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Efficacy of montelukast sodium chewable tablets combined with inhaled budesonide in treating pediatric asthma and its effect on inflammatory factors

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The aim of this study was to explore the clinical effect of montelukast sodium chewable tablets combined with inhaled budesonide in the treatment of pediatric asthma and its influence on inflammatory factors. One hundred and thirty-five asthmatic children were randomly divided into montelukast sodium group, budesonide group and combined group. Clinical symptoms, lung function, inflammatory factors and immune related indices of patients in each group were observed and recorded. After treatment, the times to disappearance of wheezes, dyspnea, asthma and hospital stay in the combined group were significantly shorter than those in the single-drug group (all $p < 0.001$). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), peak expiratory flow (PEF) were significantly higher than those before treatment, and in the combined group value were significantly higher than in the single-drug group in the same period (all $p < 0.001$). Tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), IL-8 and hypersensitive C-reactive protein (hs-CRP) were significantly lower than before treatment, and the combined group was significantly lower than the single-drug group in the same period (all $p < 0.05$). The number of $CD4^+$ and $CD3^+$ cells in the combined group was significantly higher than that in the single-drug group, while the number of $CD8^+$ cells and the expression level of immune globulin E (IgE) were significantly lower (all $p < 0.05$). There was no difference in the incidence of adverse reactions between the groups during treatment ($p > 0.05$). Six months after treatment, the incidence of asthma in the combined group was significantly lower than that in the single-drug group (both $p < 0.05$). Montelukast sodium chewable tablets combined with inhaled budesonide can shorten the discomfort duration of asthmatic children and help them restore lung function. Moreover, it reduces the level of inflammatory factors and increases the resistance of children, which is worthy of further promotion and application.

1. Introduction

Pediatric bronchial asthma (pediatric asthma for short) is often diagnosed due to persistent or repeated sneezing, cough, runny nose, nasal obstruction and other symptoms. It is characterized by airway inflammation, airway hyperresponsiveness (AHR) and other pathological features, and has the symptom of recurrent attacks and is difficult to cure (Jesenak et al. 2017; Dem'Yanenko et al. 2018; Liu et al. 2017; Alqahtani et al.2016). The latest epidemiological studies show that the incidence rate of pediatric asthma in China is about 2%, higher than 10 and 20 years ago (Gao 2015; Orellano et al. 2018; Elizaldebeiras et al. 2017). Pediatric asthma often develops various complications such as emphysema and pulmonary heart disease due to improper treatment methods or timing. Some children even have shock and heart rate disorder. Therefore, pediatric asthma is becoming a child disease that seriously blocks growth and development and affects physical and mental health (Chang et al. 2017; Vasilopoulou et al. 2015; Bush and Griffiths 2017).

At present, clinical researchers generally believe that the occurrence of pediatric asthma is closely related to genes, environment and immune response (Cockcroft 2018; Lewis et al. 2018). However, there is no specific treatment for this disease in China, and it is often treated with antibiotics and drugs for expanding respiratory tract, which can cause serious psychological pressure to the children and their family members due to the long duration, unreasonable dosage and unsatisfactory effect (Chen and Zhang 2018). Budesonide can improve the drug concentration at local lesions, relieve AHR, and achieve better anti-inflammatory effect through atomization inhalation (Jorup et al. 2018). However, it cannot inhibit all cytokines and inflammatory mediators in the pathogenesis of asthma, including leukotrienes. Montelukast sodium can reduce the activity of leukotrienes and expand vascular permeability, thus restoring lung function (Wang et al. 2018; Yang et al. 2017). This study aimed to explore whether the combined therapy can fundamentally block the inducing factors of pediatric asthma and achieve the effect of curing and preventing relapse.

2. Investigations and results

2.1. Patient characteristics

There was no difference in age, weight, gender and course of disease among the three groups (all $p > 0.05$), and the follow-up results were comparable. See Table 1.

2.2. Disappearance of symptoms

After treatment, the disappearance time of wheezes, dyspnea and asthma and hospital stay in the combined group were significantly shorter than those in the single-drug group, and the difference was statistically significant ($p < 0.001$). There was no difference between single use of montelukast and budesonide ($p > 0.05$). See Fig. 1.

Table 1: Patient characteristics ($\bar{x}$± sd)

Group	Age (year)	Weight (kg)	Gender (male/female)	Course of disease (d)	Albumin (g/L)	History of severe episode (Yes/No)
Montelukast sodium group (n = 45)	7.0±2.4	13.95±4.91	25/20	3.74±1.30	24.00±6.11	4/41
Budesonide group (n = 45)	7.4±2.5	15.82±5.53	23/22	3.54±1.38	26.03±5.72	8/37
Combined group (n = 45)	7.8±2.4	16.22±5.82	21/24	3.06±1.04	23.77±6.37	6/39
F	1.310	2.134	0.712	2.568	2.126	1.538
p	0.273	0.122	0.701	0.080	0.126	0.463

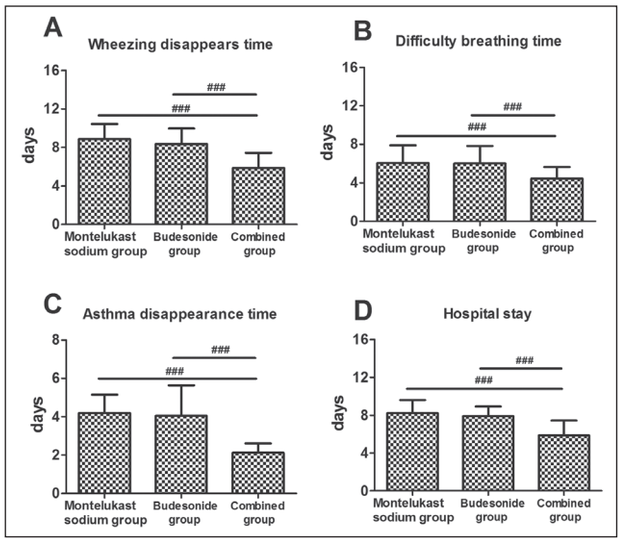

Fig. 1: Comparison of disappearance time of discomforts ($\bar{x}$ ± sd). A: Disappearance time of wheezes. B: Disappearance time of dyspnea. C: Disappearance time of asthma. D: Hospital stay. The shorter the disappearance time of wheezes, dyspnea, asthma, and hospital stay are, the better the therapeutic effect is. $^{###}p < 0.001$.

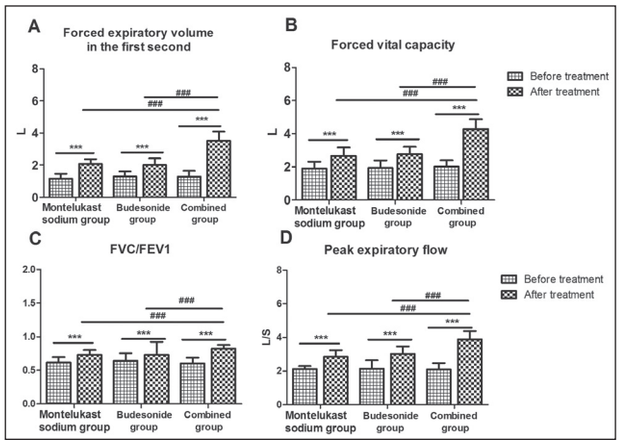

Fig. 2: Comparison of pulmonary function ($\bar{x}$ ± sd). A. Forced expiratory volume in the first second. B: Forced vital capacity. C: FVC/FEV1. D: Peak expiratory flow. The higher the FEV1, FVC and FVC/FEV1 are, the better the pulmonary function is; the higher the PEF is, the lower the airway obstruction is. Comparison among groups, $^{###}p < 0.001$; comparison within groups, $^{***}p < 0.001$. FVC/FEV1: forced vital capacity/forced expiratory volume in the first second.

2.3. Pulmonary function

Before treatment, there was no difference in FVC, FEV1, FEV1/FVC and PEF among the three groups (all $p > 0.05$). After treatment, those in the combined group were significantly higher than those in the single-drug group, and the difference was statistically significant ($p < 0.001$). See Fig. 2.

2.4. Inflammatory factors

Before treatment, there was no difference in TNF-α, IL-4, IL-8 and hs-CRP expression levels among the three groups (all $p > 0.05$). After treatment, their expression levels in the combined group were significantly lower than those in the single-drug group, with statistical difference ($p < 0.05$). See Fig. 3.

2.5. Immune indices

Before treatment, there was no difference in the number of $CD4^+$, $CD3^+$, $CD8^+$ cells and IgE expression level among the three

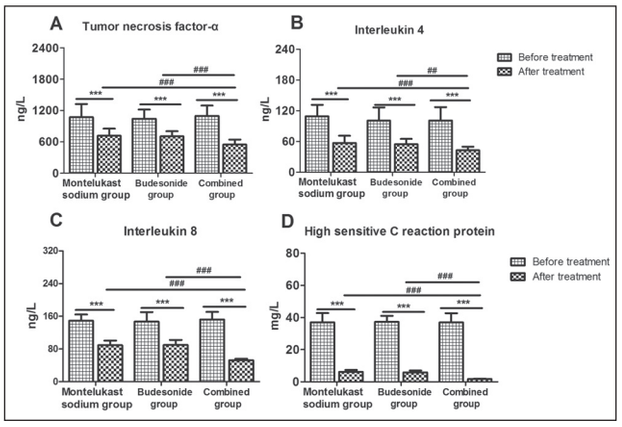

Fig. 3: Comparison of inflammatory factors ($\bar{x}$ ± sd). A: Tumor necrosis factor-α. B: Interleukin-4. C: Interleukin-8. D: High sensitive C reaction protein. The higher the value of inflammatory factors is, the more severe the inflammation is. Comparison among groups, $^{###}p < 0.001$, $^{##}p < 0.01$; comparison within groups, $^{***}p < 0.001$.

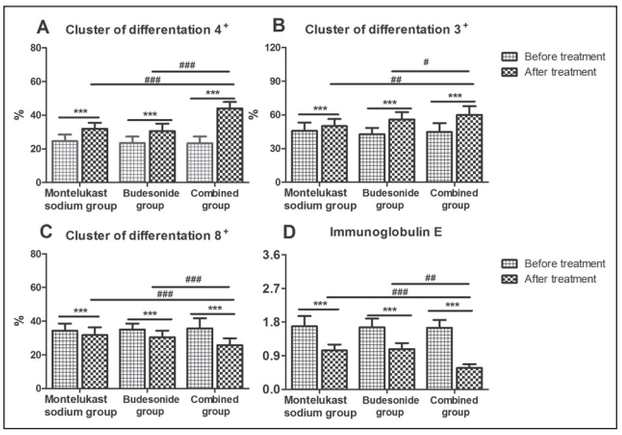

Fig. 4: Comparison of changes of immune indices ($\bar{x}$ ± sd). A: Percentage of cluster of differentiation 4^+ cells (the marker on the surface of helper T cells). B: Percentage of cluster of differentiation 3^+ cells. C: Percentage of cluster of differentiation 8^+ cells (the marker of inhibitory T cells). D: Immune globulin E. The higher the percentage of $CD4^+$ cells, $CD3^+$ cells, the lower $CD8^+$ cells, the higher the immunity of children. The lower the value of immunoglobulin E, the allergic inflammation in children can be alleviated. Comparison among groups, $^{###}p < 0.001$, $^{##}p < 0.01$, $^{#}p < 0.05$; comparison within groups, $^{***}p < 0.001$.

Table 2: Comparison of adverse reactions and attack times (n, %)

Group	Nausea	Rash	Headache	Attack times
Montelukast sodium group (n = 45)	1 (2.22)	2 (4.44)	1 (2.22)	3.62±1.45
Budesonide group (n = 45)	2 (4.44)	1 (2.22)	1 (2.22)	3.57±1.23
Combined group (n = 45)	3 (6.67)	1 (2.22)	3 (6.67)	2.70±1.06
F	1.047	0.515	1.662	3.997
p	0.593	0.773	0.436	0.021

groups (all $p > 0.05$). After treatment, the number of $CD4^+$ and $CD3^+$ cells in the combined group was significantly higher than that in the single-drug group, while the number of $CD8^+$ cells and IgE expression level were significantly lower (all $p < 0.05$). See Fig. 4.

2.6. Comparison of adverse reactions and attack times

There was no difference in the proportion of nausea, rash and headache among the groups during treatment (all $p > 0.05$). After treatment, the incidence of asthma in the combined group within 6 months was significantly lower than that in the single-drug group, with statistically significant difference ($p < 0.05$). See Table 2.

3. Discussion

In children with asthma, inhalation of allergens, seasonal changes, upper respiratory tract infections or allergies can lead to acute attack of the disease. In addition, industrial pollution, environmental deterioration and unreasonable clinical drug dosage increase the difficulty in treatment (Qu and Zhang 2017; Hughes et al. 2017; Pollock et al. 2017). At present, the specific pathogenesis of asthma is not fully understood. Although there are many effective therapeutic options, it is difficult to reach the expectations of children and their families. Therefore, it is extremely important to select appropriate and effective drugs to control the illness (Cai and Zhao 2017). The pathogenesis of pediatric asthma involves a variety of inflammatory cells and components. Cysteine leukotriene (CysLT), an important mediator, has become a hot topic in clinical research. It is mainly synthesized by airway smooth muscle and released by mast cells and eosinophils, which mediates bronchoconstriction, increases mucus secretion and reduces vascular permeability (Baron et al. 1986).

The general treatment measures for acute pediatric asthma are oxygen inhalation, rehydration, prevention of lung discomfort caused by excessive sputum, and rapid alleviation of bronchospasm and airway inflammation. Inhaled budesonide suspension is a non-halogenated adrenocortical hormone that binds specifically to glucocorticoid receptors. It can reduce the infiltration of inflammatory cells in mucosa, prevent the activation of inflammatory cells, alleviate airway spasm, and effectively control cough symptoms. However, the compliance with budesonide inhalation is generally low, and its efficacy cannot cover all inflammatory factors causing asthma, including inflammatory reactions mediated by leukotrienes (Jorup et al. 2018). Montelukast sodium, as a leukotriene receptor antagonist, effectively inhibits the release of the those factors and reduces their activity, thus effectively improving the lung function of asthmatic children, repairing fibrosis, reducing airway spasm and airflow limitation, which just makes up for the deficiency of budesonide, and is widely used in the treatment of cough variant asthma (Wang et al. 2018).

Wang's findings confirmed that after 8 weeks of treatment, montelukast sodium combined with budesonide was more effective than budesonide alone in improving lung function, and the clinical evaluation score also showed significant differences between the two groups. The main reason was that montelukast sodium chewable tablets combined with inhaled budesonide can excite bronchial smooth muscle β2 receptor, block M receptor and up-regulate the number of β2 receptor, so as to maximize the relaxation of the muscle and relieve discomfort symptoms (Wang et al. 2018). In this study, the time to disappearance of wheezes, dyspnea and wheezy cough in the combined group was obviously shortened, indicating a good therapeutic effect, which is consistent with the results of the above findings. Amaral et al. (2018) pointed out that the lung function test can reflect lung inflammation and airway obstruction in the early stage of asthma, which is an important indicator for judging disease degree and therapeutic effect. In this study, FVC, FEV1, FEV1/FVC and PEF of the children in the combined group were significantly higher than those in the control group, which indicated that the airway spasm and airflow limitation in the combined group was significantly improved. This is also consistent with Miraglia's conclusion that montelukast sodium combined with inhaled budesonide can significantly increase lung function, reduce exhaled nitric oxide, and promote the recovery of children (Miraglia et al. 2007). The expression levels of TNF-α, IL-4, IL-8 and hs-CRP in the combined group were significantly lower than those in the single-drug group, and the difference was statistically significant. Chi et al. also confirmed that budesonide can reduce IL-4 concentration, and the change of the concentration was correlated to the average FEV1 and PEF levels, with correlation coefficients of -0.468 and -0.478, respectively (Chi et al. 2016). Sun et al. (2017) and others confirmed that montelukast sodium can inhibit leukotrienes and prevent eosinophil differentiation, which is conducive to the alleviation of inflammatory response, IL-5, IL-17 and OPN are significantly reduced. Twardziok et al. (2017) revealed that the content of T-cell subgroup ($CD3^+$ and $CD4^+$) in serum of asthmatic children decreased while $CD8^+$ increased. The immune function of the body decreased and the children were vulnerable to bacterial and viral infection, which led to the occurrence of asthma. In this study, the number of $CD4^+$ and $CD3^+$ cells in the combined group was significantly higher than that in the single-drug group, while the number of $CD8^+$ cells and IgE expression level were significantly lower. This was consistent with the results of Liu, montelukast sodium tablet combined with budesonide had a good corrective effect on the disturbance of T lymphocyte subsets in peripheral blood of patients with cough variant asthma, and could activate and enhance the cellular immune function in patients with cough variant asthma (Liu et al. 2017).

There are some limitations of this study, such as small sample size, short follow-up duration and non-guaranteed compliance of the children. In addition, failure to comply with doctor's advice, improper use of drugs, unreasonable dosage or other related drugs administration during treatment led to problems such as inconsistent clinical effects and expectations. Therefore, we will expand the sample size, increase the clinical detection index and follow-up times, accurate record the development of the disease in order to make the whole research system more scientific and reasonable. At the same time, we will seek multidisciplinary cooperation to clarify the pathogenesis of pediatric asthma, find better treatment methods and improve clinical efficacy.

To sum up, montelukast sodium chewable tablets combined with inhaled budesonide can shorten the discomfort duration of asthmatic children and help them restore lung function. Moreover, it reduces the level of inflammatory factors and increases the resistance of children, which is worthy of further promotion and application.

4. Experimental

4.1. General data

This study was approved by the Ethics Committee of Heilongjiang Academy of TCM. One hundred and thirty-five asthmatic children admitted to Heilongjiang Academy of TCM from January 2017 to January 2018 were selected and divided into budesonide group, montelukast sodium group and combined group according to the random number table. The family members of the children signed the informed consent forms. Inclusion criteria: (1) Patients aged 3-12 years old; (2) patients conforming to the diagnostic criteria related to pediatric asthma revised by the National Pediatric Asthma Collaborative Group in 2008 (Straud et al. 2012); (3) patients who received no immunomodulator within 1 month; (4) patients who received no glucocorticoid for 3 months; (5) mild or moderate ill children; (6) patients without family history of asthma. Exclusion criteria: (1) Patients who have severe liver and kidney dysfunction; (2) patients who have congenital heart disease; (3) patients who have acute critical asthma attack; (4) patients who are allergic to drugs involved in this research; (5) patients who have infectious diseases such as pneumonia or sinusitis.

4.2. Research methods

All children were given oxygen inhalation, phlegm reduction and cough relief after admission. In addition, the budesonide group received budesonide suspension (AstraZeneca Pty Ltd, Australia) for atomization treatment. The dosage was adjusted according to the patient's condition. Initial dose was 0.5-1 mg/time, twice a day, and the maintenance dose was 0.25-0.5 mg/time, twice a day. Montelukast sodium group was given montelukast sodium chewable tablets (Hangzhou MSD Pharmaceutical Co., Ltd., China), 4-6 years old: 4 mg/time; 6-13 years old: 5 mg/time, every night before sleeping. In the combined group, budesonide was inhaled and montelukast sodium chewable tablets were taken every night for 4 weeks as a course of treatment.

4.3. Outcome measures

Main outcome measures: The levels of hypersensitive C-reactive protein (hs-CRP), immune globulin E (IgE), interleukin-4 (IL-4), IL-8 and tumor necrosis factor-α (TNF-α) were detected by enzyme-linked immunosorbent assay (ELISA) with a microplate reader (Bio-Rad iMark microplate reader, USA). The above reagents were all purchased from Wuhan Boster Biological Technology Co., Ltd., China. The above samples were tested in accordance with the instructions. Firstly, the fasting venous blood of the patient was drawn in the morning and naturally coagulated at room temperature for 10-20 min, then centrifuged at 2,000-3,000 rpm for about 20 min. Secondly, gradient dilution of the standard was carried out. Afterwards, 50 μL of each sample were added to each well, with the concentrations of 9 mmol/L, 6 mmol/L, 3 mmol/L, 1.5 mmol/L and 0.75 mmol/L, respectively. Thirdly, diluted samples were added into blank well and sample well, incubated at 37 °C for 30 min. After washed repeatedly for 5 times and dried, the wells were added with horseradish peroxidase (HRP)-labeled monoclonal antibody, incubated at 37 °C for 30 min, washed and dried. Fourthly, color development: TMB color development solutions A and B were prepared, and developing was carried out at room temperature for 3 min. Hydrochloric acid of 1 M was added to stop the developing, and absorbance of each well was measured.

CD3/CD4/CD8 (Invitrogen, China) was detected by flow cytometry (Beckman Coulter, USA CytoFLEX S). Peripheral blood was collected and anticoagulated with ethylenediamine tetraacetic acid (EDTA). The first tube was set as a control tube, and added with 50 μL of plasma and whole blood. The second tube was set as a testing tube, and added with 50 μL of whole blood first and then added 10 μL of FITC-CD3/PE-CD4/TRI-CD8 mixed monoclonal fluorescent antibody. The contents were mixed well and preserved at room temperature and avoided light for 15 min. Immunoprep Reagent Coulter (US Beckman Coulter) was added and mixed evenly, and preserved at room temperature and avoided light for 15 min. After 500 μL of LPBS was added and stood for 5 min, centrifugation was carried out twice at 1,200 rpm for 5 min. The cells were resuspended with 500 μL of LPBS for detection.

Secondary outcome measures: Disappearance time of wheezes, dyspnea and asthma, and discharge time of children in the three groups were recorded (patients with discomfort symptoms and signs disappeared and with relatively stable condition can be discharged from hospital) [17]. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC, and peak expiratory flow (PEF) were detected by a pulmonary function test apparatus (Japan MINATO AS-507).

4.4. Statistical methods

SPSS 21.0 software was used for statistical processing. The measurement data were expressed as mean±standard deviation ($\bar{x}$±sd). One-way analysis of variance (ANOVA) test was used for multiple independent samples, and Student-Newman-Keuls (S-N-K) was used for following pairwise comparison. Paired t-test was used for self-comparison before and after treatment. The counting data expressed as number of cases/percentage (n/%) were analyzed using χ^2 test. A value of $p < 0.05$ indicated a statistical significance.

Conflicts of interests: Non declared.

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