

## Original Article

# Efficacy and safety of montelukast sodium oral granules combined with budesonide in treating cough variant asthma in children

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**Abstract:** Objective: To explore the efficacy and safety of montelukast sodium oral granules combined with budesonide in treating cough variant asthma in children. Methods: A total of 107 children with cough variant asthma were enrolled as research subjects, and randomly divided into a control group (n=55) and an observation group (n=52). The control group was treated with budesonide through nebulization, while the observation group was treated with montelukast sodium oral granules in addition to the budesonide treatment for the control group. The changes in clinical symptoms, pulmonary function, inflammatory factors, and immune-related indexes in each group were recorded. Results: After treatment, the observation group showed significantly higher pulmonary function indexes, dramatically lower venous blood inflammatory indexes, and significantly lower eosinophil (EOS), immunoglobulin E (IgE), and fractional exhaled nitric oxide (FeNO) levels than the control group (all  $P < 0.05$ ). In addition, the observation group showed significantly higher Helper T1 (Th1) and regulatory cells (Treg) levels, and significantly lower Helper T2 (Th2), and Helper T17 (Th17) levels than the control group (all  $P < 0.05$ ), and the observation group suffered a lower incidence of asthma than the control group ( $P < 0.05$ ). Conclusion: Montelukast sodium can promote the recovery of pulmonary function, lower the levels of inflammatory factors, and strengthen patients' immunity.

**Keywords:** Montelukast sodium oral granule, variant asthma, inflammatory factor, immunity index

## Introduction

Cough variant asthma (CVA), a common respiratory tract disease in the pediatric department, is a special asthma, and is induced in about 1/3 of chronic cough cases [1, 2]. It manifests as persistent irritant dry cough without wheezing or dyspnea, so it is easily misdiagnosed as bronchitis [3]. CVA is more frequent in the morning and at night, which seriously compromises the sleep quality and growth of the children, and they will show obviously aggravated uncomfortable symptoms when they are stimulated by external factors such as cold or strenuous exercise [4]. Most of those children are accompanied by inflammatory reactions in bronchi and bronchioles, so the key to the treatment of CVA is to control and eliminate airway inflammation [5, 6]. At present, drugs such as

glucocorticoid are used as the first choice for CVA in clinical practice, but the autoimmune system of young children is not mature yet, so they face a higher incidence of adverse reactions from the drugs. In addition, their treatment compliance is poor. Therefore, the long-term effects of drugs for CVA are not ideal [7]. One study has pointed out that drugs recommended in the guidelines cannot effectively inhibit all cytokines and inflammatory mediators in the pathogenetic process of asthma, including leukotriene polypeptide [8]. Montelukast sodium is an inhibitor of the leukotriene receptor, which can selectively inhibit the activity of leukotrienes in airway smooth muscle and prevent uncomfortable symptoms caused by leukotrienes, such as vascular permeability increase and bronchospasm [9, 10]. Therefore, this mechanism provides a new idea for the

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treatment of CVA. This study aimed to find out whether the combined medication can relieve the discomfort and symptoms of CVA in children and block the inducing factors of CVA to cure and prevent it, and to explore its possible mechanism of action.

### Materials and methods

#### General materials

This study has been approved by the Ethics Committee of Dezhou People's Hospital. A total of 107 CVA children treated in Dezhou People's Hospital from June 2017 to June 2018 were selected as research subjects, and randomly divided into a control group and an observation group according to their treatment order. Family members of those children signed informed consent forms. The inclusion criteria were as follows: (1) patients between 2 and 4 years old; (2) patients meeting relevant diagnosis criteria in *Chinese Guideline on Diagnosis and Treatment of Cough* revised by the National Collaborative Group on Childhood Asthma [11]; (3) patients without infection symptoms and long history of taking antibiotics; (4) patients whose diagnostic treatment through bronchodilators was effective; (5) patients with chronic cough accompanied by irritant cough at night; (6) patients whose bronchial provocation test results were positive and (or) maximal expiratory flow rate (MEFR) and (or) daily variation rate (monitored continuously for 1-2 weeks) were larger than or equal to 20%.

The exclusion criteria were as follows: (1) patients with severe hepatic or renal dysfunction; (2) patients with congenital heart disease; (3) patients with acute and severe asthma; (4) patients allergic to drugs involved in this study; (5) patients with infectious diseases such as pneumonia or sinusitis.

#### Research methods

The control group was treated with budesonide (AstraZeneca Pty Ltd., Australia, H20140475) through nebulization, and the dosage of budesonide was gradually reduced according to the patients' severity at an initial dosage of 0.5-1 mg/time and 3-4 times a day and a maintenance dosage of 0.25-0.5 mg/time and 2 times a day. The observation group was treated with montelukast sodium oral granules

(Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd., China, J20140167). The granules were given to the children between 2 and 4 years old every night before they go to bed for 4 weeks.

#### Observation indexes

*Main indexes:* The following pulmonary function indexes of the two groups were recorded before treatment and at 2 days after treatment: The forced expiratory volume in one second (FEV1), forced expiratory volume in one second/forced vital capacity (FEV/FVC), peak expiratory flow (PEF), and peak expiratory flow rate (PEFR). The number of patients suffering from adverse reactions (nausea, vomiting, rash, etc.) and recurrence within 6 months after treatment were followed up, and a patient whose provocation test results were positive, and PEF and (or) daily variation rate (monitored continuously for 1-2 weeks) of  $\geq 20\%$  was judged as a patient with recurrent CVA, which was the recurrence criteria of CVA [12].

*Secondary indexes:* Before treatment, and at 2 days after treatment, the children were instructed to rinse their mouth with normal saline, and then they were asked to inhale atomizing salbutamol (GlaxoSmithKline Australia Pty Ltd, Spain, H20090514) and 3% atomizing saline solution in that order. In addition, the children were instructed to cough up sputum, and about 1 mL of sputum was sampled from each child, placed in sterile test tubes, and centrifuged at 2000 r/min for 10 min. Subsequently, the absolute value of eosinophils (ESO) in the sputum was measured by Gimsa staining. The enzyme-linked immuno-sorbent assay (ELISA) test was employed to determine the levels of interleukin-4 (IL-4, item number: EK0404), interleukin-8 (IL-8, item number: EK0413), high sensitive C reaction protein (hs-CRP, item number: EK7040), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ , item number: EK0525) in the sampled sputum. The above reagents were all purchased from Wuhan Bosch, China. A Sunvou-D100 Nano Coulomb breath analyzer (Wuxi SUNVOU Medical Electronics Co., Ltd.) was used to determine the fractional exhaled nitric oxide (FeNO) level. Before treatment and at 4 weeks after treatment, 3 mL of fasting venous blood was sampled from each child, and a Beckman flow cytometry from the BD corporation (United

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**Table 1.** General data comparison ( $\bar{x} \pm sd$ )

Groups	Number of cases	Age (years)	Weight (kg)	Sex (male/female)	Course of disease (month)
Control group	55	2.24±0.38	15.87±3.13	25/30	3.37±0.68
Observe group	52	2.27±0.41	14.79±3.12	20/32	3.51±0.83
t/x <sup>2</sup>		1.410	1.795	0.288	0.100
P		0.161	0.076	0.592	0.320

**Table 2.** General information comparison continued ( $\bar{x} \pm sd$ )

Group	Number of cases	BMI (kg/m <sup>2</sup> )	Anemia (have/none)	Recent cold (have/none)	Previous seizure history (have/none)
Control group	55	14.59±0.26	13/42	33/22	43/12
Observe group	52	14.32±0.20	15/37	29/23	38/14
t/x <sup>2</sup>		0.823	0.154	0.061	0.152
P		0.412	0.695	0.805	0.697

Note: BMI: body mass index.

States) was used to determine the levels of Helper T1 (Th1, CDK001), Helper T2 (Th2, CDK002), Helper T17 (Th17, CDK003C), and regulatory T cells (Treg, CDK006) in the sampled blood. The above reagents were all purchased from the R&D system company in the United States.

## Statistical analysis

SPSS 21.0 was employed for statistical processing, and measurement data were expressed by the mean  $\pm$  standard deviation ( $\bar{x} \pm sd$ ). Comparison between groups was carried out using the independent-samples T test, and inter-group comparison was conducted using the self paired T test. The enumeration data were expressed by the number of cases/percentage (n/%). P<0.05 indicated a significant difference.

## Results

### General data

There was no significant difference between the two groups in age, weight, sex, course of disease, body mass index (BMI), anemia, recent cold, and previous seizure history (all P>0.05). See **Tables 1** and **2**.

### Pulmonary function indexes of the two groups

Before treatment, the two groups had no difference in FEV1, FEV/FVC, PEF and PEFr (all P>0.05), while after treatment, both groups

showed significantly increased FEV, FEV/FVC, PEF and PEFr, and the observation group showed dramatically higher levels of these measures than the control group (all P<0.05). See **Figure 1**.

### Inflammatory factors of the two groups

Before treatment, the two groups had no difference in IL-4, IL-8, hs-CRP, and TNF- $\alpha$  (all P>0.05), while after treatment, both groups showed significantly decreased IL-4, IL-8, hs-CRP, and TNF- $\alpha$  levels, and the observation group showed significantly lower levels of these measures than the control group (all P<0.001). See **Figure 2**.

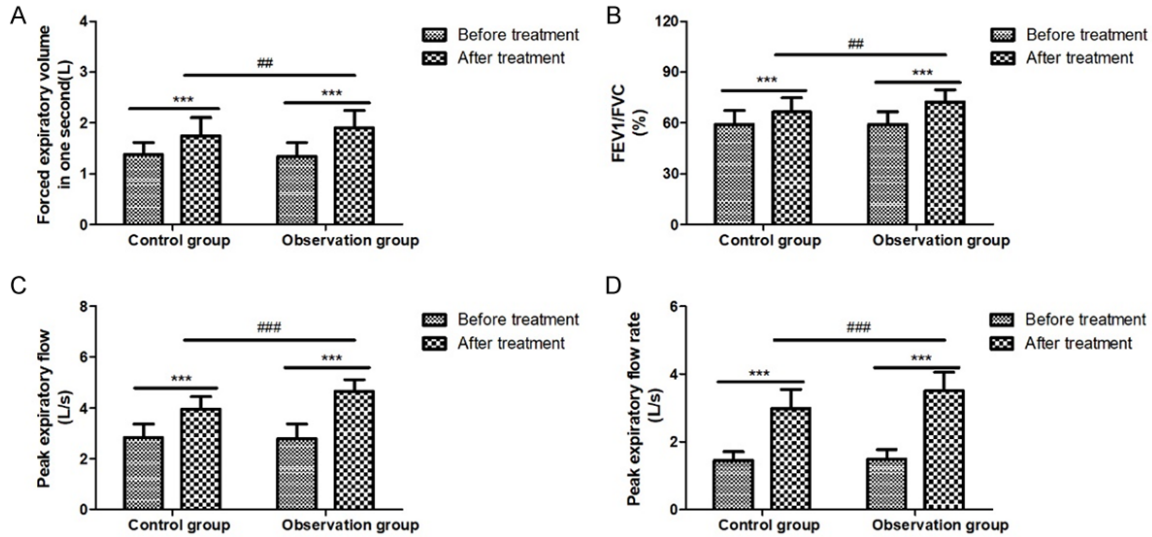
### EOS, IgE, and FeNo in induced sputum of the two groups

Before treatment, the two groups had no difference in absolute value of EOS, EOS percentage, FeNo, and immunoglobulin E (IgE) (all P>0.05), while after treatment, both groups showed significantly decreased absolute value of EOS, EOS percentage, FeNo, and IgE, and the observation group showed significantly lower levels of these measures than the control group (all P<0.001). See **Figure 3**.

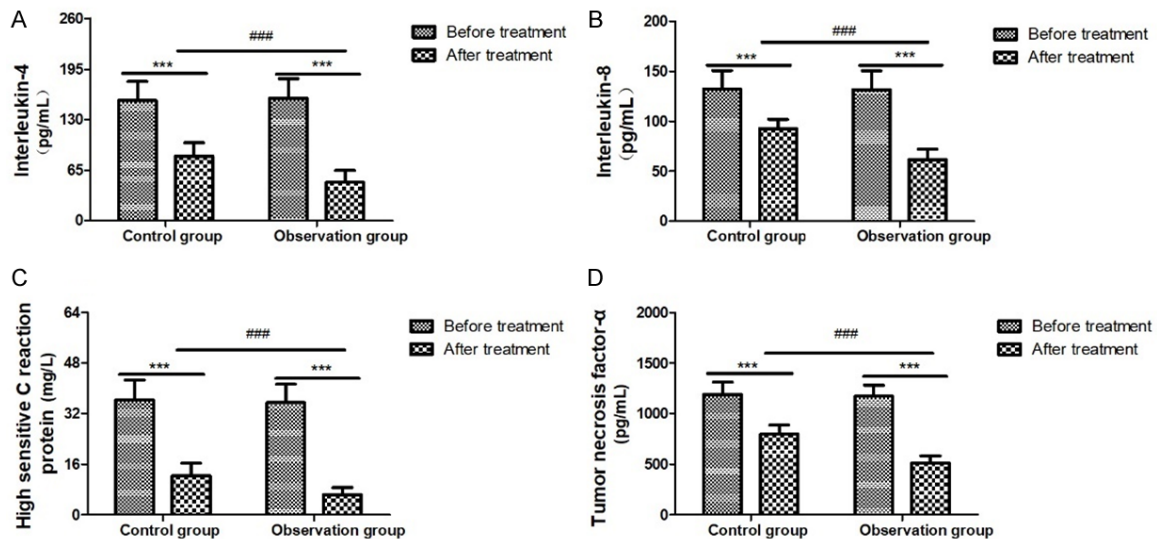
### T lymphocyte subsets of the two groups

Before treatment, the two groups had no difference in the expression of Th1, Th2, Th17, and Treg (all P>0.05), while after treatment, both groups showed significantly increased expres-

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**Figure 1.** Comparison of pulmonary function indexes of the two groups ( $\bar{x}\pm sd$ ). Note: group ## represents  $P<0.01$ , ### represents  $P<0.001$ , and group \*\*\* represents comparison  $P<0.001$ . A. FEV<sub>1</sub>. A larger FEV<sub>1</sub> value indicates better pulmonary function; B. FEV<sub>1</sub>/FVC. A larger FEV<sub>1</sub>/FVC indicates better pulmonary function; C. PEF. A larger PEF value indicates a milder airway obstruction; D. PEFR. A larger PEFR value indicates better pulmonary function. FEV<sub>1</sub>: forced exhalation in the first second; FVC: forced vital capacity; FVC/FEV<sub>1</sub>: forced vital capacity/forced exhalation in the first second; PEF: peak expiratory flow; PEFR: peak expiratory flow.



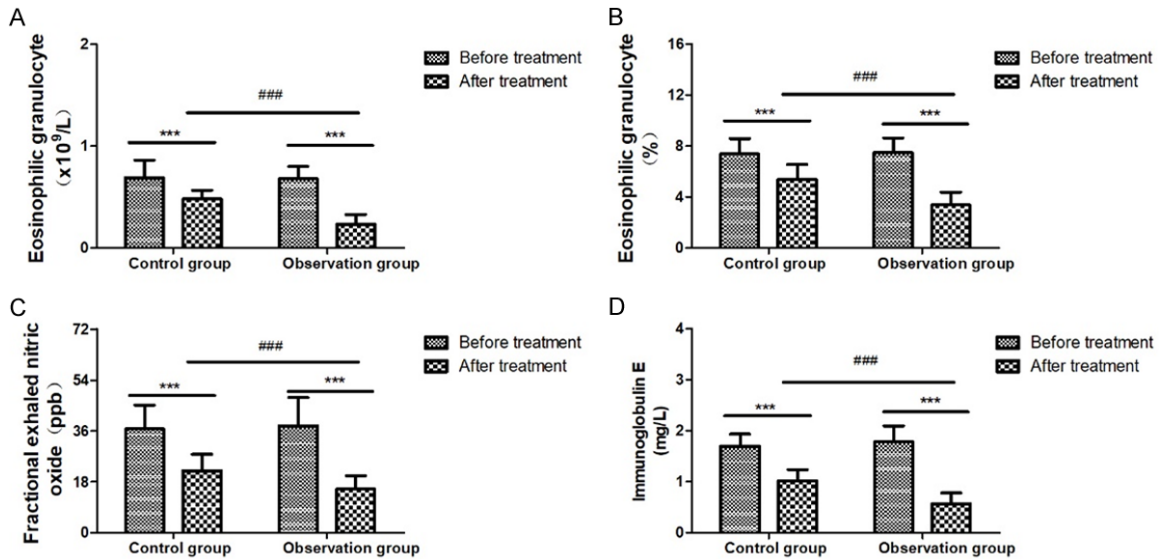
**Figure 2.** Comparison of inflammatory factors of the two groups ( $\bar{x}\pm sd$ ). Note: group ### represents  $P<0.001$ , group \*\*\* represents comparison  $P<0.001$ . A. IL-4. A higher IL-4 level indicates more severe inflammation; B. IL-8. A higher IL-8 level indicates more severe inflammation; C. hs-CRP. A higher hs-CRP level indicates more severe inflammation; D. TNF-α. TNF-α promotes T cells to generate various inflammatory factors. IL-4: interleukin-4; IL-4: interleukin-4; hs-CRP: hypersensitive C-reactive protein; TNF-α, tumor necrosis factor-α.

sion of Th1 and Treg, and significantly decreased expression of Th2 and Th17, and the observation group showed significantly higher expression of Th1 and Treg, and significantly lower expression of Th2 and Th17 than the control group at the same period (all  $P<0.001$ ). See **Figure 4**.

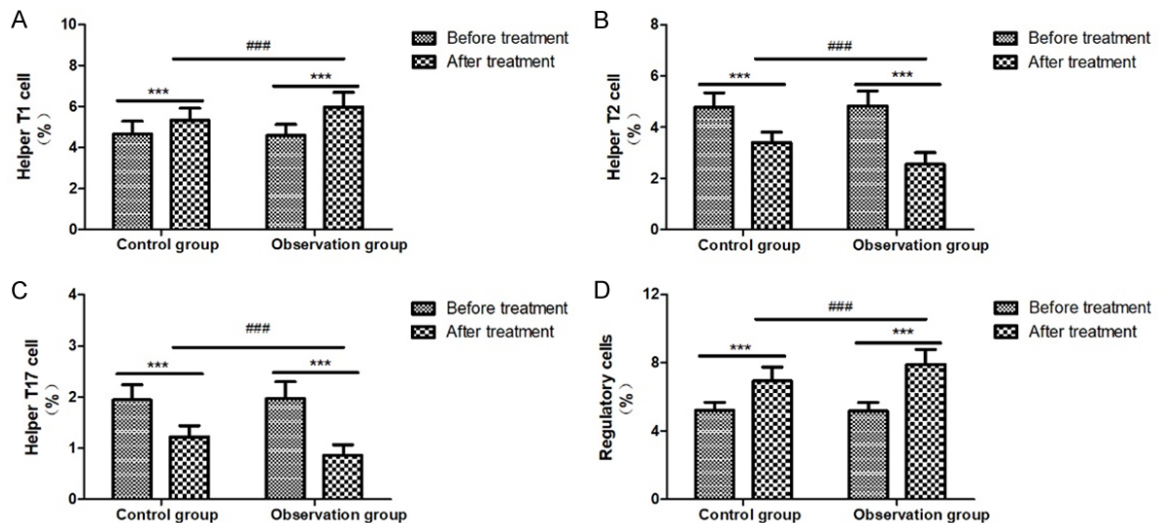
### Adverse reactions and recurrence rate of the two groups

There was no difference between the two groups in the number of patients suffering from adverse reactions such as nausea, headache, and rash (all  $P>0.05$ ), and at 6 months after

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**Figure 3.** Comparison of EOS, IgE, and FeNo in induced sputum of the two groups ( $\bar{x} \pm sd$ ). Note: group ### represents  $P < 0.001$ , group \*\*\* represents comparison  $P < 0.001$ . A. Absolute value of EOS. A larger absolute value of EOS indicates more severe asthma; B. EOS percentage. A larger EOS percentage indicates more severe asthma; C. FeNo. A higher FeNo indicates more severe airway inflammation. D. IgE. A lower IgE level indicates a better relief of allergic inflammation. EOS: eosinophils; FeNo: exhaled nitric oxide; IgE: immunoglobulin E.



**Figure 4.** Comparison of T lymphocyte subsets of the two groups ( $\bar{x} \pm sd$ ). Note: group ### represents  $P < 0.001$ , group \*\*\* represents comparison  $P < 0.001$ . A. Th1 cells. A lower Th1 level indicates a weaker immune response of the body; B. Th2 cells. Th2 is involved in allergy, and a high level of it will suppress cellular immune response. C. Th17 cells. A too high Th17 level will destroy immune balance and induce inflammatory reaction. D. Treg. A higher Treg level indicates better body immune function. Th1: helper T cell 1; Th2: helper T cell 2; Th17: helper T cell 17; Treg: regulatory T cell.

treatment, the recurrence rate of the observation group was significantly lower than that of the control group ( $P < 0.05$ ). See **Table 3**.

### Discussion

CVA in children, a disease with intractable cough as its main symptom, belongs to a potential or precursor form of asthma, which seri-

ously threatens children's physical and mental health, and brings a huge burden to families [13]. Most studies believe that CVA is a chronic inflammatory disease of the respiratory tract involving a variety of cells and cytokines such as eosinophils, mast cells, and T lymphocytes; which brings bronchial hyper-responsiveness and can directly lead to airway obstruction [14,

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**Table 3.** Adverse reactions and recurrence rate of the two groups (n%)

Group	Number of cases	Adverse reactions				Recurrence rate
		Nausea	Headache	Rash	Total	
Control group	55	1 (1.82)	0	1 (1.82)	2 (3.64)	10 (18.18)
Observation group	52	2 (3.85)	1 (1.92)	2 (3.85)	5 (9.62)	2 (3.85)
t/x <sup>2</sup>		0.002	0.000	0.002	0.738	4.171
P		0.961	0.978	0.961	0.390	0.041

15]. Therefore, if it is not treated in a timely manner, it will result in irreversible damage to the airway of the child [16]. Inhaled budesonide suspension is a non-halogenated glucocorticoid, which can combine with glucocorticoid receptors in a targeted way to lower the infiltration of mucosal inflammatory cells, prevent the activation of inflammatory cells, and relieve airway spasm, thus effectively controlling cough [17]. However, some studies have shown that the body has a certain dependence on glucocorticoid drugs, and the dosage increase of the drugs will bring adverse events such as osteoporosis and growth retardation in infants and young children [18]. Leukotriene is a main mediator in the inflammatory process of bronchial asthma, which increases the secretion of mucus glycoprotein, eventually inducing asthma aggravation [19]. Montelukast sodium, as a leukotriene receptor antagonist, can effectively inhibit the release of the above factors and reduce their activity, thus effectively improving the pulmonary function of asthmatic children, alleviating fibrosis, and relieving airway spasm and airflow limitation, which makes up for the deficiency of budesonide, so it is widely used in the treatment of CVA. However, there are no special reports on montelukast sodium combined with other drugs for young CVA patients. After all, children of different ages respond to drugs with different metabolisms and show different drug efficacies, so we have specifically studied the population at 2-4 years old, so as to better observe the efficacy of montelukast sodium.

Wang et al. confirmed that drug combination was more effective than budesonide alone in improving pulmonary function. Similarly, the combined treatment group got a significantly higher clinical evaluation score than the budesonide treatment group, and no serious adverse events occurred in both groups [20]. A study by Sathish Babu et al. proved that the levels of FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC in people with

poorly controlled asthma were dramatically lower than those in people with well controlled asthma [21]. In this study, after treatment, the indexes of FEV, FEV/FVC, PEF and PEFR in the observation group were significantly higher than those in the control group. Therefore, to some extent, it can be confirmed that the asthma control effect of the observation group was significantly better than that of the control group. A study by Ling et al. revealed that TNF- $\alpha$  was an important pro-inflammatory cytokine and an initiator of the systemic inflammatory response, which could activate inflammatory factors and further participate in the inflammatory response, causing airway mucosal injury, edema and airway hyper-responsiveness [22]. A study by Cao et al. showed that the TNF- $\alpha$  level in the extracellular matrix of asthmatic rats was significantly higher than that in normal rats in the control group, but the level in the normal rats fed with montelukast sodium was significantly lower than that in the asthma group. Moreover, one study also confirmed that montelukast sodium could relieve lung injury by normalizing abnormal protein expression [23]. In our study, children in the observation group after treatment showed significantly lower indexes of IL-4, INF- $\gamma$ , hs-CRP, and TNF- $\alpha$  than children in the control group at the same period. The main reason was that both IL-4 and INF- $\gamma$  are cytokines involved in airway inflammatory response of CVA in children, and the increase of IL-4 level would cause asthma. This was consistent with Peng's results that the IL-4 level in sputum of the CVA group was significantly higher than that of the control group ((257.37 $\pm$ 53.57) ng/L vs. (228.60 $\pm$ 52.93) ng/L) [24].

Robledo et al. proved that the onset of asthma in children was clearly correlated with the EOS and serum IgE levels ( $r^2=0.89$ ). The EOS percentage increased in the induced sputum of CVA patients, which may lead to clinical symptoms such as cough [25]. In this study, after

treatment, the observation group showed a significantly decreased absolute value of EOS, EOS percentage, FeNo, and IgE, and also showed significantly lower levels of the above indexes than the control group at the same period. Song et al. pointed out that FeNo could provide some accuracy in diagnosing CVA in patients with chronic cough, and with an total area under the curve of 0.87 (95% CI, 0.83-0.89), it can be employed to assess the airway inflammation level of asthma patients to judge their compliance and reactivity of hormone therapy and predict acute attack and recurrence of asthma [26]. A study by Zhang et al. revealed that the activation of serum mTOR, increase of Th17 cells and IL-4, and decrease of Treg cells and IFN- $\gamma$  were the key pathological links of asthma attack, and also the important mechanisms of bronchial hyper-responsiveness and inflammatory response [27]. In this study, the observation group showed significantly higher Th1 and Treg, and significantly lower Th2 and Th17 than the control group at the same period. A study by Hao et al. also confirmed that Th1/Th2 balance played a key role in the process of bronchial asthma, and the content of EOS cells increased along with the increase of Th2, causing its infiltration in the airway and leading to inflammation. Furthermore, Th17 cells are negatively correlated with Treg cells [28]. Therefore, we speculated that montelukast may promote cell apoptosis and increase CD4<sup>+</sup> T-lymphocyte subset content in peripheral blood of children and CD4<sup>+</sup> Th1 lymphocyte subsets by inducing Fas antigen expression, thus enhancing anti-inflammatory effects of the lung and improving Th1/Th2 cell ratio and function imbalance, which suppresses asthmatic airway inflammation and airway hyper-responsiveness.

The sample size involved in this study is small, and the observation period after medication is short, so the research results and conclusions may have certain limitations. In addition, the children are young, so their compliance is not well controlled. There may be cases in which the children have not received treatment according to the doctor's advice, including cases about drugs such as delayed drug taking and unreasonable drug dosage, resulting in disagreements between clinical effects and expectations, etc. In the future, we will expand the sample size, and extend the observation

period to compare the changes of more biological indexes during the treatment of CVA children, so as to further clarify the clinical efficacy and potential mechanism of Montelukast in treating CVA. Moreover, we will give regular training lectures to parents of children so that they can have a scientific understanding of the importance of correct medication, regular follow-up, and monitoring of lung function. We will also correct the irregular treatment in patients in time to fully or better control CVA.

To sum up, montelukast sodium can make up for the deficiency of budesonide and play a synergistic and complementary role. It can effectively strengthen the pulmonary ventilation function of CVA children, reduce the expression of inflammatory factors, increase the resistance of children, and thus increase the clinical efficacy. Therefore, it is worthy of further clinical application.

### Disclosure of conflict of interest

None.

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### References

- [1] Imai E, Enseki M, Nukaga M, Tabata H, Hirai K, Kato M and Mochizuki H. A lung sound analysis in a child thought to have cough variant asthma: a case report. *Allergol Int* 2018; 67: 150-152.
- [2] Enseki M, Nukaga M, Tadaki H, Tabata H, Hirai K, Kato M and Mochizuki H. A breath sound analysis in children with cough variant asthma. *Allergol Int* 2019; 68: 33-38.
- [3] Jin YT, Chen S and Xuan LH. Effect and safety of stimulating acupoints in children with cough variant asthma: a meta-analysis. *J Tradit Chin Med* 2018; 38: 480-489.
- [4] Liu W, Chen H, Zhang D, Wu F and Zhou L. A retrospective study of clinical features of cough variant asthma in Chinese adults. *Allergy Asthma Clin Immunol* 2019; 15: 3.
- [5] Tagaya E, Kondo M, Kirishi S, Kawagoe M, Kubota N and Tamaoki J. Effects of regular treatment with combination of salmeterol/fluticasone propionate and salmeterol alone in

## Montelukast sodium oral granules combined with budesonide in treating CVA

- cough variant asthma. *J Asthma* 2015; 52: 512-518.
- [6] Fujimura M. Pathophysiology, diagnosis and treatment of cough variant asthma. *Rinsho Byori* 2014; 62: 464-470.
- [7] Hang CJ, Zhao FZ, Chen FF and Zhang CQ. Inhaled glucocorticoids can effectively control airway inflammation in bronchial asthma. *Chinese Journal of Tuberculosis and Respiratory Diseases* 2018; 41: 912.
- [8] Guo YH. Discussion on clinical treatment plan for children with cough variant asthma. *Chinese Medicine and Clinical* 2017; 17: 260-261.
- [9] Bratton DL, Lanz MJ, Miyazawa N, White CW and Silkoff PE. Exhaled nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: a preliminary study. *Pediatr Pulmonol* 1999; 28: 402-407.
- [10] Li WS, Yang FZ, Su GX and Min YY. Clinical analysis of Meng Lu oral montelukast sodium in the treatment of 35 cases with infantile cough variant asthma. *Modern Preventive Medicine* 2012; 39: 2968-2969, 2971.
- [11] Straub DA, Minocchieri S, Moeller A, Hamacher J and Wildhaber JH. The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old. *Chest* 2005; 127: 509-514.
- [12] Zhou MJ, Lin L and Xu YJ. A follow-up study on the criteria for acupuncture withdrawal of cough variant asthma. *Chinese Journal of Practical Internal Medicine* 2013; 33: 89.
- [13] Sugawara H and Saito A. Comparison of therapeutic effects of inhaled corticosteroids on three subtypes of cough variant asthma as classified by the impulse oscillometry system. *Respir Res* 2019; 20: 41.
- [14] Enseki M, Nukaga M, Tadaki H, Tabata H, Hirai K, Kato M and Mochizuki H. A breath sound analysis in children with cough variant asthma. *Allergol Int* 2018; 68: 33-38.
- [15] Li GX, Li LW and Li Q. Effect of montelukast sodium on FeNO and inflammatory factors in patients with cough variant asthma. *Journal of Clinical Pulmonary Medicine* 2017; 22: 2110-2112.
- [16] Dai X. Clinical study on glucocorticoid combined with montelukast medication in treatment patients of cough variant asthma. *China Health Standard Management* 2015; 11: 56-57
- [17] Chen SY, Fang ZK, Fang S, Shen QX, He X, Wang CL and Yu HP. Comparison of functional parameters of small airways between patients with typical asthma and cough-variant asthma. *Nan Fang Yi Ke Da Xue Xue Bao* 2017; 37: 330-336.
- [18] Achuth Rao MV, Kausthubha NK, Shivani Yadav, Dipanjan Gope, Uma Maheswari Krishnaswamy and Prasanta Kumar Ghosh. Automatic prediction of spirometry readings from cough and wheeze for monitoring of asthma severity. *European Signal Processing Conference* 2017; 8081165.
- [19] He ZM, Guo YB and Xie CM. Effect of leukotriene receptor antagonist on cough variant asthma. *Nan Fang Yi Ke Da Xue Xue Bao* 2009; 29: 694-696.
- [20] Wang XP, Yang LD and Zhou JF. Montelukast and budesonide combination for children with chronic cough-variant asthma. *Medicine (Baltimore)* 2018; 97: e11557.
- [21] Sathish Babu M, Sreesoorya KP, Menon SK, Saha S, Srinivasan AR, Arul Vijaya Vani S, Reeta R and Kuzhandai Velu V. Putative role of cardio metabolic risk among poorly controlled asthmatics in south indian population. *Indian J Clin Biochem* 2017; 32: 225-229.
- [22] Qi L, Wang WY, Zhang YC, Cai SX, Yang NJ and Liu XL. Effects of TNF- $\alpha$  signal pathway in pathogenesis of asthma in children. *Journal of Jilin University* 2015; 41: 379-382.
- [23] Cao WQ, Li ZY and Su JZ. The involvement of extracellular matrix remodeling and up-regulated TNF- $\alpha$  in asthma rat and the interventions of montelukast sodium. *Journal of Hainan Medical University* 2015; 1-3.
- [24] Peng QF and Kong LF. The levels of nerve growth factor and IL-4 in induced sputum and characteristics of airway inflammation in cough variant asthma. *Zhonghua Nei Ke Za Zhi* 2011; 50: 221-224.
- [25] Robledo Aceves M, Barron Balderas A and Jaime Ornelas ML. Most commonly isolated viruses in asthma exacerbation and their correlation with eosinophil and total serum immunoglobulin E levels. *Arch Argent Pediatr* 2018; 116: 192-197.
- [26] Song WJ, Kim HJ, Shim JS, Won HK, Kang SY, Sohn KH, Kim BK, Jo EJ, Kim MH, Kim SH, Park HW, Kim SS, Chang YS, Morice AH, Lee BJ and Cho SH. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2017; 140: 701-709.
- [27] Zhang HY, Zhao SY and Tian F. Effects of Huaiqihuang Granule on immunoglobulin, T lymphocyte subsets and cytokines in children with cough variant asthma. *Journal of Hainan Medical University* 2017; 23.
- [28] Hao M, Song W and Lu L. The influence of montelukast on the balance of Th17/Treg and lung function of children with bronchial asthma. *Contemporary Medicine* 2017; 23: 11-14.