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Original Article

The effect of montelukast sodium plus budesonide on the clinical efficacy, inflammation, and pulmonary function in children with cough variant asthma

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Abstract: Objective: The aim of this study is to explore the clinical efficacy of montelukast sodium (MKST) combined with budesonide (BUD) on children with cough variant asthma (CVA) and its influence on inflammation and pulmonary function (PF). Methods: One hundred and sixty-six children with CVA treated in the Affiliated Nanhua Hospital, University of South China from May 2017 to August 2019 were randomized into a joint group (JG, n=92) for the combination therapy of MKST and BUD, and a control group (CG, n=74) for BUD monotherapy. Their clinical symptoms, total response rates (RR), PF, and inflammatory factor expressions were evaluated before and after treatment. The adverse reactions during the treatment were statistically compared between the two groups, and the factors influencing the curative effect were analyzed using logistic regression. Results: The JG presented markedly less cough resolution times, expectoration and wheezing, and a shorter body temperature recovery time than the CG after the treatment. The post-treatment forced expiratory volume in 1 second (FEV1), the forced vital capacity (FVC), the FEV1/FVC and the peak expiratory flow (PEF) levels as well as the Asthma Control Test (ACT) scores were statistically higher in the JG than in the CG. The JG had notably lower IgE, TNF-α, and IL-8 levels than the CG after the treatment. The total RR in the JG was observably higher than it was in the CG after the treatment, but the total adverse reaction rate identified no evident difference between the two series. Children with a family history of allergies, a family medical history, low ACT scores, high IgE expressions, high TNF-α expressions, and high IL-8 expressions, as well as BUD intervention are at increased risk of reduced efficacy. Conclusions: The reduction of efficacy in children with CVA results from multiple risk factors. MKST combined with BUD can ameliorate the PF of children with CVA, reduce their inflammatory factors, and improve the curative effect and the prognosis.

Keywords: Montelukast sodium combined with budesonide, children with cough variant asthma, clinical effect, inflammation, pulmonary function

Introduction

A bronchial disorder, cough variant asthma (CVA) is a peculiar type of chronic recurrent cough that manifests as an exacerbation of cough in the morning and evening and involves a variety of cells and cellular components [1]. CVA as a common cause of chronic cough in children, and has the pathophysiological characteristics of classic asthma, including atopic and chronic airway inflammation and bronchial hyperresponsiveness (BHR) [2]. Also, evidence has shown that without effective therapeutic intervention, approximately 30% of CVA cases will develop into classic asthma [3]. Unfortunately, the incidence of CVA goes in parallel with the changes in society and lifestyles, which greatly affects the learning and physical and mental health of children with asthma [4]. Hence, seeking effective, feasible, and safe therapies is paramount.

The occurrence and development of asthma symptoms are affected by leukotrienes secreted by inflammatory cells, which can lead to enhanced vascular permeability, contraction of smooth muscle, increased secretion of viscous substances in the airway, and increased airway viscosity, thus resulting in airway obstruction [5, 6]. At present, antiallergic drugs, inhaled glu-

cocorticoids and bronchodilators are commonly used to treat childhood asthma. However, children are prone to dependence and relapse after drug withdrawal due to long-term use [7]. Therefore, in this study, children with CVA were intervened using montelukast sodium (MKST) and budesonide (BUD) to observe the efficacy of the combination therapy. MKST is a selective cysteinyl leukotriene receptor antagonist with a high selectivity and specificity. Its binding with leukotriene receptor can alleviate bronchospasm and airway mucosal edema, thus lowering inflammatory cell infiltration and mucus secretions, reducing BHR, and facilitating the improvement of the disease [8-10]. There are studies pointing out that combined with other anti-asthma drugs, MKST can better control symptoms and ameliorate patients' pulmonary function (PF) [11, 12]. BUD is a non-halogenated glucocorticoid, characterized by its potent first-pass effect, short absorption phase and half-life, reduced metabolism, and high affinity for glucocorticoid receptors [13]. Due to its strong local anti-inflammatory and drug action, as well as its low systemic adverse effects, BUD is extensively used to treat asthma through inhalation and anesthesia in clinical practice [14]. For instance, Zhang and Wang [15] found that the use of MKST chewable tablets and the inhalation of BUD can help children with asthma restore their PF, reduce the inflammatory factor expressions, and effectively enhance their resistance.

In our research, MKST combined with BUD was administered to children with CVA to observe the efficacy of the combined treatment on children and its effect on the improvement of clinical symptoms. Also, a multivariate logistic regression analysis was carried out after the treatment to analyze the risk factors affecting its therapeutic effect on children.

Materials and methods

General information

One hundred and sixty-six children with CVA treated in the Affiliated Nanhua Hospital, University of South China from May 2017 to August 2019 were randomly placed into one of two groups according to the treatment regime each received: the children treated with MKST combined with BUD were placed in the joint group (JG, 92 cases), and the children treated with BUD were placed in the control group (CG, 74 cases). Inclusion criteria: All the children were diagnosed with CVA [16] and received follow-up treatment in our hospital after their diagnosis. The children had normal chest radiographs and blood routine tests, with no history of foreign body inhalation, and they had complete clinical data. The Ethics Committee of the Affiliated Nanhua Hospital, University of South China approved this study without reservations, and the children's parents and guardians were informed of the study and provided written, informed consent. Exclusion criteria: Children with chronic cough caused by other causes, children also suffering from infectious diseases such as fever, sinusitis, and pneumonia, children who had not taken the study medication or who were allergic to the drugs used in this study, children who withdrew from the study halfway, and children who were lost to follow up. The inclusion criteria were applicable to all participants.

Treatment methods

The children in the CG were treated with BUD aerosol (Sine Pharmaceutical Laboratories Co., Ltd., Shanghai, China, H20010552), which was administered once for 6-8 hours at a dose of 0.8 mg each time for 8 weeks.

The children in the JG were supplemented with MKST chewable tablets (Otsuka Pharmaceutical Co., Ltd., Sichuan, China, H20064828) in addition to the BUD aerosol therapy. The dose was 4 mg each time if the patient was ≤5 years old, and 5 mg each time for children 5 years old or older. The children were instructed to take the medicine orally before going to bed every night for 8 weeks.

Outcome measures

1. Clinical indicators: The time to the resolution of the cough, expectoration, and wheezing, and the time to the recovery of body temperature in the two groups were observed after treatment.

2. PF index: The patients' forced expiratory volume in 1 second (FEV1), the forced vital capacity (FVC), and the FEV1/FVC, peak expiratory flow (PEF) were measured before and after the treatment using a lung function instrument (Zeao Medical Technology Co., Ltd., Beijing, China, z00502).

Table 1. Comparison of the general data between the two groups [n (%)] (mean ± SEM)

Classification	Joint group (n=92)	Control group (n=74)	t/χ^2 value	*P* value
Gender			0.011	0.916
Male	48 (52.17)	38 (51.35)		
Female	44 (47.83)	36 (48.65)		
Course of disease (year)	1.86±0.15	1.83±0.14	1.319	0.189
Average age (years)	6.69±0.27	6.75±0.25	1.417	0.143
Family history of allergy			0.210	0.647
Yes	53 (57.61)	40 (54.05)		
No	39 (42.39)	34 (45.95)		
Family medical history			0.165	0.683
Yes	32 (34.78)	28 (37.84)		
No	60 (65.22)	46 (62.16)		
Diet			0.322	0.570
Light	57 (61.96)	49 (66.22)		
Spicy	35 (38.04)	25 (33.78)		
Residence			0.119	0.729
Rural	51 (55.43)	43 (58.11)		
City	41 (44.57)	31 (41.89)		
Smoking history of parents			0.042	0.837
Yes	57 (61.96)	47 (63.51)		
No	35 (38.04)	27 (36.49)		

3. Asthma Control Test (ACT) [17]: The score covers the frequency of asthma, the frequency of drug use, dyspnea, etc., and each question is worth 1-5 points for a total possible score of 25 points. The higher the score is, the better the asthma control will be.

4. Measuring the inflammatory factors: 5 mL of blood was drawn intravenously before and after the treatment in both groups, centrifuged at 1500×g and at 4°C for 10 min, and the obtained serum was stored in a freezer at -70°C for later use. Enzyme-linked immunosorbent assays (ELISA) [18] were used to examine the expression levels of immunoglobulin E (IgE), tumor necrosis factor-α (TNF-α), and interleukin-8 (IL-8) (C-reagent Biotechnology Co. Ltd., Shanghai, China, CS-12666E, CS-12638E, CS) following the manufacturer's protocol.

5. Efficacy evaluation: The curative effect was evaluated after the treatment. Markedly effective was indicated if the inflammatory indicators and PF of the child reached normal levels after the treatment, with profoundly improved clinical symptoms and an ACT score increased by ≥80%. If the inflammation indexes and PF of the child decreased but did not reach the normal range after the treatment, the clinical symptoms were alleviated, and the ACT score increased by ≥50%, it was rated as effective. If the symptoms, inflammation indexes, PF and ACT scores of the children were not improved after the treatment, it was rated as ineffective. Total response rate (RR) = (markedly effective + effective) cases/total cases × 100%.

6. Adverse reactions: a series of adverse reactions occurred during the treatment and were observed and recorded, and the effective treatment rate was compared.

7. After the treatment, the patients were divided into an effective group and an ineffective group according to the RR, and the factors affecting the efficacy of the treatment of the children with CVA were analyzed using a multivariate logistic regression.

Statistical analysis

The statistical analysis was performed using SPSS 25.0 (EasyBio Technology Co., Ltd., Beijing, China). The count data were described in the form of cases/percentage (n/%) and compared using chi-square tests between the groups. Expressed as the (mean ± SEM), the measurement data were compared using independent sample t-tests between the groups and paired t-tests within the same group before and after the treatment. When the theoretical frequency in a chi-square test was less than 5, a continuity correction chi-square test was applied. The factors influencing the efficacy of the children with CVA were analyzed using multivariate logistic regression. A *P*-value < 0.05 was considered significant.

Results

Comparison of the general data between the two groups

The children's general data, including gender, onset time, average age, family allergy history,

Table 2. Clinical symptoms (mean ± SEM) of the children in the two groups after the treatment

Groups	n	Cough resolution time	Body temperature recovery time	Expectoration resolution time	Wheezing resolution time
Joint group	92	7.18±0.59	5.48±0.47	4.33±0.29	4.13±0.36
Control group	74	9.37±1.04	7.93±1.05	7.02±0.61	6.84±0.58
t	-	17.080	20.030	37.390	36.86
P	-	< 0.001	< 0.001	< 0.001	< 0.001

family medical history, diet, residence, or parents' smoking history showed no significant differences between the two groups (P > 0.05) (**Table 1**).

Clinical symptoms after the treatment in the two groups

Observing the clinical symptoms of the children, it was found that the resolution time of the cough, expectoration, and wheezing, and the body temperature recovery times were observably less in the JG than they were in the CG after the treatment (P < 0.001) (**Table 2**).

Improvement of the PF of the children in the two groups before and after the treatment

The observation of the PF of the children revealed that there was no noteworthy difference in the FEV1, FVC, PEF, or FEV1/FVC levels between the two series before the therapy (P > 0.05), and these parameters improved dramatically in both groups after the treatment, and the improvement was more evident in the JG (P < 0.001) (**Table 3**).

ACT scores of the children in the two groups before and after the treatment

The ACT scores did not differ substantially between the two groups before the therapy (P > 0.05). However, the ACT scores increased noticeably in both groups after the treatment (P < 0.05), and the scores were lower in JG than they were in the CG (P < 0.05) (**Figure 1**).

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

The IgE, TNF-α, and IL-8 levels were not statistically different between the two series before the therapy (P > 0.05), but they were significantly reduced after the treatment (P < 0.05). Moreover, it was observed that the post-treatment levels in the JG were observably lower as compared to the CG (P < 0.05) (**Figure 2**).

Comparison of the efficacy between the two groups before and after the treatment

The total RR after treatment was 93.48% in the JG and 74.32% in the CG. The results indicated that the JG had an observably higher total RR than the CG after the treatment (P < 0.001) (**Table 4**).

Adverse reactions of the children in the two groups during the treatment

Adverse reactions such as stomatitis and lethargy occurred in both groups during the treatment, but there was no noteworthy difference in the incidence of total adverse reactions between the two groups (P > 0.05). Besides, the adverse reactions were all in a controllable range, with no effect on the study.

Logistic regression analysis of the factors influencing the curative effect on the children

After comparing the differences in the clinical references and related indicators that affected the treatment efficacy, we divided the children into an effective group (141 cases) and an ineffective group (25 cases) according to the RR after the intervention. Significant differences were absent in gender, course of the disease, age, diet, residence, and parents' smoking history between the effective group and the ineffective group, but were present in terms of family history of allergy, asthma degenerative constitution, family medical history, poor PF recovery, ACT scores, and the IgE, TNF-α, and IL-8 expression levels. Further, a multivariate logistic regression analysis indicated that a family history of allergy (P=0.022), family the medical history (P=0.011), the ACT scores (P=0.012), IgE (P=0.008), TNF-α (P=0.005), IL-8 (P=0.003), and the treatment methods (P=0.001) were independent risk factors influencing the treatment efficacy in children with CVA. Thus, children with a family history of allergy, a family

Table 3. Improvement of PF before and after the treatment in the two groups (mean ± SEM)

Groups	n	FEV1 (V/L)		FVC (V/L)		PEF (V/L·min^{-1})		FEV1/FVC	
		Before therapy	After treatment	Before therapy	After treatment	Before therapy	After treatment	Before therapy	After treatment
Joint group	92	1.51±0.17	2.23±0.29	1.88±0.17	3.09±0.37	61.79±5.83	87.79±8.15	69.23±6.47	85.32±8.83
Control group	74	1.49±0.15	1.83±0.21	1.90±0.22	2.43±0.32	61.04±5.81	80.17±8.01	69.48±6.42	75.82±7.36
t	-	0.793	9.949	0.661	12.120	0.825	6.034	0.248	7.412
P	-	0.428	< 0.001	0.509	< 0.001	0.411	< 0.001	0.804	< 0.001

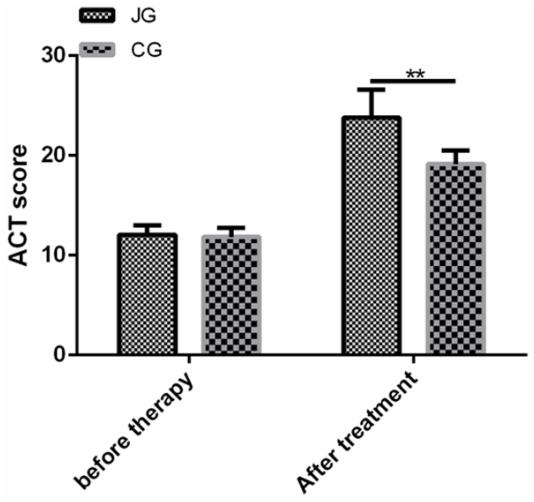

Figure 1. The ACT scores before and after the treatment in the two groups. There were no significant differences in the ACT scores between the two groups before the therapy, but the scores in the JG were significantly higher than the scores in the CG after the treatment. Note: * indicates $P < 0.05$ compared with before the therapy; ** indicates $P < 0.01$ compared between the two groups.

medical history, low ACT scores, high IgE expressions, high TNF-α expressions, high IL-8 expressions, and BUD intervention were at an increased risk of reduced therapeutic efficacy (**Tables 5**-**7**).

Discussion

CVA, with the characteristics of BHR and a rapid and acute onset, is a peculiar type of asthma with chronic cough as the main or only clinical manifestation, and it is prone to recurrent attacks and persistent cough, as well as respiratory infections [19, 20]. Long course and complex condition of CVA predisposes tremendous physical and mental pain among the children, and at the same time, the disease will also cause a variety of complications, and it can even lead to the death of the children in serious cases and without timely treatment [21]. Currently, drug therapy is often used to improve the clinical symptoms of children with CVA, alleviate their pulmonary ventilation difficulties, and reduce the condition's recurrence after the treatment [22].

We used MKST combined with BUD to treat CVA children and found that the children's clinical symptoms were improved after the treatment. In comparison with the CG, the cough resolution times, the expectoration and wheezing, and the body temperature recovery times of the children in the JG after the treatment were evidently less, indicating that the combined intervention can effectively shorten the remission and resolution times of the symptoms and relieve the cough symptoms of children with CVA, thereby ameliorating the clinical symptoms of the children and facilitating their recovery from the disease. Li et al. [23] found that MKST intervention can effectively reduce airway remodeling in asthmatic mice, alleviate immune disorders, and reduce airway inflammation. Zhang et al. showed [24] that BUD inhalation for children with mild persistent asthma can reduce the efficiency of FeNO and increase the efficiency of FEV1% pred, thus effectively controlling asthma. The preceding findings were similar to ours. Moreover, the post-treatment FEV1, FVC, PEF and FEV1/FVC levels were observed to be significantly higher in the JG than in the CG, demonstrating that MKST combined with BUD can profoundly relieve smooth muscles, repair edema mucosa and metabolize toxins in the body, thus effectively improving the PF of children. It is shown [25] that the level of asthma control is a key feature in determining the optimal asthma treatment required, and ACT is often used to evaluate the asthma control in clinical practice. Our study showed that the JG had notably higher ACT scores than the CG, implying that compared with BUD monotherapy, the combination with MKST can more effectively reduce trachea damage and relieve tracheal spasms, thereby resolving the coughing and asthma in children.

The aggravation of CVA is positively associated with an elevated expression of the inflammatory factors, so weakening the children's inflammatory reactions and carrying out airway remodeling are essential components of the clinical treatment of CVA [26]. The combination of BUD and MKST can reduce the release of the pro-inflammatory factors, restrain the aggregation and activation of the inflammatory factors, and inhibit the airway inflammatory response, so as to achieve the purpose of controlling asthma [27]. This also agrees with the results of the present study, that is, IgE, TNF-α, and IL-8 were significantly reduced in the JG compared to the CG after the treatment, indicating that MKST combined with BUD can make up for their respective defects and play a synergistic

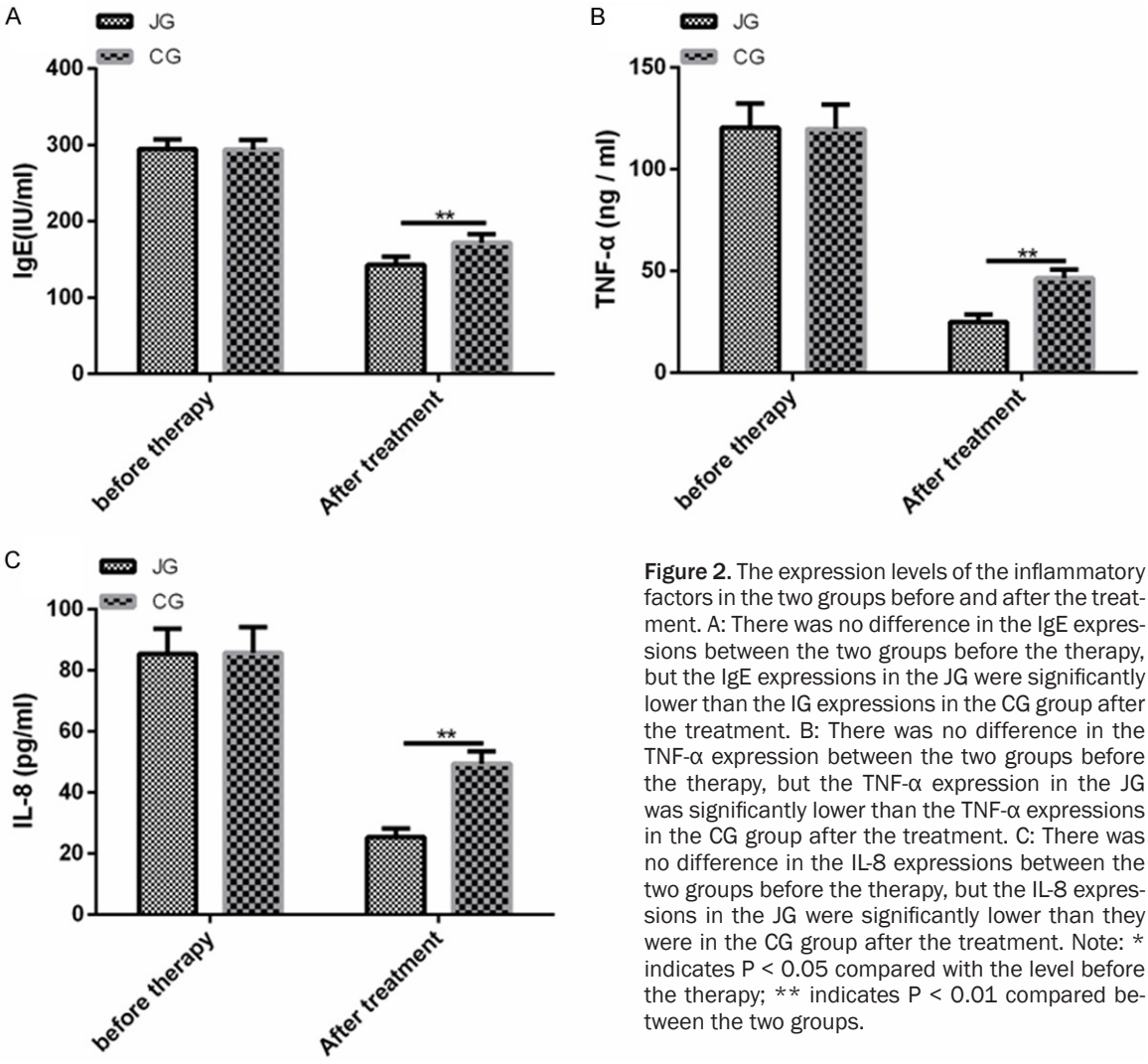

Figure 2. The expression levels of the inflammatory factors in the two groups before and after the treatment. A: There was no difference in the IgE expressions between the two groups before the therapy, but the IgE expressions in the JG were significantly lower than the IG expressions in the CG group after the treatment. B: There was no difference in the TNF-α expression between the two groups before the therapy, but the TNF-α expression in the JG was significantly lower than the TNF-α expressions in the CG group after the treatment. C: There was no difference in the IL-8 expressions between the two groups before the therapy, but the IL-8 expressions in the JG were significantly lower than they were in the CG group after the treatment. Note: * indicates $P < 0.05$ compared with the level before the therapy; ** indicates $P < 0.01$ compared between the two groups.

Table 4. Comparison of the efficacy between the two groups after the treatment [n (%)]

Groups	n	Markedly effective	Effective	Ineffective	Total response rate (%)
Joint group	92	50 (54.35)	36 (39.13)	6 (6.52)	86 (93.48)
Control group	74	26 (35.14)	29 (39.19)	19 (25.68)	55 (74.32)
χ^2	-	-	-	-	11.761
P	-	-	-	-	0.001

role, thus effectively reducing BHR and relieving chronic airway inflammation and alleviating the condition of the children with CVA. We also evaluated the total RR after the treatment. The results revealed a noticeably higher RR in the JG than in the CG, suggesting that compared with BUD alone, its combination with MKST can better improve the clinical symptoms and PF of children, thus improving the condition of the children. However, no significant difference was observed in the incidence of adverse reactions between the two groups. This indicates that BUD monotherapy and its combination with MKST were both safe, but compared with other regimens, the combination therapies is more effective in children with CVA. There are many factors leading to chronic cough in children, such as respiratory tract infections, upper respiratory tract cough syndrome, and cough variant asthma [28]. Our study showed that children with a family history of allergy, the family medical history, low ACT scores, high IgE

Table 5. Univariate analysis of the efficacy of the treatment of the children with CVA [n (%)] (mean ± SEM)

Classification	n	Effective group (n=141)	Ineffective group (n=25)	t/χ^2 value	*P* value
Gender				0.718	0.396
Male	86	75 (87.21)	11 (12.79)		
Female	80	66 (82.50)	14 (17.50)		
Course of disease (year)	166	1.88±0.16	1.84±0.12	1.191	0.235
Average age (years)	166	6.65±0.26	6.71±0.23	1.081	0.281
Family history of allergy				6.867	0.009
Yes	93	73 (78.49)	20 (21.51)		
No	73	68 (93.15)	5 (6.85)		
Family medical history				12.941	0.001
Yes	60	43 (71.67)	17 (28.33)		
No	106	98 (92.45)	8 (7.55)		
Diet				0.189	0.663
Light	106	91 (85.85)	15 (14.15)		
Spicy	60	50 (83.33)	10 (16.67)		
Residence				0.891	0.345
Rural	94	82 (87.23)	12 (12.77)		
City	72	59 (81.94)	13 (18.06)		
Smoking history of parents				0.556	0.455
Yes	104	90 (86.54)	14 (13.46)		
No	62	51 (82.26)	11 (17.74)		
ACT scores	166	24.79±2.01	13.68±1.05	26.940	< 0.001
IgE (IU/ml)	166	153.79±10.54	258.63±12.54	44.500	< 0.001
TNF-α (ng/ml)	166	38.46±3.37	103.68±10.04	60.790	< 0.001
IL-8 (pg/ml)	166	37.47±3.18	71.47±8.73	35.220	< 0.001
Treatment methods				11.761	0.001
Combination therapy	92	86 (93.48)	6 (6.52)		
Monotherapy	74	55 (74.32)	19 (25.68)		

Table 6. Assignment of the multivariate logistic regression analysis

Factor	Variable	Assignment
Family history of allergy	X1	Yes=0, no=1
Family medical history	X2	Yes=0, no=1
Low ACT scores	X3	High=0, low=1
High expression of IgE	X4	High=0, low=1
High expression of TNF-α	X5	High=0, low=1
High expression of IL-8	X6	High=0, low=1
Treatment methods	X7	Combination therapy=0, monotherapy=1

expressions, high TNF-α expressions, high IL-8 expressions, and BUD intervention increased the risk of reduced therapeutic efficacy.

Although this study confirmed that MKST combined with BUD can bring more benefits to children with CVA, there is still room for improvement in this study. For example, we can supplement the basic experiment of the therapeutic mechanism of the two therapies, and explore the risk factors affecting the efficacy of children from the molecular level. In the future, we will gradually improve the study from the above perspectives.

In summary, the reduced curative effect in children with CVA results from the combined effects of multiple risk factors. Our paper argues that MKST combined with BUD can ameliorate the PF of children with CVA, reduce the inflammatory factors in the body, enhance the curative effect, and ameliorate the prognoses of children.

Table 7. A logistic regression analysis of the factors influencing the curative effect of children

Variable	B	S.E	Wals	P	OR	95% CI
Family history of allergy	1.981	0.706	4.841	0.022	4.983	1.208-2.416
Family medical history	1.941	0.778	6.113	0.011	7.027	1.597-3.158
Low ACT scores	1.783	0.736	5.233	0.012	6.436	1.538-3.076
High expression of IgE	1.937	0.749	6.372	0.008	7.384	1.974-3.948
High expression of TNF-α	1.984	0.942	6.894	0.005	8.372	1.984-3.968
High expression of IL-8	2.046	0.478	7.371	0.003	8.742	2.051-4.102
Budesonide intervention	2.224	0.715	9.362	0.001	9.273	2.173-4.346

Disclosure of conflict of interest

None.

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