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Effect of Montelukast and Budesonide Aerosol Inhalation in the Treatment of Allergic Rhinitis And asthma in Children and Its Effect on the Inflammatory Response of Children

Hui Li[1], Lei Nie[1], Tiecheng Zhang[1], Ziwei Chen[1], and Shipei Gao[2]

[1] Department of Otolaryngology, Baoding Hospital of Beijing Children's Hospital, Capital Medical University, Hebei, China
[2] Department of Stomatology, Baoding Hospital of Beijing Children's Hospital, Capital Medical University, Hebei, China

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ABSTRACT

Studies have investigated montelukast and budesonide aerosol inhalation for treating allergic rhinitis (AR) and bronchial asthma (BA) in children. However, there are significant variations in dosage and duration of administration. This research evaluated the efficacy in children with AR and BA and analyzed montelukast's impact on the inflammatory response.

This retrospective cohort study involved 100 children with AR and BA who were admitted to "Baoding Hospital, Beijing Children's Hospital Affiliated with the Capital Medical University" from October 2022 to September 2023. They were divided into a budesonide group (budesonide n=50) and a combination group (montelukast and budesonide, n=50). Comparisons were made between the two groups in terms of clinical efficacy, severity scores of AR and BA before and after treatment, inflammatory indicators (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)), pulmonary function indicators (forced expiratory volume in the first second (FEV_1), peak expiratory flow rate (PEF)), and adverse reactions.

After treatment, the severity scores of AR and BA in the combination group were 4.00±0.93 points and 2.64±0.56 points, which were lower than those in the budesonide group (5.14±0.66 points and 3.31±0.65 points, respectively). The total response rate of the combination group (96.00%) was higher than that of the budesonide group (80.00%). The levels of IL-6 and TNF-α in the combination group were lower than those in the budesonide group, and the levels of FEV_1 and PEF in the combination group were higher than those in the budesonide group.

Mometasone combined with budesonide shows good treatment effects in children with AR and BA.

Keywords: Allergic rhinitis; Asthma; Budesonide; Inflammatory response; Montelukast

Corresponding Author Shipei Gao, MD;
Department of Stomatology, Baoding Hospital of Beijing Children's Hospital, Capital Medical University, Hebei, China. Tel: (+86 0312) 15930 281137, Fax: (+86 0312) 3377 641, Email: gaoshipei001@hotmail.com

INTRODUCTION

Allergic rhinitis (AR) is a type I allergic disease involving the nasal mucosa.[1] Allergens are inhaled through the nasal mucosa of a sensitized body and bind with immunoglobulin E (IgE) antibodies on mast cells,

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which causes the cells to release bioactive mediators. The main clinical symptoms are nasal itching, sneezing, hypersecretion, and swelling of the nasal mucosa.[2] Bronchial asthma (BA) is a chronic airway inflammatory disease of the airways that is caused by allergens and characterized by reversible airway obstruction and increased mucus production.[3] Due to the structural similarity and continuity of the nasal mucosa and lower airway mucosa, the pathophysiological processes of AR and BA are closely related, so the two diseases are also known as chronic inflammatory diseases of the same airway, and AR patients are often more susceptible to asthma.[4]

In recent years, due to changes in the environment and lifestyle changes, the number of patients with respiratory allergic diseases has increased every year, which is causing huge economic burdens in many countries.[5] About 30% of children with AR are reported to have BA, and >60% of children with BA also have AR. Both AR and BA are local responses mediated by IgE, their cooccurrence is relatively common, and the incidence is increasing every year.[6] The occurrence of AR combined with BA in children is mainly related to various internal and external factors. When children are stimulated by such factors, AR and BA cause airway obstruction, affect lung function, and lead to abnormal expression of serological indicators.[7] Interactions between AR and BA can accelerate the progression of the disease, worsen the severity of the disease, and increase the difficulty of clinical treatment.[8]

Studies have shown that the combined onset of AR and BA in children is affected by inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[9] The clinical treatment of children with AR and BA mainly involves inhalation of glucocorticoids, such as budesonide. This drug has an obvious local anti-inflammatory effect and can enhance the stability of endothelial cells, smooth muscle cells, and lysosomal membrane in children, which reduces antibody synthesis and suppresses the immune response.[10] Budesonide can also inhibit the synthesis of bronchoconstrictors, control immune response, and reduce the release of histamine-related allergic mediators, which alleviates the contraction of smooth muscles.

Additionally, budesonide has anti-allergic and anti-edematous effects, which can proficiently alleviate nasal symptoms such as nasal itching, nasal congestion, sneezing, and rhinorrhea. It also relieves ocular symptoms like ocular itching, red eyes, and lacrimation in patients with rhinitis and can prevent the recurrence of AR. Although budesonide can alleviate children's clinical symptoms to a certain extent, once the drug is stopped, relapse tends to occur.[11]

Montelukast sodium is a selective leukotriene receptor antagonist that blocks the synthesis and release of inflammatory mediators by inhibiting the action of leukotrienes. This results in reduced airway inflammation and protects the airway from excessive contraction and pathological changes. Compared with glucocorticoid drugs, montelukast sodium has minimal impact on the immune function of the body and does not elicit side effects such as antibiotic resistance or effects on growth and development. This confers a unique advantage to montelukast for the long-term maintenance treatment of pediatric AR and BA as it not only alleviates symptoms, but also reduces the risk of recurrence.[12]

In-depth studies have been done on the etiology of AR and BA in children and have found that removing leukotrienes in the body could effectively alleviate adverse clinical symptoms of children.[13] There have been clinical studies on the combination of montelukast and budesonide aerosol inhalation for the treatment of children with AR and BA, but there have been significant differences in the specific dosage, frequency, and duration of administration. The aim of this study was to investigate the efficacy of montelukast combined with budesonide aerosol inhalation in the treatment of children with AR and BA and to analyze the effect of montelukast on the inflammatory response.

MATERIALS AND METHODS

Participants

This retrospective study examined 100 children with AR and BA who were admitted to "Baoding Hospital, Beijing Children's Hospital Affiliated to Capital Medical University" from October 2022 to September 2023. The inclusion criteria were (1) the diagnostic criteria of BA[14] and AR[15], (2) age≤15 years, (3) no use of immunomodulators in the past month, and (4) complete clinical data. The exclusion criteria were (1) abnormal mental states, (2) heart, liver, or kidney diseases, and (3) drug intolerance. This study was approved by the ethics committee of our hospital (2022101823240807). The children were divided into budesonide a group (n=50) and a combination group (n=50). There was no significant difference in baseline data between groups (p>0.05), as shown in Table 1.

Observation Index

The specific observation indicators are shown in Table 2. The severity scores of AR and BA were assessed before and after treatment.[16] AR severity scores of 1–6 in were classified as mild cases that had no significant effect on sleep and daily activities, and 7–12 was classified as moderate clinical symptoms that are more obvious and have a greater impact on daily life. Scores of 13–18 were classified as severe cases with more serious clinical symptoms that have a great impact on daily life. BA severity scores of 2–8 were classified as mild, 9–14 were moderate, and 15–19 were severe.

The clinical manifestations of the children were recorded after treatment and were divided into 4 grades. In cases graded as "optimal," the patient completely recovered from asthma, sputum, cough, runny nose, and other symptoms, or symptoms were relieved by > 90% and normal work and rest were possible. In cases graded as "good," asthma, sputum, cough, runny nose, and other symptoms were significantly improved with occasional occurrence of mild chest tightness, shortness of breath, sputum, and cough. Symptoms were relieved by 70% to 90%, the quality of work and rest was improved, and budesonide aerosol or montelukast sodium tablets were still needed.

Treatments

All enrolled children were given routine treatment. According to the clinical manifestations of asthma, expectoration, cough, and runny nose, they were given bronchodilation, antitussive expectorant, oxygen inhalation, and anti-infection treatment, respectively. Both groups received budesonide inhalation aerosol (Gi Shu, Lunambert Pharmaceutical Co., LTD., China). According to their condition, the initial dose was 0.5–1 mg/time twice/day divided into early and late inhalations. The maintenance dose was individualized in the range of 0.25–0.5 mg/time (also 2 times/day divided into early and late inhalations).

Table 1. Comparison of baseline data between the budesonide group and the combination group

Group	Sex		Age (years)	Duration of disease (month)
	Male	Female		
budesonide group (n=50)	23(46.00)	27(54.00)	7.00±2.59	18.54±6.08
combination group (n=50)	25(50.00)	25(50.00)	7.84±2.42	18.94±6.17
χ^2/t	0.160		1.795	0.326
P	0.689		0.076	0.745

Table 2. Specific observation indicators

Observation index	Situation of indicators
Severity assessment of AR and BA	Scoring and Grading for AR: 1~ 6 were classified as mild, 7 ~ 12 as moderate, and 13~ 18 as severe. Scoring and Grading for BA: 2~8 was classified as mild, 9 ~ 14 as moderate, and 15~ 19 as severe
Treatment efficacy	Divided into 4 grades: Optimal, Good, can be, and Poor
Inflammatory index	IL-6, TNF-α
Lung function	FEV_1, PEF
Adverse reactions	rash, secondary infection, nausea and vomiting, abdominal pain and diarrhea

AR: allergic rhinitis; BA: bronchial asthma; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; FEV1: the forced expiratory volume in the first second; PEF: peak expiratory flow

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In addition, the combination group also received montelukast sodium chewable tablets (Singulair, Hangzhou MSD Pharmaceutical Co., LTD., China). The dosages were as follows: age<6 years old: once/day, 4 mg/time; for age≥6 years old: once/day, 5 mg/time. The children received the tablets before going to bed for 4 weeks. Both groups were treated for 2 consecutive courses.

In "moderate" cases, asthma, sputum, cough, runny nose, and other symptoms improved, symptoms were reduced by 30% to 69%, work and rest were still affected, and the patient still needed budesonide aerosol or montelukast sodium. In "poor" cases, asthma, sputum, cough, runny nose, and other symptoms had no significant change or worsened, symptom relief was<30%, patients often woke up at night or woke up early and had chest tightness and shortness of breath, and sputum cough, nasal congestion, runny nose, and other symptoms were aggravated. The total clinical effectiveness rate was calculated as follows: Total clinical effectiveness rate=(excellent cases + good cases + acceptable cases)/total cases ×100%.

Inflammation Indicators, Lung Function, and Adverse Reactions

Before and after treatment, 5 ml of venous blood were collected after fasting from both groups in the morning for testing. Following the instructions of the instrument and reagent kit, the blood samples were centrifuged at a speed of 3,000 revolutions per minute (rpm) for 10 minutes using a low-temperature centrifuge with an 8 cm radius. The supernatant serum was extracted, and the expression levels of IL-6 and TNF-α were measured using an enzyme-linked immunosorbent assay (ELISA). Lung function was assessed using the forced expiratory volume (FEV_1) and peak expiratory flow rate (PEF) in the first second in the auxiliary examinations. Adverse reactions were also recorded, including rash, secondary infection, nausea, vomiting, abdominal pain, and diarrhea.

Statistical Methods

The statistical software SPSS version 29.0 was used to process the data. Data with a normal distribution are presented as the mean±standard deviation, and count variables were presented as numbers and percentages (n (%)). The data were analyzed using a *t* test and χ^2 test, and $p<0.05$ indicated that differences were statistically significant.

RESULTS

Severity Scores

Before treatment, the severity scores of AR and BA of the combination group were 9.32±0.65 points and 8.88±1.08 points. Those in the budesonide group were 9.27±0.57 points and 8.98±1.14 points, respectively, but the difference was not significant ($p>0.05$). After treatment, as shown in Figure 1, the scores in the combination group were 4.00±0.93 points and 2.64±0.56 points, which were lower than those in the budesonide group (5.14±0.66 points and 3.31±0.65 points, respectively; $p<0.05$).

Efficacy and Adverse Reactions

The total response rate of the combination group (96.00%) was higher than that of the budesonide group (80.00%) ($p<0.05$), as shown in Table 3. Before treatment, the levels of IL-6 and TNF-α in the combination group were 9.32±0.65 ng/L and 8.88±1.08 ng/L, while those in the budesonide group were 9.27±0.57 ng/L and 8.98±1.14 ng/L, respectively, but there was no significant difference ($p>0.05$). After treatment, the levels of IL-6 and TNF-α in the combination group were 4.00±0.93 ng/L and 2.64±0.56 ng/L, while those of the other group were significantly lower at 5.14±0.66 ng/L and 3.31±0.65 ng/L, respectively ($p<0.05$), as shown in Figure 2.

There was no significant difference in pulmonary function between groups before treatment ($p>0.05$). After treatment, the levels of FEV1 and PEF were increased in both groups, but the increase was more significant in the combination group ($p<0.05$), as shown in Table 4. There was no significant difference in the total incidence of adverse reactions between groups ($p>0.05$), as shown in Table 5. There was also no significant difference in the total incidence of adverse reactions between groups ($p>0.05$), as shown in Table 4.

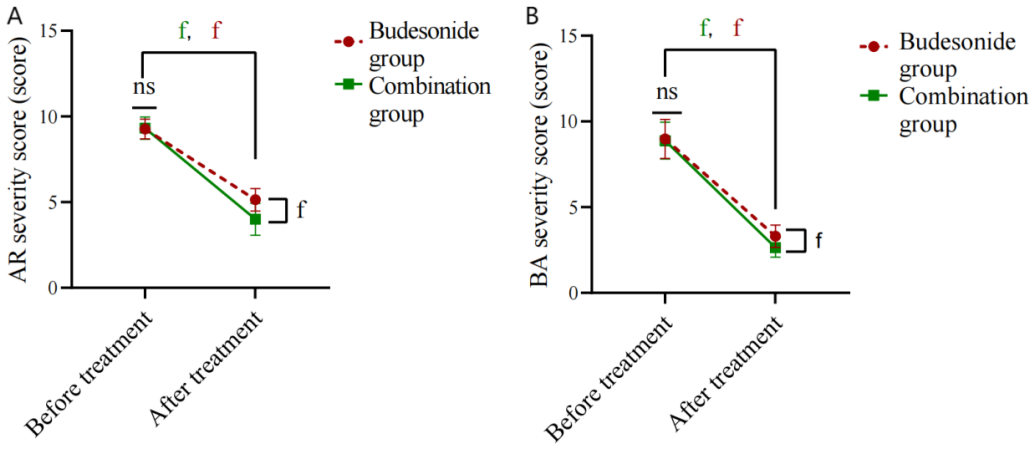

Figure 1. AR and BA severity scores of the combination group and the budesonide group before and after treatment; A, Comparison of AR severity score before and after treatment; B, Comparison of BA severity score before and after treatment; AR, allergic rhinitis; BA, bronchial asthma; $^{ns}p>0.05$; $^{f}p<0.000001$

Table 3 Comparison of clinical efficiency between the combination group and the budesonide group

Group	Excellent	Good	Can be	Poor	Total effective rate（%）
budesonide group (n=50)	11(22.00)	18(36.00)	11(22.00)	10(20.00)	40(80.00)
combination group (n=50)	21(42.00)	17(34.00)	10(20.00)	2(4.00)	48(96.00)
χ^2					8.585
p					0.036

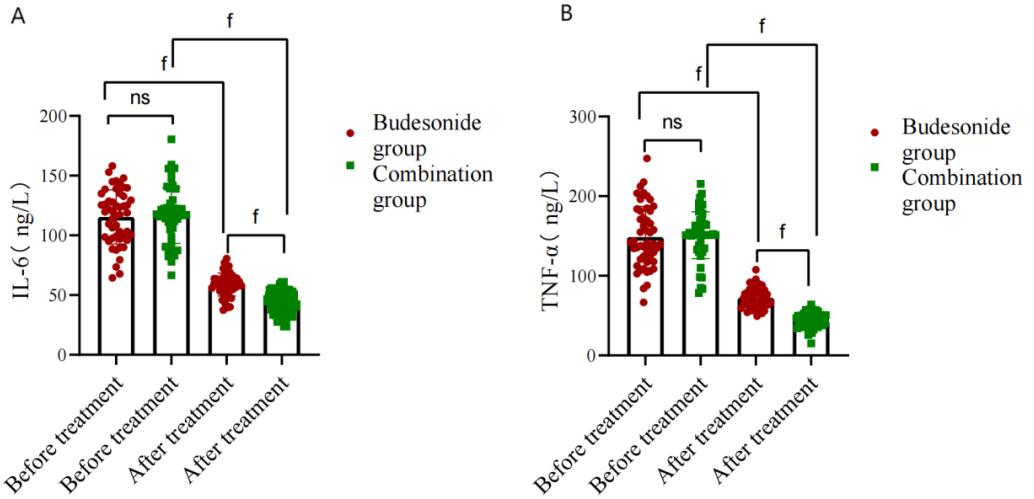

Figure 2. Changes of IL-6 and TNF-α levels in the combination group and the budesonide group before and after treatment; A, Comparison of IL-6 level before and after treatment; B, Comparison of TNF-α level before and after treatment; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; $^{ns}p>0.05$; $^{f}p<0.000001$

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Table 4. Changes in lung function in the combination group and the budesonide group before and after treatment

Group	FEV_1(%)		PEF（s/L）	
	Before treatment	After treatment	Before treatment	After treatment
budesonide group (n=50)	51.90±1.91	72.54±1.40[f]	3.16±0.42	4.14±0.73[f]
combination group (n=50)	52.46±1.66	80.88±1.01[f]	3.18±0.44	5.04±0.40[f]
t	1.567	33.298	0.233	7.647
p	0.120	＜0.001	0.816	＜0.001

[f]p＜0.000001; FEV_1: the forced expiratory volume in the first second; PEF: peak expiratory flow

Table 5. Comparison of adverse reactions between the combination group and the budesonide group

Group	Nausea and vomiting	Abdominal pain and diarrhea	Secondary infection	Rash	Total incidence (%)
budesonide group (n=50)	0(0.00)	1(2.00)	2(4.00)	2(4.00)	5(10.00)
combination group (n=50)	1(2.00)	2(4.00)	1(2.00)	2(4.00)	6(12.00)
χ^2					1.678
p					0.795

DISCUSSION

BA is one of the most prevalent chronic respiratory diseases in childhood and a polygenic hereditary condition that is influenced by multiple factors, which include genetics, environmental factors, immunity responses, and pathological mechanisms. Acute asthma can be easily triggered by viral infection, allergen exposure, and inappropriate vigorous exercise.[17] Research indicates that the overall management and prevention of childhood asthma in China remain suboptimal, and the incidence of childhood asthma is increasing annually.[18] AR occurs after individual exposure to allergens and often cooccurs with BA in children and significantly impacts their growth and development. Studies have demonstrated that AR and BA exhibit similar clinical responses to certain pharmacological treatments,[19] so a synergistic treatment approach for both conditions may enhance the clinical efficacy to some extent.

Glucocorticoids are the first choice for the treatment of AR and BA, and budesonide is widely utilized as a local anti-inflammatory agent for these conditions. The onset of action for budesonide through the classical drug pathway occurs in approximately 4–6 hours, and during this time, the hormone binds to specific receptors in the cytoplasm, moves to the nucleus, and influences nucleic acid transcription, which results in anti-inflammatory effects. However, non-classical drug administration can produce effects more rapidly.

This mechanism involves the interaction of hormone medications with cell membrane receptors, which can inhibit ATP transformation, obstruct the formation of neuronal proteins in smooth muscle cells of the airway, and facilitate smooth muscle contraction. This process ultimately enhances airway inflammation and blood flow, which leads to rapid alleviation of edema and asthma symptoms.[20] However, there is limited impact of simple glucocorticoid inhalation on disease control in children with AR and BA, particularly following re-exposure to allergens, as it is challenging to suppress the recurrence of inflammatory responses.

It has been reported that the expression levels of proinflammatory cytokines are elevated in the serum of children with BA and AR.[21] As a critical proinflammatory cytokine in the human body, serum

TNF-α can enhance the proliferation and differentiation of T lymphocytes in conjunction with IL-6. Glucocorticoids disrupt the chemotaxis and activation of eosinophils, which reduces cytokine synthesis through inhibition of the metabolic processes of arachidonic acid. This action decreases the body's inflammatory response and has an anti-inflammatory effect.[22] Additionally, in the context of respiratory tract treatment, glucocorticoids can inhibit the release of substantial amounts of histamine and alleviate the clinical symptoms associated with antigen-antibody reactions.

Clinical applications of glucocorticoids for treating AR and BA in children have demonstrated that these medications do not reduce leukotriene synthesis or block the airway hyperreactivity induced by exogenous leukotrienes. Thus, the effectiveness of treatment is limited. For instance, merely aiming for short-term efficacy by increasing drug dosages can lead to adverse effects, including drug dependence in children. The primary roles of leukotrienes in the inflammatory response encompass increasing vascular permeability, inducing contraction of respiratory smooth muscle, and attracting a significant number of inflammatory cells.[23]

Montelukast sodium chewable tablet is a novel leukotriene receptor antagonist that inhibit eosinophil production in the bloodstream by blocking the leukotriene pathway. This action mitigates the inflammatory response in children and effectively alleviates clinical symptoms associated with BA and AR. Given that the pharmacological mechanism of montelukast differs from that of glucocorticoids, their combination can address the limitations inherent in glucocorticoid monotherapy. Keith et al[24] found that the combination of montelukast sodium with glucocorticoid drugs can lead to a more significant improvement in clinical symptoms of AR and BA.

The total efficacy rate of the combination group after treatment (96.00%) was higher than that of the budesonide group (80.00%) in the present study. After treatment, the AR and BA severity scores, IL-6, and TNF-α in the combination group were lower than those in the budesonide group. The results suggest that the treatment combination can significantly reduce the clinical symptoms and the inflammatory response in children.

The primary reason lies in the fact that montelukast can mitigate the inflammatory response resulting from AR and asthma by suppressing the activity of leukotriene. Budesonide limits the occurrence and progression of the inflammatory response by inhibiting the production and release of cytokines and minimizing the infiltration of inflammatory cells. Consequently, the combined therapy can significantly reduce the level of inflammatory cells within the body, reduce airway inflammation, protect lung-related epithelial cells and smooth muscle cells, and ease airway hyperreactivity in children. Additionally, the synergy between the medications can significantly enhance the anti-sensitivity and anti-inflammatory effects, as well as expedite the alleviation of clinical symptoms, which would benefit lung function in children.

Guo et al[11] also examined montelukast sodium combined with budesonide and found that the total effective rate of the combination group was significantly higher than that of the control group ($p<0.05$). After treatment, the FEV_1% and PEF of the combination group were higher than those of the control group. This indicated that the combination could significantly improve the lung function and alleviate the symptoms of asthma and rhinitis in children.

In the present study, FEV_1 and PEF levels increased after treatment in both groups, especially in the combination group ($p<0.05$). In addition, there was no significant difference in the incidence of adverse events between groups. Thus, the treatment combination did not increase adverse drug reactions and is relatively safe. Nevertheless, it should be noted that the observation period was short, and the sample size was limited, so the long-term effects still need to be confirmed. In conclusion, combined treatment with montelukast and budesonide aerosol can reduce clinical symptoms, relieve inflammation, and improve lung function in children with AR and BA without increasing adverse effects.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Baoding Hospital of Beijing Children's Hospital, Capital Medical University (2022101823240807).

FUNDING

Not applicable

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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