Allergol Immunopathol (Madr). 2023;51(4):151-157 eISSN:1578-1267, pISSN:0301-0546

Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Effect of budesonide combined with montelukast sodium on pulmonary function parameters and immunoglobulin levels in children with bronchial asthma

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Received 27 April 2023; Accepted 15 May 2023
Available online 1 July 2023

KEYWORDS
budesonide;
montelukast sodium;
bronchial asthma;
pulmonary function;
immunoglobulin

Abstract
Background and aim: Bronchial asthma is a prevalent type of respiratory disease that affects a large proportion of pediatric patients. The purpose of this study is to further investigate the clinical effects of budesonide combined with montelukast sodium in treating bronchial asthma.
Methods: Eighty six children with bronchial asthma were equally divided into study and control groups via randomized double-blind controlled trial. The control group was treated with aerosol inhalation of budesonide combined with placebo, while the study group was treated with budesonide combined with montelukast sodium. Pulmonary function parameters, immunoglobulin, and recovery of related symptoms, along with the adverse reaction rate, were observed and compared between both groups.
Results: Before treatment, there was no marked difference in pulmonary function parameters and immunoglobulin indexes between both groups ($P > 0.05$). All pulmonary function indicators and immunoglobulin indexes in both groups improved following therapy, with the study group outperforming the control group ($P < 0.05$). The recovery time of related symptoms in the study group was shorter than that in the control group ($P < 0.05$). The incidence of adverse reactions in both groups was compared, with notable differences ($P < 0.05$).
Conclusion: Budesonide combined with montelukast sodium in the treatment of bronchial asthma has the value of clinical application and promotion.

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https://doi.org/10.15586/aei.v51i4.897

Introduction

Bronchial asthma has emerged as a common type of respiratory disease. Pediatric patients of bronchial asthma account for a substantial proportion of the patient population, especially infants before the age of 5 years.[1] The disease has a distinct pathophysiology relative to other prevalent disorders of the pediatric respiratory system, and it typically manifests clinically as respiratory tract infections, chronic airway inflammation, and airway hyperreactivity.[2] The prominent clinical symptoms of bronchial asthma include dyspnea, wheezing, and cough that aggravate or attack in the early morning and night. As found in relevant clinical studies,[3,4] leukotrienes play a critical role in the process of airway inflammation in bronchial asthma. Leukotrienes can interact with leukotriene receptors present locally in patients, thereby promoting the convergence of eosinophils. Inhaled corticosteroids are the primary treatment for bronchial asthma at the moment. Budesonide is the most commonly used agent. The drug can effectively repress the development of inflammation, improve smooth muscle spasm, and stimulate the endothelial function to return to normal. However, budesonide has no evident effect on leukotrienes and their receptors during the progression of bronchial asthma.[3,5,6] As a result, despite receiving budesonide medication, children did not experience optimal improvement in linked symptoms. Montelukast sodium belongs to a type of leukotriene antagonist that is selective.[7-9] It can prevent leukotriene from attaching to receptors, thus regulating inflammation while compensating for budesonide's limitations.[10-12] Therefore, to further investigate the clinical therapeutic effect of budesonide combined with montelukast sodium in bronchial asthma, 86 children with bronchial asthma admitted to our hospital from January 2019 to December 2020 were selected for the following study and report.

Materials and Methods

Clinical data

Eighty six children with bronchial asthma, admitted in our hospital from January 2019 to December 2020, were selected as the main subjects of the present study. They were equally divided into study and control groups by applying a randomized double-blind controlled trial. There was no remarkable difference in clinical baseline data between both groups ($P > 0.05$), as shown in Table 1. The study is comparable. The Ethics Committee of Anhui Provincial Children's Hospital (Approval no. EYLL-2022010) approved the study.

Treatment methods

All children received basic treatment including anti-infection and oxygen inhalation. Active symptomatic treatment measures were given according to individual differences in children.

Inclusion criteria

(1) All of them met the definition and diagnostic criteria for asthma in children in the Guidelines for the Diagnosis and Prevention of Bronchial Asthma in Children; (2) Bronchial provocation test was positive; (3) No previous treatment with glucocorticoids, β^2 receptor agonists, and histamines was given to them.

Exclusion criteria

(1) Patients with a history of drug allergy; (2) Patients with severe heart, liver, and kidney dysfunction; (3) Patients

Table 1 Clinical Baseline Data.

Clinical data	Study group (n = 43)	Control group (n = 43)	t/x^2	P
Age (year)	5.21 ± 0.51	5.26 ± 0.54	0.4414	0.6600
FVC (L)	2.51 ± 0.21	2.52 ± 0.23	0.2105	0.8338
DLCO (mL/min/mmHg)	17.12 ± 1.62	17.19 ± 1.59	0.2022	0.8402
RV/TLC	39.21 ± 2.16	39.31 ± 2.09	0.2182	0.8278
Gender (n)				
Male	23	24	0.0469	0.8285
Female	20	19		
Degree of asthma (n)				
Mild	25	24	0.0474	0.8276
Severe	18	19		
Disease duration (years)	2.51 ± 0.51	2.53 ± 0.50	0.1836	0.8547
Family history (n)				
Yes	13	14	0.0540	0.8163
No	30	29		
History of respiratory infection (n)				
Yes	16	17	0.0492	0.8245
No	27	26		
Obesity (n)				
Yes	14	15	0.0520	0.8196

with hormone resistance or dependence; (4) Patients with mental disorders.

Control group

The control group was subjected to aerosol inhalation of budesonide [Budesonide suspension (manufacturer: AstraZeneca Pty Ltd., approval number: imported drug registration certificate No. H20140474; strength: 2 mL: 1 mg) + normal saline 2 mL each for mixing] twice daily and 20 min each time. According to the children's condition, the dose was controlled at 200–800 μg/d. Placebo was also given to the children, and the dosage form and smell of the drug were consistent with those of montelukast sodium tablets.

Study group

Monelukast sodium chewable tablets [manufacturer: Organon Pharma (UK) Limited (packaged by Hangzhou MSD Pharmaceutical Co., Ltd.) State medical permitment number. J20130054; strength: 5 mg] were orally administered based on aerosol inhalation of budesonide (the method was the same as the control group). For children less than 5 years old, the dose was 4 mg once a day; for children 5–10 years old, the dose was 5 mg once a day; and for children 10–15 years old, the dose was 10 mg once a day.

Outcome measures

Pulmonary function parameters (FEV1, FVC, FEV1/FVC, PEF, MMEF, MEF25%, MEF50%, DLCO, RV/TLC), immunoglobulin (IgA, IgG, IgM), and recovery of related symptoms were observed and compared between both groups.

1. Pulmonary function parameters of the children were examined by spirometry.
2. Immunoglobulin (IgA, IgG, IgM, IgE) was measured by immunonephelometry.
3. The disappearance time of wheezing, wheezing rale, cough, and dyspnea was recorded.
4. Adverse reactions were recorded.

The concrete design flowchart is presented in Figure 1.

Statistical methods

SPSS 23.0 was utilized for statistical analysis of the study data, and the enumeration data were presented as n and %, and X^2 test was applied for the comparison between groups. Measurement data were demonstrated as ($x \pm s$), and t-test was adopted for the comparison of data. P less than 0.05 indicated that the differences were significant.

Results

Comparison of pulmonary function parameters between both groups

There was no discernible difference in any of the pulmonary function metrics across the two groups prior to treatment application ($P > 0.05$). After treatment, all pulmonary function parameters in both groups improved, and the

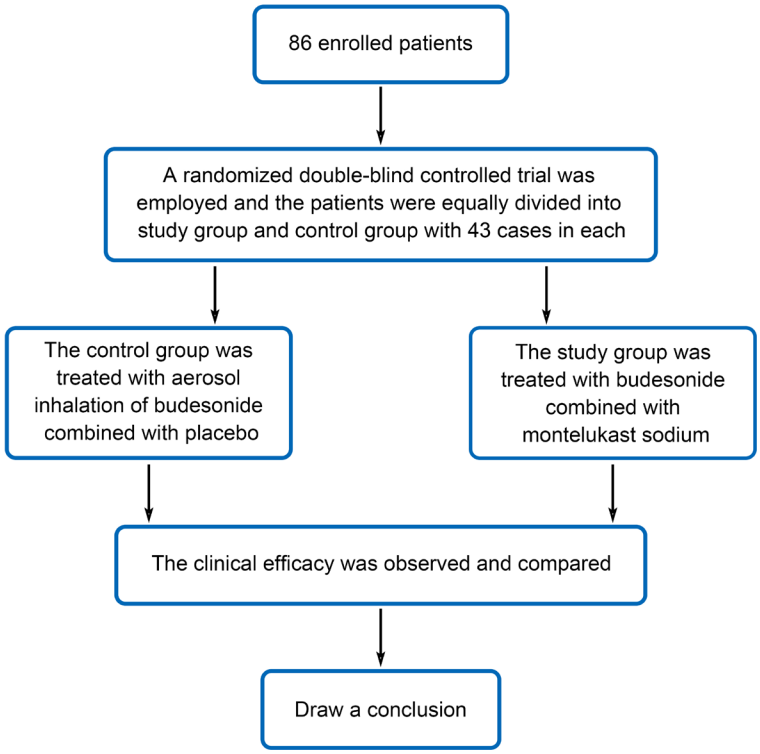

Figure 1 Design flowchart.

study group was superior to the control group ($P < 0.05$) with a remarkable difference. The results are demonstrated in Table 2.

Comparison of immunoglobulin indicators between both groups

Before treatment, there was no eminent difference in immunoglobulin indicators between both groups ($P > 0.05$). After treatment, all immunoglobulin indicators in the two groups improved, and the study group was superior to the control group ($P < 0.05$) with significant difference. The results are revealed in Table 3.

Comparison of symptom recovery between both groups

The recovery time of related symptoms in study group was shorter than that in control group ($P < 0.05$), and the difference was prominent. The results are shown in Table 4.

Comparison of adverse reactions between both groups

There was one case of sleep disorder in the study group, but the degree was mild. The patient recovered rapidly after drug withdrawal. There was one case of respiratory symptoms in the control group, which manifested as a hoarse voice. The degree was also mild, and the patient recovered rapidly after drug withdrawal. There was no significant difference in the incidence of adverse reactions between both groups ($X^2 = 0.0000$, $P = 1.0000$).

Discussion

Clinical studies have suggested that T lymphocytes, eosinophils, and other related inflammatory cells play an essential role in the development of childhood asthma.[13,14] Children clinically manifest coughing, wheezing, dyspnea, and airway hyperreactivity. Besides, children are prone to recurrent and persistent attacks.[15,16] The main triggers of the disease in children are exposure to allergens,

Table 2 Comparison of pulmonary function parameters between both groups ($\bar{x} \pm s$).

Parameters	Before and after treatment	Study group (n = 43)	Control group (n = 43)	t	P
FEV1 (L)	Before treatment	65.35 ± 5.16	65.41 ± 5.09	0.0543	0.9568
	After treatment	75.26 ± 6.95	68.35 ± 6.21	4.8617	0.0000
	T	7.5073	2.401		
	P	0.0000	0.0186		
FVC (L)	Before treatment	2.51 ± 0.21	2.52 ± 0.23	0.2105	0.8338
	After treatment	3.46 ± 0.33	3.01 ± 0.29	6.7169	0.0000
	T	15.9262	8.681		
	P	0.0000	0.0000		
FEV1/FVC (%)	Before treatment	55.16 ± 5.14	55.18 ± 5.09	0.0181	0.9856
	After treatment	69.35 ± 6.09	61.08 ± 5.34	6.6954	0.0000
	T	11.6763	5.2444		
	P	0.0000	0.0000		
PEF (L/min)	Before treatment	53.65 ± 5.34	53.71 ± 5.41	0.0518	0.9588
	After treatment	64.95 ± 6.54	59.63 ± 6.04	3.9187	0.0002
	T	8.7762	4.7875		
	P	0.0000	0.0000		
MMEF	Before treatment	4.23 ± 0.45	4.24 ± 0.46	0.1019	0.9191
	After treatment	5.26 ± 0.51	5.00 ± 0.57	2.2291	0.0285
	T	9.9304	6.804		
	P	0.0000	0.0000		
MEF25%	Before treatment	6.35 ± 0.64	6.37 ± 0.59	0.1507	0.8806
	After treatment	8.16 ± 0.76	7.04 ± 0.65	7.344	0.0000
	T	11.9457	5.0049		
	P	0.0000	0.0000		
MEF50%	Before treatment	4.75 ± 0.46	4.78 ± 0.49	0.2927	0.7705
	After treatment	5.56 ± 0.54	5.09 ± 0.54	4.0357	0.0001
	T	7.4877	2.7878		
	P	0.0000	0.0066		
DLCO (mL/min/mmHg)	Before treatment	17.12 ± 1.62	17.19 ± 1.59	0.2022	0.8402
	After treatment	22.65 ± 2.14	19.35 ± 1.81	7.7207	0.0000
	T	13.5105	5.8792		
	P	0.0000	0.0000		
RV/TLC (%)	Before treatment	39.21 ± 2.16	39.31 ± 2.09	0.2182	0.8278
	After treatment	53.25 ± 4.26	47.25 ± 4.11	6.6467	0.0000
	T	19.2756	11.292		
	P	0.0000	0.0000		

Table 3 Comparison of immunoglobulin indicators between both groups ($\bar{x}$ ± s).

Indicators	Before and after treatment	Study group (n = 43)	Control group (n = 43)	t	P
IgA (g/L)	Before treatment	1.09 ± 0.12	1.10 ± 0.11	0.4028	0.6881
	After treatment	2.09 ± 0.19	1.58 ± 0.15	13.8151	0.0000
	T	29.1802	16.9214		
	P	0.0000	0.0000		
IgG (g/L)	Before treatment	10.86 ± 1.05	10.89 ± 1.06	0.1319	0.8954
	After treatment	17.06 ± 1.25	13.25 ± 1.19	14.4762	0.0000
	T	24.9045	9.7108		
	P	0.0000	0.0000		
IgM (g/L)	Before treatment	1.05 ± 0.12	1.06 ± 0.13	0.3706	0.7118
	After treatment	1.49 ± 0.19	1.29 ± 0.18	5.0109	0.0000
	T	12.8393	6.7926		
	P	0.0000	0.0000		
IgE (g/L)	Before treatment	201.25 ± 21.35	202.14 ± 20.16	0.1988	0.8429
	After treatment	154.35 ± 14.69	188.35 ± 17.65	9.709	0.0000
	T	11.8671	3.3748		
	P	0.0000	0.0011		

Table 4 Comparison of symptom recovery between both groups [d, ($\bar{x}$ ± s)].

Group	Case	Wheezing disappeared	Wheezing rale disappeared	Cough disappeared	Dyspnea disappeared
Study group	43	5.21 ± 0.51	7.56 ± 0.63	5.26 ± 0.49	7.44 ± 0.63
Control group	43	6.98 ± 0.67	9.98 ± 0.94	7.56 ± 0.59	9.67 ± 0.81
T		13.725	14.0236	19.6653	14.2503
P		0.0000	0.0000	0.0000	0.0000

non-specific stimulation, as well as emotional and weather changes. As confirmed by clinical practice, effective treatments for children with bronchial asthma mainly include drug therapy, traditional Chinese medicine treatment, anti-IgE monoclonal antibodies, anti-tumor necrosis factor, and bronchial thermoplasty.[17,18]

Drug therapy remains the dominant treatment employed in clinical practice. The optimal drugs in drug therapy are glucocorticoids.[19] These medications significantly reduce the inflammatory effects associated with bronchial asthma. Budesonide is one of the most widely used glucocorticoids.[20] It can effectively promote the efficacy of endogenous glucocorticoids, inhibit the inflammatory response in the respiratory tract of children, and then fully inhibit the activity of IgE. Hence, budesonide can achieve the dual efficacy of anti-allergy in the process of anti-inflammation.[21] However, atomization inhalation is the most efficient method of delivery due to the drug's significant hepatic first-pass effect.

Nonetheless, clinical trials have confirmed[22,23] that increasing the dose of the budesonide in children does not produce a synchronous improvement in efficacy. When budesonide reached 800 μg/d, the efficacy was not improved by adding atomization inhalation, and the adverse reactions of the children showed an increasing trend. Since budesonide cannot directly affect leukotriene-mediated processes, as suggested by multiple studies, it has demonstrated inadequate clinical effectiveness in reducing leukotriene-mediated inflammatory reactions.[24,25] Meanwhile, long-term use of budesonide in children easily leads to osteoporosis, decreased adrenocortical function, and other adverse reactions. Therefore, the clinical efficacy of this drug is limited.

Montelukast sodium, as a non-hormonal anti-inflammatory drug, can bind to cysteinyl leukotriene receptors, participate in leukotriene-mediated processes, and block their activity, fundamentally inhibiting the production of leukotrienes, which compensates for the disadvantages of budesonide.[26,27] The integration of the two can complement each other, exert synergistic effects, and enhance clinical efficacy.[28] Therefore, the combination of the two in treating children with bronchial asthma achieved better results.

In accordance with clinical investigations, asthmatic children's pulmonary function is significantly decreased compared to children without the condition. This is mainly characterized by the reduced ability of the large and small airways in children. The data of this study showed that before treatment, there was no conspicuous difference in all pulmonary function parameters between both groups ($P > 0.05$); after treatment, all pulmonary function parameters in both groups increased, and the study group was superior to the control group with a significant difference ($P < 0.05$). This result disclosed that, compared with aerosol inhalation of budesonide alone, oral administration of montelukast sodium in children with asthma can efficiently promote the synchronous improvement of large and small airway function in children. Montelukast sodium enhances the clinical efficacy of budesonide and further boosts the efficacy of drugs to improve airway function.[29]

In terms of immune indicators, the data of this study showed that after treatment, all immunoglobulin indicators in the two groups were promoted, and the study group was

statistically and significantly superior to the control group ($P < 0.05$). It was concluded that the integration of drugs was conducive to the recovery of immune capacity in children. It mainly benefits from the enhanced inhibitory effect of montelukast sodium on leukotrienes, which reduces the destructive impact of leukotrienes on the immune system, improves immune capacity, and effectively promotes the rehabilitation of children.[30,31] This result is consistent with similar reports at home and abroad. In this study, we also found that the recovery time of related symptoms in the study group was shorter than that in the control group ($P < 0.05$), and the difference was prominent. This result further validates the above notion.[32,33]

With the deepening of asthma-related research, the focus of treatment has changed from relieving bronchospasm, anti-allergy, and anti-infection to comprehensive treatment based on the prevention and treatment of airway inflammation. Respiratory rehabilitation is a critical part of comprehensive treatment, which can not only improve the pulmonary function of children with asthma, promote improved exercise capacity, asthma control level, and quality of life, but also reduce the need for drug use to treat the severity of asthma in children. However, asthma in children features diverse inducements, recurrent attacks, and reversibility. Besides, some children are younger and cannot master various training methods well in a short period of time, which requires long-term, continuous, and standardized treatment and care. The longer the rehabilitation time, the more obvious the effect. Therefore, for clinical medical staff, it is feasible to improve the rehabilitation compliance of children and promote healthy behaviors through the Internet or door-to-door follow-up in the community.

In brief, the use of budesonide combined with montelukast sodium in the treatment of bronchial asthma can considerably improve the pulmonary function of children, enhance the protective potential of the immune system, and promote the early recovery of children. These elements have valuable clinical applications. Given that the cases in this study were derived from the same hospital and the sources were relatively single, the study had some limitations. In the next step, the study of budesonide combined with montelukast sodium in the treatment of bronchial asthma should further expand the scope of study subjects to verify the scientificity and effectiveness of the treatment.

Acknowledgements

Not applicable.

Funding

No funding was used in this study.

Competing Interests

The authors state that there are no conflicts of interest to disclose.

Ethics Approval

Ethical approval was obtained from the Ethics Committee of Anhui Provincial Children's Hospital (Approval no. EYLL-2022010).

Consent to Participate Statement

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Data Availability

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

Contribution of Authors

Fangfang Chu and Lei Liang designed the study and carried them out, supervised the data collection, analyzed the data, interpreted the data. Fangfang Chu, Lei Liang, and Fuzhe Chen prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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