

Review Article

The efficacy of montelukast combined with budesonide in asthma patients and the combination's effects on the patients' immune and pulmonary functions

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Abstract: This study was designed to determine the efficacy of montelukast sodium tablets combined with budesonide on patients with asthma and the combination's effects on the patients' immune and pulmonary functions. A total of 98 patients with asthma admitted to our hospital from March 2018 to June 2019 were recruited as the study cohort and assigned to a monotherapy group (n=46) treated with montelukast sodium tablets and a combination group (n=52) treated with montelukast and budesonide. The efficacy of the two treatments and their effects on the patients' immune function, pulmonary function, and inflammatory factors were analyzed, and the following indexes in the two groups were evaluated and recorded after the treatment: The time to symptom alleviation, the incidence of toxic and side effects, the discharge time, and the quality of life. The clinical efficacy in the combination group was better than it was in the monotherapy group ($P<0.05$), and after the treatment, the combination group showed significantly better pulmonary function-related indexes, higher CD4+ and CD4+/CD8+ levels, and lower CD8+ and inflammatory factor levels than the monotherapy group (all $P<0.05$). Additionally, the combination group had earlier disappearance times of cough, wheezing, and dyspnea than the monotherapy group ($P<0.05$), and there was no significant difference between the two groups in the incidence of toxic and side effects ($P>0.05$). Furthermore, the combination group experienced shorter hospitalization times and a higher quality of life than the monotherapy group ($P<0.05$). Montelukast combined with budesonide is safe and effective in treating asthma and can improve patients' pulmonary and immune functions, so it is worth popularizing.

Keywords: Montelukast, budesonide, asthma, immune function, pulmonary function

Introduction

Asthma is chronic airway inflammation involving various cells and cellular components. It often intensifies airway reactivity, so patients with asthma may suffer from wheezing, anhelation, chest distress, and cough [1]. People at any age can suffer from asthma, and it currently affects about 358 million people around the world according to published data [2, 3]. One study estimates that the incidence of asthma will continue to rise in the future along with the increasing severity of air pollution [4]. At this point, in clinical practice, asthma patients are usually treated with β_2 receptor agonists and

timed-release theophylline, but these drugs only control the symptoms and cannot cure asthma [5]. If asthma deteriorates into severe asthma due to untimely treatment, it is likely to affect the patients' lives [6]. Therefore, it is of great significance in the clinical treatment of asthma to strengthen the emphasis on asthma and seek effective and safe drugs for a scientific, reasonable, and effective intervention.

Montelukast sodium is an oral leukotriene receptor antagonist suitable for the prevention and long-term treatment of asthma in adults and children over 1 year old [7]. The drug can specifically inhibit the cysteinyl leukotriene

receptor (CysLT₁), thus alleviating airway inflammation and effectively controlling the asthma symptoms [8]. According to some studies, montelukast sodium can effectively control asthma symptoms, and its mechanism of action has also been confirmed in clinical practice [9]. Budesonide is a solid, pale-beige chemical substance and a glucocorticoid with highly-efficient, local anti-inflammatory effects [10]. It can improve the stability of smooth muscle cells, endothelial cells, and lysosomal membranes, reduce the release and activity of the allergic active medium, and weaken the contraction reaction of smooth muscle [11]. It is usually used for patients with glucocorticoid-dependent or non-dependent bronchial asthma and chronic asthmatic bronchitis in clinical practice [12]. The function of montelukast sodium combined with budesonide in asthma has been clinically verified [13]. However, most studies on the drug are limited to clinical medication guidance, and there are still few studies on the efficacy and safety of the two drugs. Therefore, this study focused on the efficacy of montelukast combined with budesonide on patients with asthma and the two drugs' influences on patients' immune and pulmonary functions, with the goal of providing a reliable reference for the future clinical treatment of asthma.

Materials and methods

Patient data

A total of 98 asthma patients admitted to The First People's Hospital of Linhai from March 2018 to June 2019 were recruited as the study cohort and assigned either to a monotherapy group (n=46) treated with montelukast sodium tablets or a combination group (n=52) treated with montelukast combined with budesonide. This study was approved by the Ethics Committee of The First People's Hospital of Linhai and was carried out in accordance with the Helsinki Declaration. All participants signed informed consent forms after gaining an understanding of the study.

Patient inclusion and exclusion criteria

The inclusion criteria: Patients diagnosed with bronchial asthma by our hospital's laboratory, patients with dyspnea, patients with detailed clinical data, patients willing to cooperate with

the follow-up, and patients who had signed informed consent forms after understanding the study.

The exclusion criteria: Patients with cardiovascular disease, other comorbid lung diseases, or malignant tumors, patients with language disorders, mental disorders, or severe immunodeficiency, and referred patients.

Treatment methods

Monotherapy group: The patients in the monotherapy group were given regular oxygen inhalation and also given anti-infection and fluid infusion treatment to maintain their internal environmental balance. In addition to this treatment, they were also treated with montelukast sodium tablets (State Food and Drug Administration (SFDA) approval number: J20130047, Merck Sharp & Dohme Pharmaceutical Co., Ltd., Hangzhou, China) through oral administration before sleep, 10 mg each time and once a day.

Combination group: In addition to the treatment given to the monotherapy group, the patients in the combination group were treated with budesonide (SFDA: H20140475, AstraZeneca Pharmaceutical Co., Ltd., Wuxi, China) through atomization inhalation, 400 mcg each time and twice a day.

Outcome measures

The following effects in the two groups were evaluated: The drug's efficacy in the two groups [14], the changes in the pulmonary function-related indexes (forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), IC, and peak expiratory flow (PEF)) of the two groups before and after the treatment, and the changes in the immune function indexes (CD4⁺, CD8⁺, CD4⁺/CD8⁺) of the two groups before and after the treatment. Fasting peripheral blood was sampled from each patient in the two groups, and the changes in the T lymphocyte subsets in the sampled blood were determined using flow cytometry. Briefly, peripheral blood (4 mL) was sampled and transferred to a coagulation-promoting tube containing ethylenediaminetetraacetic acid (EDTA), and then diluted with 4 mL phosphate buffer saline (PBS). Then, 10 mL of a lymphocyte separation medium was added into a 20 mL centrifuge

tube, and 10 mL diluted blood was added into the centrifuge tube along the tube wall, centrifuged for 30 min (1505×g, 4°C). Subsequently, centrifuged monocytes were pumped out and then added into a 5 mL centrifuge tube, and 200 µL erythrocyte splitting liquor was added into the centrifuge tube, mixed well, and then centrifuged for 5 min (1505×g, 4°C) to discard the supernatant. PBS buffer (2 mL) was added into the centrifuge tube and centrifuged for 15 min (1505×g, 4°C) to discard the supernatant, and this was repeated twice. PBS buffer (0.5 mL) was added to resuspend the monocytes, and the cell concentration was adjusted to 1×10^6 cells/mL under microscope. The monocyte resuspension (100 µL) was taken and mixed with mouse anti-human monoclonal antibodies of CD3, CD4 and CD8 (10 µL each), mixed well, and incubated at room temperature in the dark for 30 min. Then, 500 µL PBS buffer was added for washing, and the resuspension was centrifuged to discard the supernatant. Finally, the resuspension was resuspended with 0.5 mL PBS buffer, and analyzed. In addition, the changes in the inflammatory factors (interleukin-4 (IL-4), interleukin-6 (IL-6)), and tumor necrosis factor- α (TNF- α) of the two groups before and after the treatment were determined: Peripheral blood (4 mL) was sampled from each patient, transferred to a coagulation-promoting tube containing EDTA, and left to stand at room temperature for 30 min. Subsequently, the upper serum was collected and analyzed using an enzyme-linked immunosorbent assay (ELISA). The IL-4 ELISA kit (DXT-EK0404) was purchased from Shanghai Kemin Biotechnology Co., Ltd., and the IL-6 ELISA kit (MM-0049H1) and the TNF- α ELISA kit (MM-0122H1) were both purchased from Wuhan Yipu Biotechnology Co., Ltd. All related operations were carried out in an aseptic environment in strict accordance with the kits' instructions. The time to symptom alleviation in the two groups after the treatment and the incidence of the toxic and side effects in the two groups after the treatment were evaluated. The discharge times were recorded, and their quality of life was scored using the MOS-36-item short-form health survey (SF-36) [15].

Statistical analysis

In this study, the data were statistically analyzed using SPSS 22.0 and visualized into the required figures using GraphPad 7. The enu-

meration data were expressed as a rate and compared between groups using the chi-square tests. The measurement data were expressed as the mean \pm standard deviation. $P < 0.050$ indicates a significant difference.

Results

A comparison of the general patient data

There were no significant differences between the two groups in terms of age, course of the disease, body mass index (BMI), sex, smoking history, family medical history, history of respiratory tract disease, or residential environment (all $P > 0.05$) **Table 1**.

Treatment efficacy in the two groups

The efficacy in the two groups after the treatment was compared, and it was found that the total effective rate of the combination group was significantly higher than it was in the monotherapy group (82.61% vs. 96.15%, $P < 0.05$) **Table 2**.

Changes in pulmonary function in the two groups before and after therapy

The changes in the pulmonary function-related indexes (FEV1, FVC, IC, and PEF) before and after the treatment were compared between the two groups. It turned out that before the treatment, no significant differences were found in the FEV1, FVC, IC or PEF levels between the two groups ($P > 0.05$), but after the treatment, both groups showed elevated FEV1, FVC, IC, and PEF levels, and the combination group showed higher levels of these indexes than the monotherapy group did ($P < 0.05$) **Figure 1**.

Changes of the immune function of the two groups before and after the treatment

The immune function index (CD4+, CD8+, and CD4+/CD8+) levels in the two groups before and after the therapy were compared, and it turned out that before the therapy, there were no significant differences between the two groups in their CD4+, CD8+ or CD4+/CD8+ levels, but after the treatment, the combination group showed significantly higher CD4+ and CD4+/CD8+ levels and significantly lower CD8+ levels than the monotherapy group (all $P < 0.05$). **Figures 2-4**.

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Table 1. A comparison of the general patient data in the two groups [n (%)]

	The monotherapy group (n=46)	The combination group (n=52)	t or X ²	P-value
Age (Y)	62.9±8.42	61.1±7.63	1.110	0.270
Course of disease (Y)	1.84±0.62	1.76±0.65	0.621	0.536
BMI (kg/cm ²)	25.16±2.42	24.98±2.53	0.359	0.721
Sex			0.121	0.728
Male	29 (63.04)	31 (59.62)		
Female	17 (36.96)	21 (40.38)		
Smoking history			0.120	0.730
Yes	34 (73.91)	40 (76.92)		
No	12 (26.09)	12 (23.08)		
Family medical history			0.096	0.757
Yes	20 (43.48)	21 (40.38)		
No	26 (56.52)	31 (59.62)		
History of respiratory tract diseases			0.697	0.404
Yes	26 (56.52)	25 (48.08)		
No	20 (43.48)	27 (51.92)		
Residential environment			0.145	0.704
Urban area	36 (78.26)	39 (75.00)		
Rural area	10 (21.74)	13 (25.00)		

Table 2. Patient efficacy [n (%)]

	Monotherapy group (n=46)	Combination group (n=52)	X ²	P-value
Patients with markedly effective treatment	22 (47.83)	37 (71.15)		
Patients with effective treatment	18 (36.13)	13 (25.00)		
Patients with ineffective treatment	8 (17.39)	2 (3.85)		
Total effective rate (%)	38 (82.61)	50 (96.15)	4.887	0.027

The inflammatory factor levels in the two groups before and after the treatment

The changes in the inflammatory factor (IL-4, IL-6, and TNF- α) levels in the two groups before and after the treatment were compared. It turned out that before the treatment, there were no significant differences between the two groups in their IL-4, IL-6, or TNF- α levels (all $P>0.05$), but after the treatment, both groups showed significantly lower IL-4, IL-6, and TNF- α levels, and the levels of the factors in the combination group were significantly lower than they were in the monotherapy group (all $P<0.05$) **Figure 5**.

Comparison of the times to symptom alleviation in the two groups after treatment

The times to symptom alleviation in the two groups after the treatment were compared, and it was found that the combination

group experienced significantly earlier disappearances of cough, wheezing, and dyspnea than the monotherapy group ($P<0.05$) **Figure 6**.

The incidences of toxic and side effects in the two groups after the treatment

The incidences of toxic and side effects in the two groups were evaluated, and we found that there were no significant differences in the total incidences of toxic and side effects between the two groups (6.52% vs. 7.69%, $P>0.05$) **Table 3**.

Discharge times in the two groups

The discharge times in the two groups were analyzed, and it was found that the monotherapy group experienced significantly longer hospitalization times than the combination group ($P<0.05$) **Figure 7**.

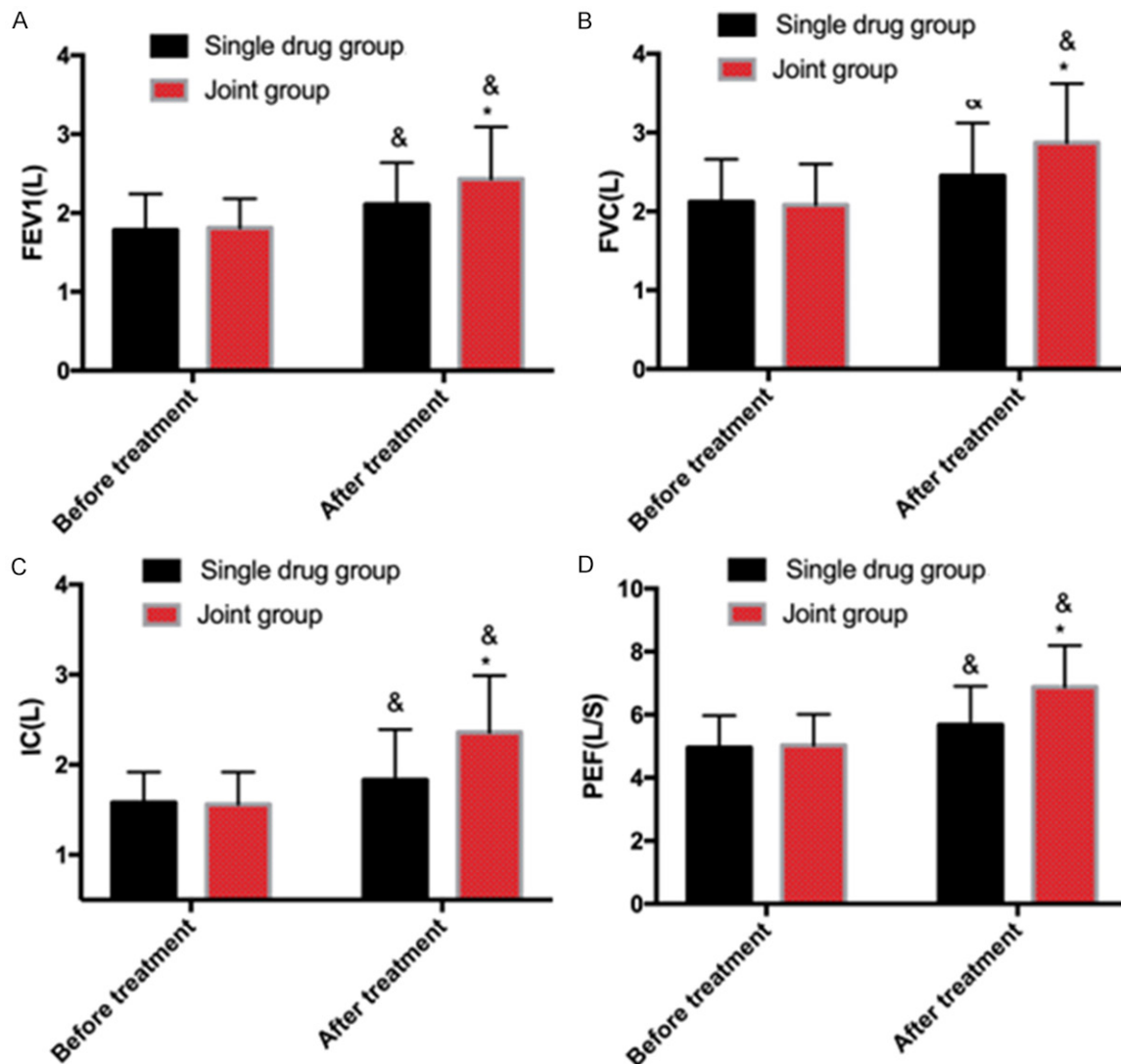


Figure 1. Changes in the pulmonary functions of the two groups before and after the treatment. A. Changes in the FEV1 levels in the two groups before and after the treatment. B. Changes in the FVC levels in the two groups before and after the treatment. C. Changes in the IC levels in the two groups before and after the treatment. D. Changes in the PEF levels in the two groups before and after the treatment. Note: &P<0.05 vs. the situation before the treatment; *P<0.05 vs. the monotherapy group.

Quality of life in the two groups after the treatment

After the treatment, the mental state, psychological function, social function, and physical health scores in the combination group were significantly higher than they were in the monotherapy group (P<0.05) **Figure 8**.

Discussion

Bronchial asthma is a common disease with a relatively high incidence in respiratory departments. In recent years, bronchial asthma shows

an annually increasing incidence rate. Bronchial asthma is mainly characterized by the long course of the disease and its common recurrence. If it is not well controlled for a long time or not treated in time when it breaks out, it will seriously threaten patient safety. Currently, asthma is mainly treated with drugs, including glucocorticoids and antibiotics, in clinical practice. It is of great significance to choose effective and safe treatment methods among the various drug treatment methods available to improve the clinical efficacy in patients. Therefore, this study focused on the efficacy of montelukast combined with budesonide on

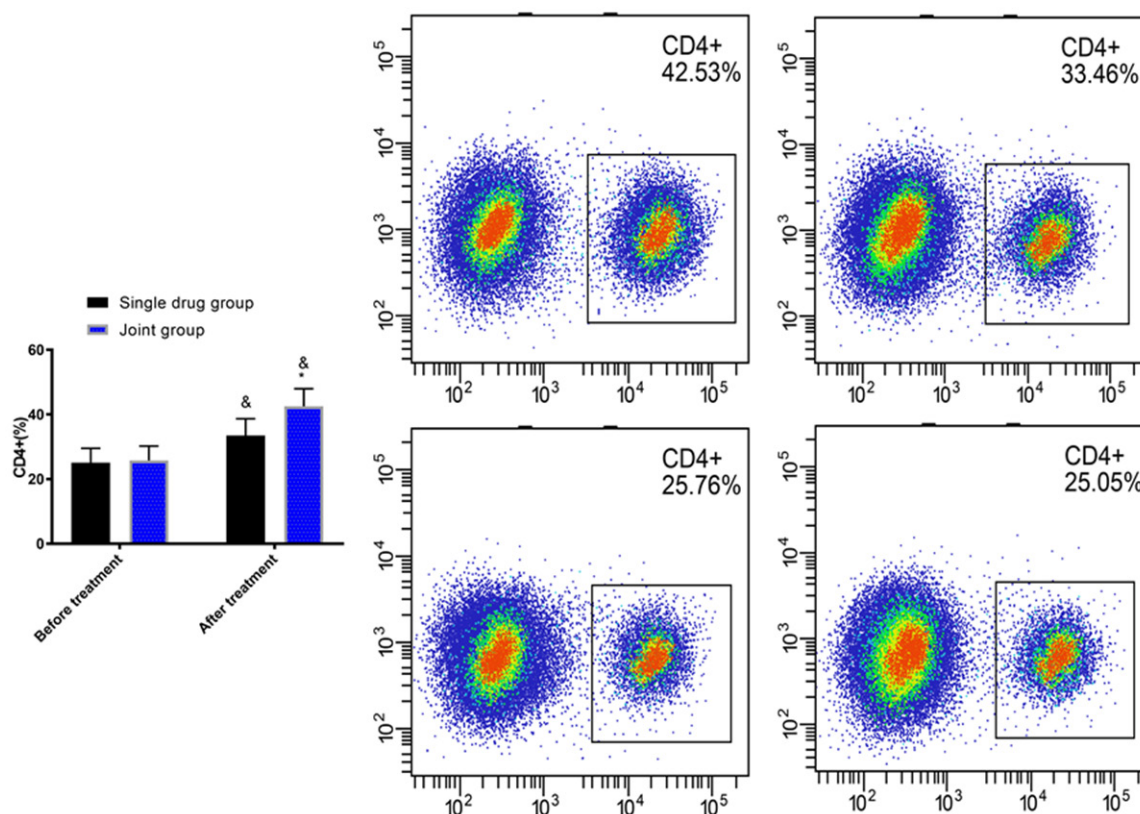
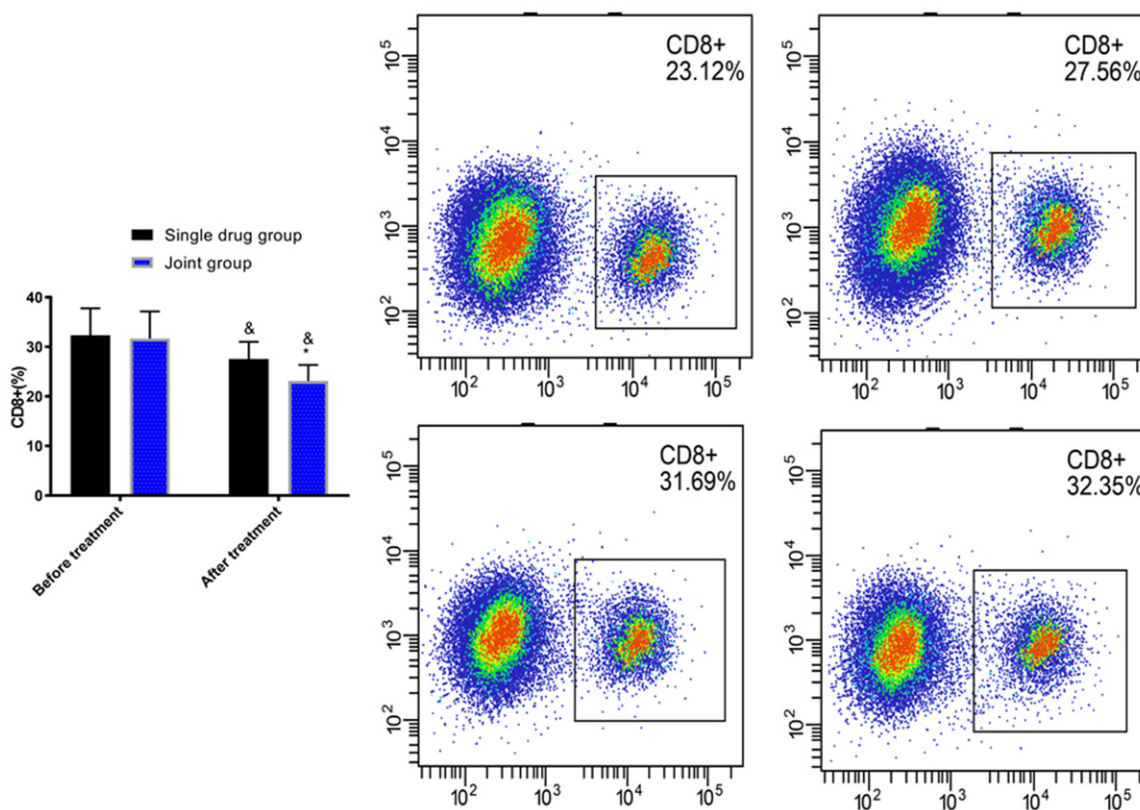


Figure 2. Changes in the two groups' immune function before and after the treatment. Changes in the CD4+ levels in the two groups before and after the treatment. Note: &P<0.05 vs. the situation before the treatment; *P<0.05 vs. the monotherapy group.



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Figure 3. Changes in the CD8+ levels in the two groups before and after the treatment. &P<0.05 vs. the situation before the treatment; *P<0.05 vs. the monotherapy group.

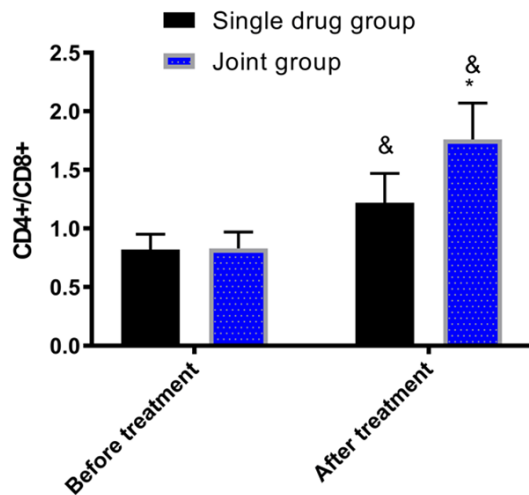


Figure 4. Changes in the CD4+/CD8+ levels in the two groups before and after the treatment. &P<0.05 vs. situation before treatment; *P<0.05 vs. the monotherapy group.

asthma patients and the combination's influences on the immune and pulmonary functions of the patients, and the results are reported as follows:

First of all, we compared the efficacy in the monotherapy group treated with montelukast sodium tablets and the efficacy in the combination group treated with montelukast and budesonide. It turned out that the total effective rate in the combination group was significantly better than it was in the monotherapy group, indicating the efficacy of montelukast combined with budesonide in patients with bronchial asthma. The findings are consistent with those of previous studies [16], which support the conclusion of this experiment. We also compared the pulmonary functions of the two groups and found that the pulmonary function-related indexes of the combination group were superior to those of the monotherapy group after the treatment, which also confirmed that montelukast combined with budesonide can improve the pulmonary function more significantly. Montelukast is a leukotriene receptor antagonist that specifically inhibits leukotriene receptors, reduces the production of airway secretions, relieve smooth muscle spasms, hinders the infiltration of the inflammatory factors

and airway remodeling, and improves airway function [17]. Budesonide is a glucocorticoid for disease prevention and treatment and is rapidly distributed in the whole lungs through atomization inhalation and can stabilize smooth muscle cells and inhibit inflammatory chemokines, thus effectively weakening airway hyper-responsiveness and improving the pulmonary function [18]. We speculated that in the treatment of bronchial asthma, montelukast sodium combined with budesonide can give full play to the synergistic effect, thus further improving the clinical efficacy. According to previous data, Chen et al. [19] pointed out that montelukast sodium combined with budesonide can exert a better therapeutic effect on seasonal allergic rhinitis. The course of bronchial asthma is long, and its repeated attacks may stimulate systemic inflammatory reactions and lower patients' immune function [20]. One study found that the inflammatory response has a pivotal role in the development of asthma, and T lymphocyte subsets play a significant role in the airway inflammatory response, and their imbalance is an important part of the pathogenesis of asthma [21]. In this study, we analyzed the changes in the immune function index (CD4+, CD8+, and CD4+/CD8+) levels before and after the treatment in the two groups and found that after treatment, both groups showed significantly increased CD4+ and CD4+/CD8+ levels and decreased CD8+ levels, and the combination group showed higher CD4+ and CD4+/CD8+ levels and lower CD8+ levels than the monotherapy group, which suggests that montelukast combined with budesonide can significantly enhance the immune function of patients with bronchial asthma and alleviate their clinical symptoms. According to one study, budesonide suspension, a glucocorticoid drug, is mainly used through inhalation and is widely used in acute asthma episodes and has the characteristic of taking effect quickly and can reduce the release of the allergic active medium and inhibit the local immune response [22]. It also supports our experimental results. The reason for the difference in immune function between the two groups is presumed to be related to the complementary advantages of the combined use of drugs, which can effectively control different pathological properties,

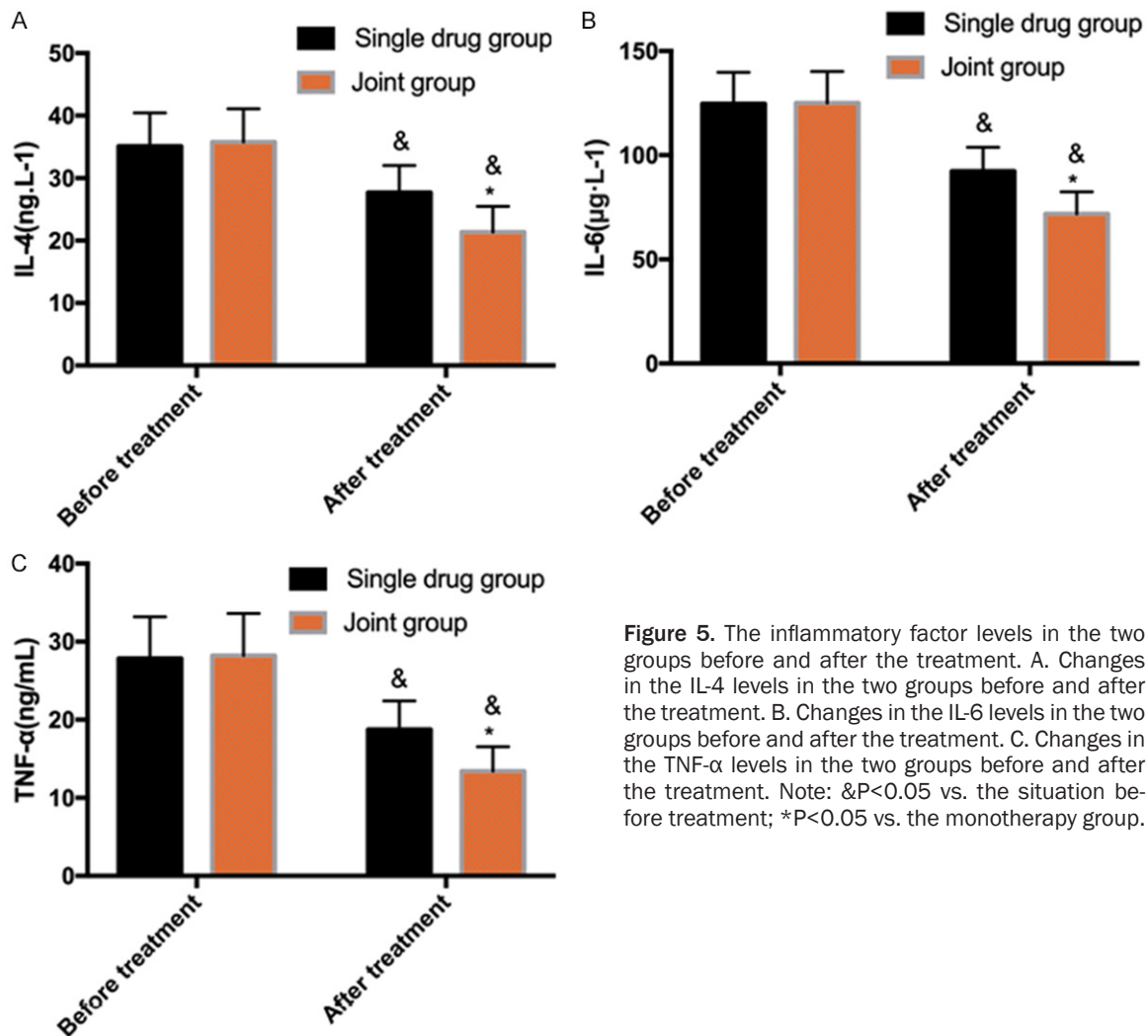


Figure 5. The inflammatory factor levels in the two groups before and after the treatment. A. Changes in the IL-4 levels in the two groups before and after the treatment. B. Changes in the IL-6 levels in the two groups before and after the treatment. C. Changes in the TNF-α levels in the two groups before and after the treatment. Note: &P<0.05 vs. the situation before treatment; *P<0.05 vs. the monotherapy group.

reduce mucus secretions, and promote patient recovery. In addition, we also compared the IL-4, IL-6, and TNF-α changes between the two groups before and after the treatment, finding that after treatment, both groups showed lowered IL-4, IL-6, and TNF-α levels, and their levels in the combination group were lower than they were in the monotherapy group, suggesting that montelukast combined with budesonide has a certain inhibitory effect on the inflammatory factors. Bronchial asthma is a heterogeneous disease characterized by persistent airway inflammation, and inflammatory reactions may bring about asthma symptoms such as wheezing and anhelation, seriously threatening patient health. One previous study found that the anti-inflammatory effect of montelukast alone is insufficient, but the effect of the combined use of montelukast and budesonide can

provide a high curative effect on patients [23], which is in line with the results of our study. Furthermore, we also evaluated the times to symptom alleviation in the two groups after the treatment and found that the combination group experienced earlier disappearances of cough, wheezing, and dyspnea, and shorter hospitalizations than the monotherapy group, which further supports the conclusion that the combined use of the two drugs can effectively improve the treatment effect and shorten the hospitalization and disappearance times of the symptoms. In addition, we determined that the incidences of toxic and side effects in the two groups after the treatment had no significant differences, which also implied that the combined use of the two drugs can effectively ensure patient safety. Finally, we evaluated the quality of life in the two groups after the treat-

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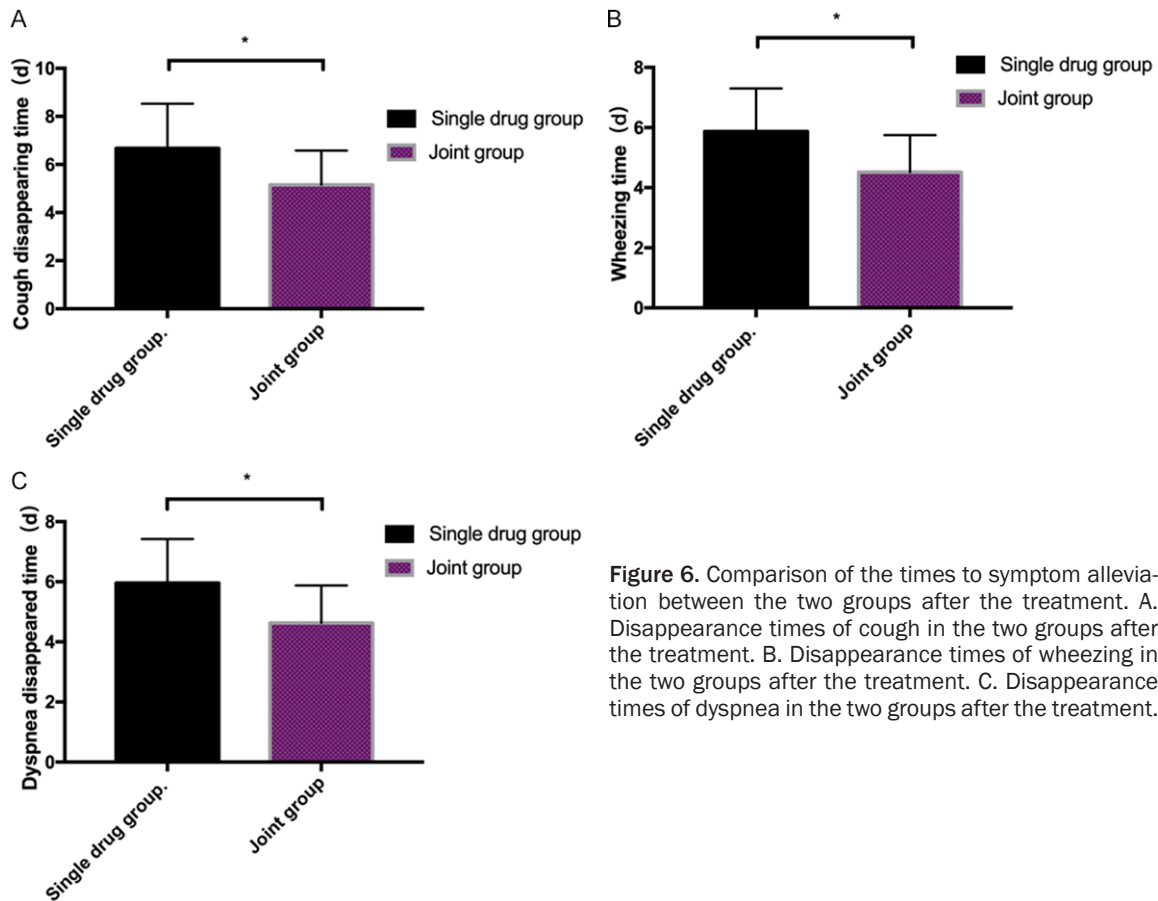


Figure 6. Comparison of the times to symptom alleviation between the two groups after the treatment. A. Disappearance times of cough in the two groups after the treatment. B. Disappearance times of wheezing in the two groups after the treatment. C. Disappearance times of dyspnea in the two groups after the treatment.

Table 3. The incidences of toxic and side effects in the two groups after the treatment [n (%)]

	Monotherapy group (n=46)	Combination group (n=52)	X ²	P-value
Rash	1 (2.17)	1 (1.92)		
Headache	1 (2.17)	1 (1.92)		
Palpitation	1 (2.16)	1 (1.92)		
Nausea and vomiting	0 (0.00)	1 (1.92)		
The total incidence (%)	3 (6.52)	4 (7.69)	0.050	0.822

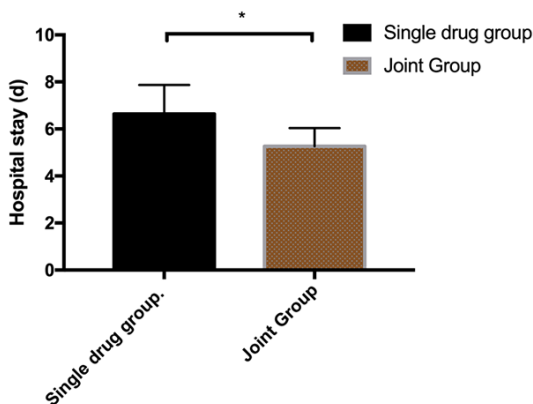


Figure 7. Discharge times in the two groups.

ment and found that the mental state, physiological function, social function, and physical health scores in the combination group were all significantly higher than they were in the monotherapy group, which is also in line with the results of previous studies on montelukast combined with budesonide and further reflects the research significance of this study. Some previous studies have also analyzed the effects of montelukast combined with budesonide on asthma [24], but they are different from our study in the following aspects: First, the research subjects of those studies were patients with variant asthma, but the research

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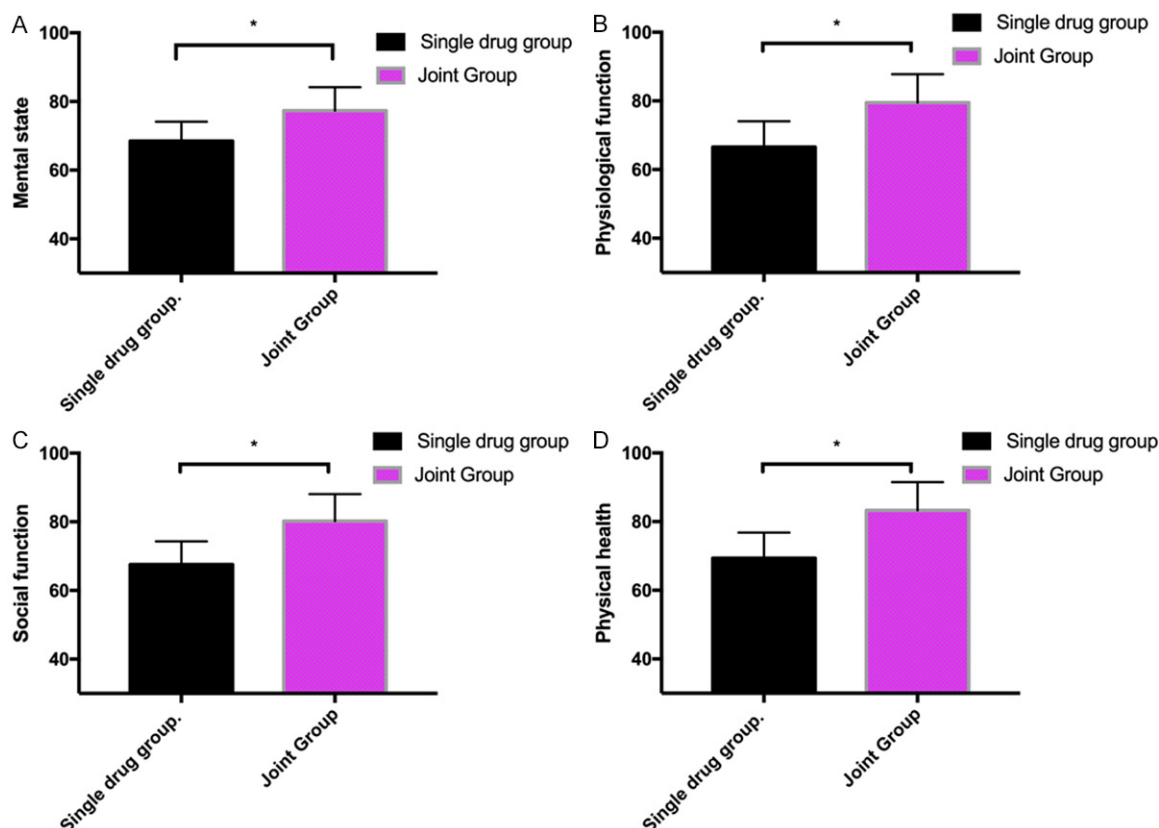


Figure 8. Quality of life in the two groups after the treatment. A. The mental state scores of the two groups after the treatment. B. The physiological function scores of the two groups after the treatment. C. The social function scores of the two groups after the treatment. D. The physical health scores of the two groups after the treatment.

subjects of our study were patients with bronchial asthma. Second, in terms of the outcome measures, we not only analyzed the clinical efficacy and safety and the patients' inflammatory factors, we also analyzed their T lymphocyte subsets (patient immunologic function), so we analyzed the efficacy of montelukast combined with budesonide more extensively. Moreover, some studies have confirmed that the atomization inhalation of montelukast combined with budesonide can significantly ameliorate the airway inflammation response of patients [25], which also supports the research significance of this study.

However, due to the limited experimental conditions, there are still some deficiencies in this study. For example, the research period was too short to analyze the long-term prognosis of the two groups of patients. In addition, at present, there are many other clinical drugs for asthma in addition to montelukast and budesonide, so we also need to incorporate more drugs in our research to improve the com-

prehensiveness of our study. Moreover, due to the lack of basic experiments, we could not determine the exact mechanisms of montelukast and budesonide on patients. We will carry out more comprehensive experimental analyses to address the above deficiencies as soon as possible in order to obtain more effective experimental results for clinical reference.

To sum up, montelukast combined with budesonide is safe and effective in treating patients with asthma and can improve patients' pulmonary function and immune functions, so it is worth popularizing.

Disclosure of conflict of interest

None.

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