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Original Article

Clinical study of the treatment of variant asthma in children through nebulized inhalation of montelukast combined with different doses of budesonide suspension

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Abstract: Objective: To study the effect of nebulized inhalation of montelukast combined with different doses of budesonide suspension on pulmonary function in children with variant asthma. Methods: In this prospective study, 93 children with variant asthma were randomly divided into three groups (n = 31). Based on montelukast treatment, different doses of budesonide suspension were inhaled by three groups, namely low dose group (200 μg/d), medium-dose group (400 μg/d) and high dose group (800 μg/d). The clinical efficacy, the time of disappearance of clinical symptoms, the changes of pulmonary function indexes before and after treatment (forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), maximum respiratory flow (PEF)), inflammatory response indexes (tumor necrosis factor (TNF-α), hypersensitive C-reactive protein (Hs-CRP)) and adverse reactions were compared among the three groups. Results: The effective rate in the medium and high dose groups was higher than that in the low dose group. And the disappearance time of clinical symptoms in the medium-dose group and high dose group was shorter than that in the low dose group (all $P<0.05$). Compared with those before treatment, the pulmonary function indexes of the three groups were improved after treatment. The pulmonary function indexes in the medium-dose group and high dose group were better than those in the low dose group (all $P<0.05$). Compared with those before treatment, the inflammatory response indexes of the three groups were improved after treatment. The inflammatory response indexes of the medium-dose group and high dose group were better than those in the low dose group (all $P<0.05$). Conclusion: Nebulized inhalation of montelukast combined with medium-dose (400 μg/d) of budesonide suspension is effective and safe in the treatment of children with variant asthma. It can improve the pulmonary function of patients and relieve inflammatory responses.

Keywords: Montelukast, budesonide suspension, aerosol inhalation, different doses, childhood variant asthma, pulmonary function

Introduction

As a common pediatric respiratory disease, childhood variant asthma is characterized by airway remodeling and airway hyperresponsiveness. The clinical manifestation of affected children is chronic recurrent cough, which is difficult to heal. Without effective treatment in time, variant asthma can develop into severe asthma, which is a serious threat to the life and health of children [1, 2]. At present, the clinical treatment of children with variant asthma is mainly to relax bronchial smooth muscle, reduce the inflammatory reaction, and improve ventilatory function in children [3].

At present, drug therapy is often used to alleviate the clinical symptoms of patients. Montelukast sodium and budesonide are the two most commonly used drugs. The combined use of the two drugs can alleviate patients' clinical symptoms and condition in a short time and promote the recovery of children. These two drugs are widely used in the clinical treatment of variant asthma [4]. However, although some children with variant asthma receive a certain curative effect through nebulized inhalation of the clinically recommended low-dose budesonide combined with montelukast, some patients are easy to relapse after drug withdrawal and need long-term treatment with drugs [5].

Therefore, it is a thorny problem in clinical work about how to choose the appropriate dose of budesonide combined with montelukast for aerosol inhalation in the treatment of children with variant asthma. The instruction for budesonide shows that the right dose for children between 2 and 7 years old is 200-400 μg/d and the right dose for children over 7 years old is 200-800 μg/d. This study primarily explored the effect of nebulized inhalation of montelukast combined with different doses (200, 400, 800 μg/d) of budesonide suspension on pulmonary function in children with variant asthma. The purpose of this study is to provide a reference for the clinical formulation of a reasonable treatment plan for children with variant asthma.

Materials and methods

General information

A total of 93 children with variant asthma, aged from 3 to 14 years old, who were treated in First Affiliated Hospital, Heilongjiang University of Chinese Medicine from November 2018 to January 2020, all met the relevant diagnostic criteria in the guidelines for the diagnosis and treatment of bronchial asthma in children [6], were included in the study. The parents of the children all signed the informed consent form. At the same time, children with upper respiratory tract infection, pneumonia, bronchopneumonia, and other diseases, children who were allergic to the drugs used in this study or children who had recently used drugs that affected the efficacy evaluation of this study were excluded. 93 children were randomly divided into three groups with 31 cases in each group. This study was examined and approved by the Medical Ethics Committee of the First Affiliated Hospital, Heilongjiang University of Chinese Medicine.

Methods

All patients were given routine treatment such as anti-infection, anti-allergy, and oxygen inhalation. Montelukast (Mudanjiang Hengyuan Pharmaceutical Co., Ltd., China) was given orally at 10 mg/time, once a day. The low-dose group was given low-dose budesonide suspension (Shanghai Xinyi Bailuda Pharmaceutical Co., Ltd., China) through aerosol inhalation at 200 μg/time, once a day. The medium-dose group was treated through aerosol inhalation of a medium-dose of budesonide suspension, 200 μg/time, twice a day. The high dose group was treated with a high dose of budesonide suspension through aerosol inhalation, 200 μg/time, 4 times a day. Both groups received treatment for 12 weeks.

Outcome measures

The clinical efficacy, the changes in pulmonary function before and after treatment were compared between three groups. The disappearance time of clinical symptoms, the changes of inflammatory reaction before and after treatment, and the occurrence of adverse reactions were compared between two groups.

The main indicators include clinical efficacy, pulmonary function, and inflammatory reaction, while the secondary indicators include the disappearance time of clinical symptoms and adverse reactions.

Clinical efficacy: It is regarded as significantly effective when clinical symptoms disappeared or significantly improved, bronchiectasis and provocation test results were negative. It is regarded as effective when clinical symptoms are improved and the frequency of acute attack of asthma significantly decreased. It is regarded as ineffective with failure to meet the above criteria. The total effective rate = markedly effective + effective rate.

Pulmonary function: Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and maximum respiratory flow (PEF) were measured by pulmonary ventilation function tester before and after treatment.

The disappearance time of clinical symptoms: The disappearance time of coughing and wheezing were counted.

Inflammatory reaction: 5 mL of fasting venous blood was drawn from patients before and after treatment, and the levels of tumor necrosis factor (TNF-α) and hypersensitive C-reactive protein (Hs-CRP) were measured by enzyme-linked immunosorbent assay (Elisa). The kit was provided by Shanghai Tongwei Biotechnology Co., Ltd. and was operated in accordance with the instructions of the kit.

Adverse reactions: Including dizziness, fatigue, dry mouth, abdominal pain, etc. For a patient

Table 1. Comparison of general data among three groups

Groups	Gender (n%)		Average age ($\bar{x}$±sd, years of old)	Average age ($\bar{x}$±sd, week)
	male	female		
Low dose group (n = 31)	17 (54.84)	14 (45.16)	8.3±1.8	13.0±3.4
Medium-dose group (n = 31)	16 (51.61)	15 (48.39)	8.4±1.7	13.3±4.0
High dose group (n = 31)	18 (58.06)	13 (41.94)	8.6±1.6	13.5±3.4
χ^2/F	0.261		0.261	0.150
P	0.878		0.771	0.861

Table 2. Comparison of efficacy among three groups (n, %)

Groups	Efficacy	Efficiency	Invalid	Effective rate
Low dose group (n = 31)	13 (41.94)	8 (25.81)	10 (32.26)	21 (67.74)
Medium-dose group (n = 31)	19 (61.29)	10 (32.26)	2 (6.45)	29 (93.55)#
High dose group (n = 31)	18 (58.06)	12 (38.71)	1 (3.23)	30 (96.77)#
χ^2				12.598
P				0.002

Note: Compare with low dose group, #P<0.05.

with multiple adverse reactions, it is calculated according to the number of adverse reactions.

Statistical processing

The data were processed by SPSS22.0 software. The measurement data were expressed as mean ± standard deviation ($\bar{x}$±sd). A paired t-test was used to compare the mean before and after intervention in the same group. One-way analysis of variance (ANOVA) was used to compare the mean among groups. SNK-q test was used for pairwise comparison when the data conforms to the homogeneity of variance and Dennett T3 method was used when the data does not conform to the homogeneity of variance. The counting data were expressed as n (%) and the χ^2 test was used for the comparison of rate. P<0.05 means the difference was statistically significant. The pairwise chi-square test uses the chi-square partition method and the test level after correction is $\alpha' = 0.017$.

Results

Comparison of general data

There was no significant difference in age, sex, and course of disease among the three groups (P>0.05). See **Table 1**.

Clinical efficiency

The effective rate of a medium-dose group and high dose group was higher than that of the low dose group (all P<0.05). There was no significant difference in the effective rate between the medium-dose group and the high dose group (P> 0.05). The results suggested that the efficiency of nebulized inhalation of montelukast combined with high and medium-dose budesonide suspension is better in the treatment of children with variant asthma than that of low dose group. See **Table 2**.

Time of disappearance of clinical symptoms

The time of disappearance of clinical symptoms in the medium and high dose groups was shorter than that in the low dose group (all P<0.05). There was no significant difference in the disappearance time of clinical symptoms between the medium-dose group and the high dose group (P>0.05). The results suggested that the nebulized inhalation of montelukast combined with high and medium-dose budesonide suspension in the treatment of cough and asthma in children with variant asthma is better than that in the combined low dose group. See **Table 3**.

Pulmonary function

Compared with those before treatment, FEV1, FVC, and PEF in the three groups increased after treatment and the levels in the medium and high dose groups were higher than those in the low dose group (all P<0.05). There was no significant difference in FEV1, FVC, and PEF between the medium-dose group and the high dose group after treatment. The results suggested that the improvement of lung function in children with variant asthma treated by nebulized inhalation of montelukast combined with high and medium-dose budesonide suspen-

Table 3. Comparison of the disappearance time of clinical symptoms among three groups ($\bar{x}$±sd, d)

Groups	Disappearance of coughing	Disappearance of wheezing
Low dose group (n = 31)	10.33±2.63	8.44±2.36
Medium douse group (n = 31)	7.58±1.47#	6.26±2.01#
High douse group (n = 31)	7.34±1.62#	5.98±1.92#
F	21.935	12.686
P	<0.001	<0.001

Note: Compare with low dose group, #P<0.05.

Table 4. Comparison of pulmonary function among three groups before and after treatment ($\bar{x}$±sd)

Groups	FEV1 (L)		FVC (L)		PEF (L/s)	
	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment
Low dose group (n = 31)	1.03±0.58	1.48±0.33*	1.52±0.35	1.69±0.24*	2.37±0.53	2.78±0.35*
Medium-dose group (n = 31)	1.09±0.63	1.88±0.52*,#	1.50±0.32	1.96±0.27*,#	2.41±0.49	3.10±0.39*,#
High dose group (n = 31)	1.07±0.55	1.91±0.41*,#	1.57±0.41	1.99±0.29*,#	2.36±0.54	3.08±0.41*,#
F	0.084	9.106	0.308	11.831	0.080	6.750
P	0.920	0.000	0.736	0.000	0.923	0.002

Note: FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; PEF: Maximum respiratory flow. Compare with indicators before the treatment, *P<0.05; compare with low dose group, #P<0.05.

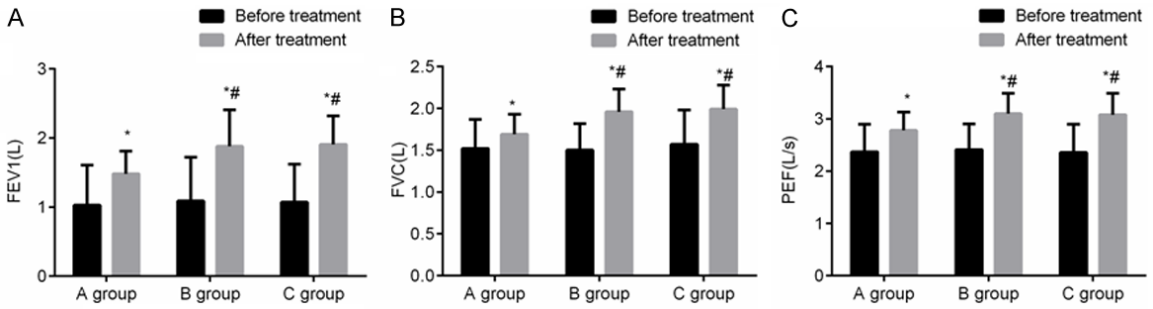

Figure 1. Comparison of pulmonary function among three groups before and after the treatment. A: Comparison of FEV1 (forced expiratory volume in 1 second) among three groups before and after the treatment; B: Comparison of FVC (forced vital capacity) among three groups before and after the treatment; C: Comparison of PEF (peak expiratory flow) among three groups before and after the treatment. A group: low dose group (200 μg/d); B group: medium-dose group (400 μg/d); C group: high dose group (800 μg/d). Compare with indicators before the treatment, *P<0.05; compare with low dose group, #P<0.05. FEV1: forced expiratory volume in the first second; FVC: forced vital capacity.

sion was better than that of low dose group. See **Table 4** and **Figure 1**.

Inflammatory responses

Compared with those before treatment, the levels of serum TNF-α and Hs-CRP in the three groups decreased after treatment. The levels in the medium and high dose groups were lower than those in the low dose group (all P<0.05). After treatment, there was no significant difference in the levels of serum TNF-α and Hs-CRP between the medium-dose group and the high dose group (P>0.05). The results suggested that the improvement of the level of inflammatory factors in children with variant asthma treated with nebulized inhalation of montelukast combined with high and medium-dose budesonide suspension was better than that in low dose group. See **Table 5** and **Figure 2**.

Adverse reactions

The incidence of adverse reactions in the high dose group was significantly higher than that in the low dose group (P<0.05). There was no sig-

Table 5. Comparison of inflammatory responses among three groups before and after treatment ($\overline{x}$ ±sd)

Groups	TNF-α (ng/L)		Hs-CRP (mg/L)	
	Before the treatment	After the treatment	Before the treatment	After the treatment
Low dose group (n = 31)	48.33±8.52	28.36±6.21*	3.68±0.85	2.12±0.75*
Medium-dose group (n = 31)	47.57±9.12	14.85±5.85*,#	3.71±0.89	1.52±0.56*,#
High dose group (n = 31)	47.12±8.12	14.77±5.65*,#	3.67±0.95	1.49±0.63*,#
F	0.157	54.359	0.017	9.227
P	0.855	0.000	0.984	0.000

Note: TNF-α: Tumor necrosis factor-α; Hs-CRP: Hypersensitivity C reactive protein. Compare with indicators before the treatment, *P<0.05; compare with the low dose group, #P<0.05.

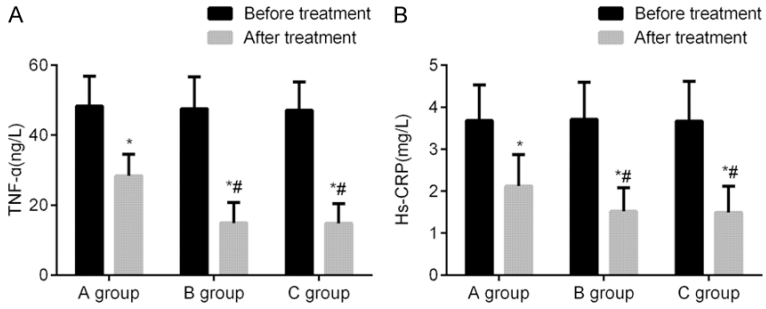

Figure 2. Comparison of inflammatory responses among three groups before and after treatment. A: Comparison of the levels of TNF-α (tumor necrosis factor-α) among three groups before and after the treatment; B: Comparison of the levels of Hs-CRP (hypersensitivity C reactive protein) among three groups before and after the treatment. A group: low dose group (200 μg/d); B group: medium-dose group (400 μg/d); C group: high dose group (800 μg/d). Compare with indicators before the treatment, *P<0.05; compare with low dose group, #P<0.05. TNF-α: Tumor necrosis factor-α; Hs-CRP: Hypersensitivity C reactive protein.

nificant difference in the incidence of adverse reactions between low dose group and middle dose group (P>0.05). The incidence of adverse reactions in the high dose group was higher than that in the middle dose group, but the difference was not statistically significant (P> 0.05). The results suggested that the incidence of adverse reactions in children with variant asthma treated by nebulized inhalation of montelukast combined with a high dose of budesonide suspension was significantly higher than that of combined medium and low dose therapy. See **Table 6**.

Discussion

The results of this study showed that compared with montelukast combined with low-dose budesonide group, the medium-dose and high-dose groups had a better curative effect, better improvement of lung function, relief of clinical symptoms and reduction of the inflammatory reaction, but there were more adverse reactions in the high-dose group. And the safety of drug usage in the high dose group was lower than that in the low-dose group and the middle dose group. In the study of Zhu et al, the efficacy of medium-dose (400 μg/d) budesonide combined with compound ipratropium bromide in the treatment of children with variant asthma was better than that of low dose 200 μg/d in terms of improving lung function and reducing inflammatory reaction. And the incidence of adverse reactions in the medium-dose group was lower than that in the high dose (800 μg/d) group [7]. In the study of Chun et al, the incidence of adverse reactions in the high dose group (14.29%) was significantly higher than that in the low dose group (2.86%), which was consistent with the results of this study [8]. We believe that the mechanism may be related to the fact that budesonide can cooperate with montelukast to inhibit inflammation.

Inflammatory responses play a very important role in the development of childhood variant asthma. Leukotriene can promote the accumulation of eosinophils, cause smooth muscle contraction, increase vascular permeability, and cause airway hyperresponsiveness [9-11]. At the same time, leukotriene interacts with other inflammatory mediators to increase the activity of inflammatory factors such as TNF-α,

Table 6. Comparison of adverse reactions among three groups

Groups	Dizziness	Weakness	Dry mouth	Abdominal pain	Summation
Low dose group (n = 31)	1 (3.23)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.23)
Medium-dose group (n = 31)	1 (3.23)	0 (0.00)	1 (3.23)	0 (0.00)	2 (6.45)
High dose group (n = 31)	2 (6.45)	2 (6.45)	3 (9.68)	3 (9.68)	10 (32.26)#
χ^2					12.598
P					0.002

Note: Compare with low dose group, #P<0.05.

Hs-CRP, and aggravate the inflammatory response. However, under the effect of inflammation and airway hyperresponsiveness, the smooth muscle of affected children will have a spasm, which will lead to airway contraction and damage the lung function [12, 13]. As a leukotriene antibody antagonist, montelukast can inhibit the activity of leukotriene polypeptides in airway smooth muscle, block the binding of leukotriene to cell surface receptors, reverse vascular permeability and reduce airway mucus secretion, reduce inflammation and airway hyperresponsiveness and then alleviate the condition of children [14, 15]. Besides, montelukast and glucocorticoids have a synergistic effect [16]. Budesonide is a glucocorticoid drug, which can inhibit the activity of arachidonic acid, reduce the release and secretion of prostaglandins, reduce the activation of eosinophils, and then reduce the secretion and synthesis of inflammatory mediators, thereby reducing airway inflammation [17-19]. Nebulized inhalation therapy also has the advantages of low dosage, quick effect, and so on. The results above showed that the efficacy of nebulized inhalation of montelukast combined with medium-dose (400 μg/d) and high dose (800 μg/d) budesonide suspension in the treatment of children with variant asthma was better than that of low dose. However, the adverse reactions in the medium-dose group were less. The reason may be that the application of medium and high dose glucocorticoids can play a rapid and echoing effect and then quickly reduce the inflammatory reaction and improve lung function. But long-term use of high dose glucocorticoids can inhibit the thalamic-pituitary-suprarenal gland axis and increase the incidence of adverse reactions [20, 21]. Therefore, the curative effect of the medium-dose group was better than that of the low dose group and the safety of medication was better than that of the high dose group.

To sum up, nebulized inhalation of montelukast combined with medium-dose (400 μg/d) budesonide suspension is effective in the treatment of children with variant asthma, which can effectively improve lung function, reduce inflammatory reaction and has high safety. This therapy is of clinical significance. However, due to the small number of samples collected and short observation time in this study, the results may be biased. In the future, the scale of the study should be expanded and the observation time should be extended for further discussion.

Disclosure of conflict of interest

None.

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