. And there are many clinical treatment options, but it is still unclear which one is most suitable in treating bronchial asthma in children [17]. By analyzing montelukast sodium, this experiment not only verified the curative effect of montelukast sodium in treating children with bronchial asthma, but also further analyzed its influence on inflammation and immune function, which has a more reference value for future use of the clinical application of montelukast sodium.

The results of this experiment showed that there was no remarkable difference in the clinical efficacy and incidence of adverse effects between montelukast sodium and ketotifen in treating the two groups, suggesting that both drugs had good clinical efficacy when treating children with bronchial asthma, and had high safety, which was worthy of promotion. The main pathological mechanism of bronchial asthma is the chronic inflammatory response and high reactivity of the airway mucosa [18].

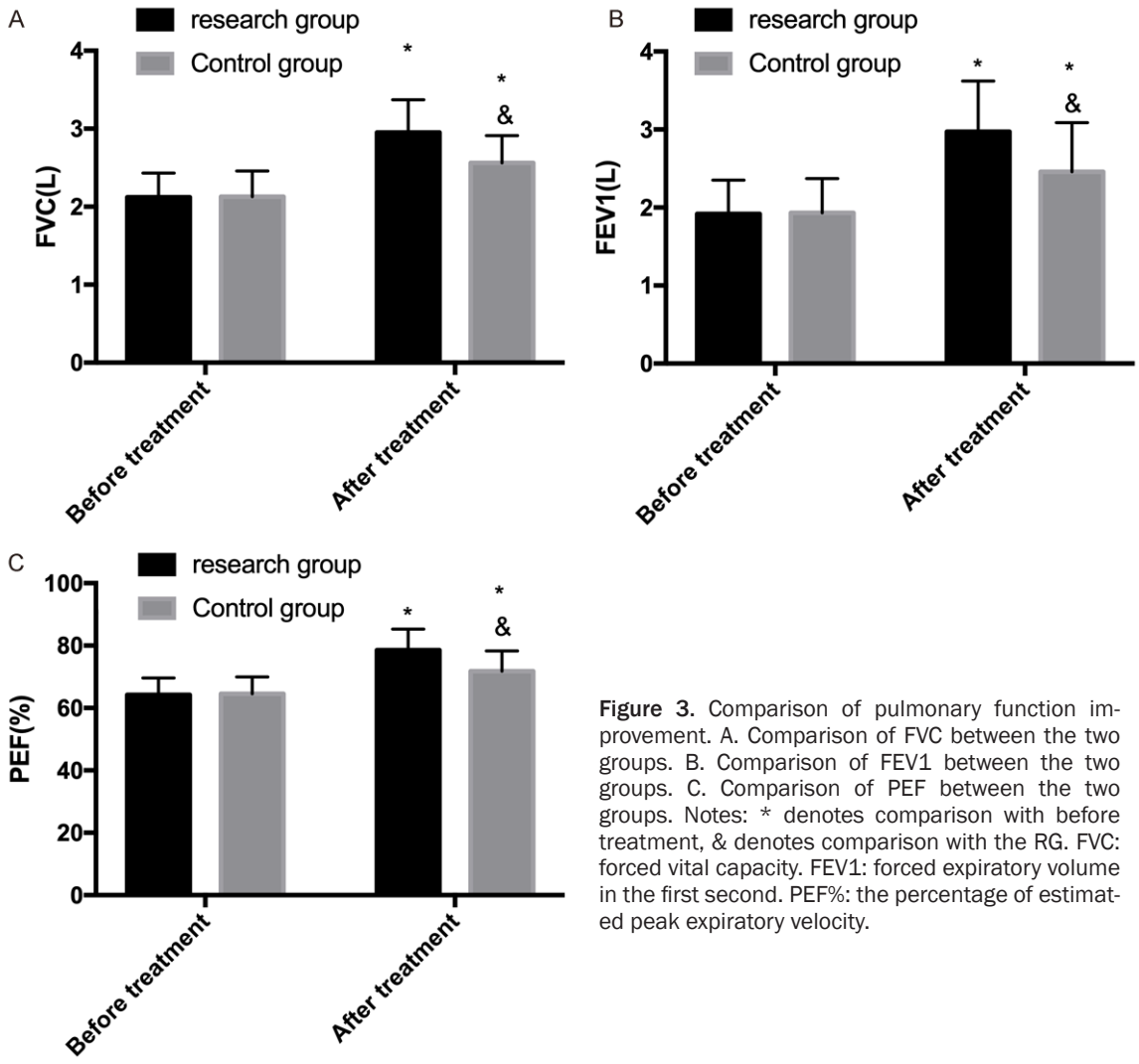

Figure 3. Comparison of pulmonary function improvement. A. Comparison of FVC between the two groups. B. Comparison of FEV1 between the two groups. C. Comparison of PEF between the two groups. Notes: * denotes comparison with before treatment, & denotes comparison with the RG. FVC: forced vital capacity. FEV1: forced expiratory volume in the first second. PEF%: the percentage of estimated peak expiratory velocity.

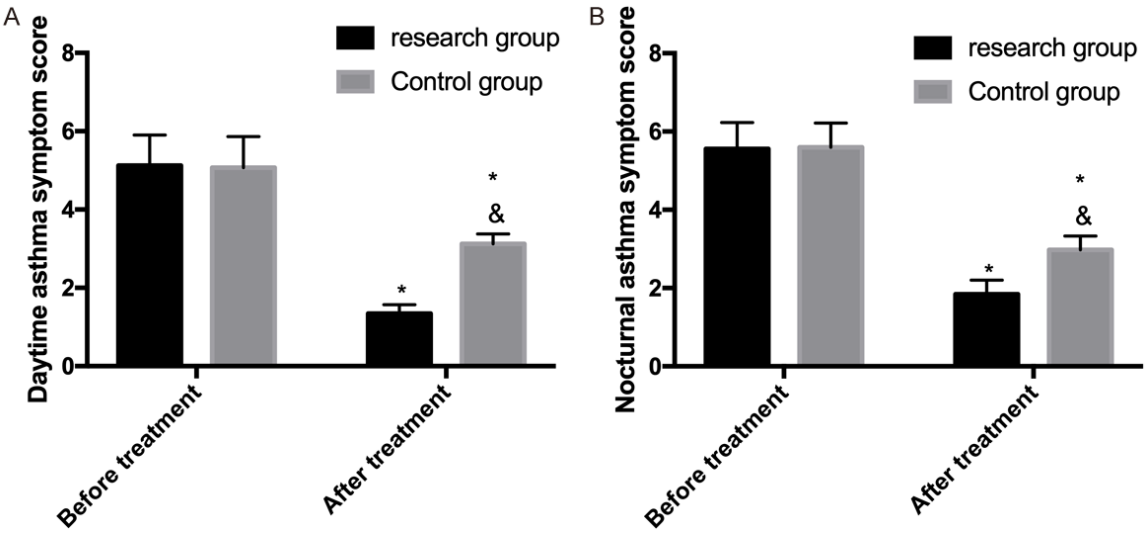

Figure 4. Comparison of children's asthma symptom scores. A. Comparison of children's daytime asthma symptoms between the two groups. B. Comparison of children's nocturnal asthma symptoms between the two groups. Notes: * denotes comparison with before treatment, & denotes comparison with the RG.

Table 3. Comparison of clinical efficacy of patients in the two groups [n (%)]

	RG (n=77)	CG (n=70)	X^2	P
Markedly effective	61 (79.22)	52 (74.29)		
Effective	13 (16.88)	15 (21.43)		
Ineffective	3 (3.90)	3 (4.29)		
Rate of treatment (%)	96.10	95.72	0.014	0.905

Table 4. Comparison of adverse effects of patients in the two groups [n (%)]

	RG (n=77)	CG (n=70)	X^2	P
Headache	3 (3.90)	2 (2.86)		
Fever	1 (1.30)	1 (1.43)		
Energielos	2 (2.60)	2 (2.86)		
Skin allergy	1 (1.30)	2 (2.86)		
Nausea and vomiting	0 (0.00)	1 (1.43)		
Ora bacterial infection	1 (1.30)	0 (0.00)		
Adverse effects rate (%)	10.40	11.44	0.041	0.840

Leukotriene, which is effective in promoting inflammation, produces a marked effect on increasing the permeability of capillaries and venules, leading to local edema [19]. However, inflammatory media antagonists can block the inflammatory effect of leukotriene [20]. Montelukast sodium, a new type of leukotriene receptor blocker with high rate of clinical utilization, can reduce the activity of leukotriene and block its inflammatory effect. In addition, montelukast sodium is well tolerated, which can reduce the incidence of adverse effects in children. And it is simple to operate, which is more suitable for the treatment of children with clinical bronchial asthma [21]. Its efficacy has been recognized clinically. In the study of McIvor [22], montelukast sodium also has a good effect as a replacement of low-dose inhaled corticosteroid in treating mild asthma. In order to further determine the therapeutic effect of this drug on this disease, we also analyzed the changes in the immune function of inflammatory cells in the two groups. The results revealed that the expressions of inflammatory cells IL-1, IL-6, IL-8 and TNF-α were notably decreased in the children treated with montelukast sodium, while the levels of CD3+, CD4+ and CD4+/CD8+ were remarkably increased in the T-cell lymphocyte subsets. This suggested that montelukast sodium could effectively reduce the level of inflammation in children and improve their immunity. In T lymphocyte subsets, the decrease of CD3+ level can directly reflect the decline in immune function. CD4+ mainly induces T cell secretion through auxiliary effects, while CD8+ inhibits T cell proliferation and antibody synthesis. Therefore, the CD4+/CD8+ ratio can reflect the balance state of the body's immune function [23]. The increase of CD3+, CD4+ and CD4+/CD8+ in the RG represented that their immune function was also in a state of improvement during treatment, and we speculated that its mechanism of action occurred by improving the condition of inflammatory factors. Previous studies have confirmed that changes in inflammatory factors may affect changes in the immune function of patients [24], while reduced IL-1, IL-6, IL-8 and TNF-α levels in peripheral blood of the RG confirmed the inhibitory effect of montelukast sodium on inflammatory factors. We conjectured that montelukast sodium inhibited the effect of leukotriene on the inflammation of small blood vessels and the number of eosinophils through blocking the binding of leukotriene and cells in patients, thus enhancing the resistance of inflammatory cells and improving the immune function of the body. Kim et al. [25] studied the treatment of bronchopulmonary dysplasia with montelukast sodium, and montelukast sodium also significantly improved the expression of inflammatory factors, which can also support our experimental results.

The purpose of this experiment was to explore the therapeutic effect of montelukast sodium on bronchial asthma, but there were many deficiencies due to limited experimental conditions. For example, there are various drugs for the treatment of bronchial asthma in clinical practice, but only ketotifen was used as the control in this paper, so it can not rule out the possibility that the advantages of montelukast sodium are not as significant as in this paper when compared with other drugs. In addition, due to the short period of this experiment, the effect of montelukast sodium on the long-term prognosis of children with bronchial asthma could not be determined. However, due to the lack of basic experiments, the exact mechanism of montelukast sodium in treating bronchial asthma cannot be determined. We will

conduct more in-depth and comprehensive analysis on the above shortcomings as soon as possible to obtain more representative experimental results.

In conclusion, montelukast sodium has significant therapeutic effect on bronchial asthma and high safety, which can effectively reduce the level of inflammatory factors in children and improve the immune function, with high clinical application value.

Disclosure of conflict of interest

None.

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