Effect of Montelukast Combined with Budesonide on Inflammatory Response and Pulmonary Function in Children with Cough Variant Asthma: A Meta-analysis

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ABSTRACT

This meta-analysis aimed to compare the efficacy of montelukast (MKST) combined with budesonide (BUD) and BUD alone in the treatment of pulmonary inflammation and pulmonary function in children with cough variant asthma (CVA). Five electronic databases were searched for studies about MKST+BUD therapy and BUD alone therapy on inflammation and pulmonary function in CVA children from inception to November 23, 2021. Twenty-two articles were included. The results showed that, compared with BUD alone, the combination treatment could achieve better improvement of pulmonary function and lower levels of inflammation (MKST+BUD group: FEV1: SMD = 2.77, 95% CI: 2.07, 3.46; FVC: SMD = 2.54, 95% CI: 1.82, 3.27; PEF: SMD = 2.27, 95% CI: 1.79, 2.75; IgE: SMD = -7.95, 95% CI: -9.66, -6.25; TNF-α: SMD = -4.67, 95% CI: -6.04, -3.31; IL-8: SMD = -8.18, 95% CI: -11.46, -4.90; BUD alone group: FEV1: SMD = 1.83, 95% CI: 1.34, 2.31; FVC: SMD = 1.39, 95% CI: 0.93, 1.84; PEF: SMD = 1.51, 95% CI: 1.13, 1.89; IgE: SMD = -4.93, 95% CI: -6.14, -3.72; TNF-α: SMD = -2.78, 95% CI: -3.76, -1.80; IL-8: SMD = -4.94, 95% CI: -7.10, -2.79). To conclude, compared with BUD alone, MKST+BUD therapy was found to be more effective in improving pulmonary function and reducing inflammation in CVA children.

Key Words: *Montelukast, Budesonide, Cough variant asthma, Children, Pulmonary function, Inflammatory markers, Meta-analysis*.

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INTRODUCTION

Cough variant asthma (CVA), also known as allergic cough, is a common subtype of bronchial asthma in children. The main clinical features of CVA are as follows: cough lasting for more than four weeks, frequent attacks at night or in the early morning, aggravated condition after exercise, exposure to cold air or smell of special odour, little sputum, no obvious signs of infection.[1,2] Most scholars believe that CVA is a chronic allergic inflammation of the airways with airway hyperreactivity, involving multiple inflammatory cells, and showing pathophysiological characteristics of typical asthma. By contrast, the clinical features are continuous, recurrent coughing without wheezing, if patients present with only airway hyperresponsiveness but with no airway spasm, no airway, or slight airway changes.[3,4] If left untreated, approximately 30% of CVA cases will develop into typical asthma.[5]

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Unfortunately, the occurrence of CVA coincides with social and lifestyle changes, and this disease significantly affects children's learning, physical and mental health.[5] Therefore, it is crucial to seek effective, safe, and feasible treatments.

Leukotrienes secreted by inflammatory cells affect the development of asthma symptoms, resulting in enhanced vascular permeability, smooth muscle contraction, increased secretion of viscous substances and airway viscosity, and ultimately airway obstruction.[6,7] The current first-line treatment for CVA is the same as for asthma, consisting primarily of antihistamines, inhaled bronchodilators, glucocorticoids, and leukotriene receptor antagonists.[8] However, long-term use of these drugs in children predisposes them to dependence and relapse after discontinuation.[9] Montelukast (MKST) is a selective cysteinyl leukotriene receptor antagonist with high selectivity and specificity. Upon administration, MKST binds to leukotriene receptors to reduce bronchospasm and airway mucosal oedema, resulting in the inhibition of inflammatory cell infiltration and mucus secretion, and ultimately leading to the reduction of airway hyperreactivity and improvement of the disease.[10] Budesonide (BUD) is a glucocorticoid drug whose efficacy has been generally recognised by clinicians, but glucocorticoids do not inhibit all inflammatory factors and show less inhibitory effect on leukotrienes.[11] It has been pointed that MKST combined with BUD can better control symptoms and improve pulmonary function in patients.[12] For example, Zhang *et al*. found that the use of MKST chewable tablets and inhaled BUD

can help asthmatic children restore lung function, reduce the expression of inflammatory factors, and effectively enhance their resistance.[13]

Understanding the efficacy of MKST combined with BUD may be pivotal to the treatment of childhood CVA and was therefore, the aim of this review. Specifically, the authors retrieved the published randomised controlled studies (RCTs) comparing MKST+BUD therapy and BUD alone therapy for childhood CVA and further investigated which therapy is superior in improving pulmonary inflammation and pulmonary function. This study is expected to provide a comprehensive evidence for the treatment of childhood CVA.

METHODOLOGY

The systematic review was performed following the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions Version 6.0[14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).[15]

Pubmed, Web of Science, Cochrane, WanFang Data, and China National Knowledge Infrastructure (CNKI) were searched for relevant RCTs related to the effects of MKST+BUD and BUD alone on the inflammatory response and pulmonary function in CVA children, comprehensively comparing the inflammatory response indicators and pulmonary function indicators after the two treatments from inception to November 23, 2021. The keywords were “Montelukast”, "Budesonide", "Cough variant asthma", and "Children". There were no restrictions on languages.

The retrieved articles meeting the following inclusion criteria were selected for the meta-analysis. Firstly, only RCTs were included in this study. Secondly, the study subjects were children with cough variant asthma. Thirdly, studies were chosen if it focused on the comparison of combined treatment of montelukast and budesonide and budesonide alone for children with cough variant asthma. Fourthly, studies were selected if it reported pulmonary function indicators like forced expiratory volume in one second, forced vital capacity, peak expiratory flow, or inflammatory response indicators like IgE, tumour necrosis factor-α, and hypersensitive-C-reactive-protein.

The articles were excluded if they met any of the following conditions. The comparison of efficacy between the two treatments was not provided. Studies with repeated publication, insufficient data, major defects, and major bias of study design were not allowed to be observed in the paper.

The two researchers independently performed the data extraction, and then cross-checked the collected data. The information extracted from each record was as follows: the title, first author, year of the publication, number of included study subjects, grouping, ages, the criteria of inclusion and exclusion, dosage, and course of treatment, pre-and post-treatment inflammatory response indicators and pulmonary function indicators, and relevant indicators of study design (mainly including study protocol and control of quality).

Subsequently, two researchers independently evaluated the quality of included RCTs according to the Cochrane Handbook for Systematic Reviews of Interventions 6.0.[14] The items of risk bias included performance bias, attrition bias, reporting bias, selection bias, and other biases. If there was a difference in the evaluation results, a third researcher would make a final decision. The conclusions are based on the quality of the included studies as low, medium, or high risk of bias.

Data were processed by STATA 15.1 software (Stata Corp MP., College Station, TX, USA).[16,17] The included studies showed good consistency, all of which provided CVA patients as study subjects, MKST+BUD therapy or BUD alone therapy as interventions. Additionally, these studies all reported the comparison of inflammatory response indicators and pulmonary function indicators before and after the treatment in CVA children. Heterogeneity among studies was quantitatively analysed by Q test and I^2 statistic, with $I^2 < 40\%$, $40\% \leq I^2 < 60\%$, and $I^2 \geq 60\%$ indicating low, medium, and high heterogeneity, respectively.[14] If $I^2 < 40\%$, a fixed-effects model was selected; in case of medium and high heterogeneity, the random-effects model was used to pool the data. The effects of the two treatments on inflammation and pulmonary function in CVA patients were compared with the standardised mean difference (SMD) and 95% confidence interval (CI) as effect sizes. The meta-analysis was performed for the pre-treatment data of the two groups, the pre-and post-treatment data of the combined group, and the pre-and post-treatment data of the BUD alone group, respectively. If there were six or more studies on inflammatory response indicators and pulmonary function indicators before and after MKST+BUD therapy versus BUD therapy in CVA children, a subgroup analysis based on the course of treatment was performed to observe whether the length of treatment affected the therapeutic effect or not. If the number of the included studies was more than six, Egger's test was adopted to judge the publication bias, with Duval and Tweedie’s trim and fill test to assess the sensitivity analysis.[18,19] Exact p-value was provided unless $p < 0.01$. $p < 0.05$ was a cut-off indicating statistical significance except for Egger’s test with $p < 0.10$ as the cut-off.

RESULTS

A total of 668 articles were retrieved from the five databases, while another 27 articles were obtained after manually searching the references of the initial retrieval articles. Subsequently, 93 duplicates were excluded, and 573 were then excluded by titles and abstracts (not related to cough-variant asthma, n = 107; review or *in vitro*, animal studies or letter or editorial or conference paper, n = 81; not related to the combination of montelukast and budesonide or budesonide alone for children with cough-variant asthma, n = 296; not related to inflammation or pulmonary function, n = 89). After reading the full text, 7 of 29 articles were excluded because they could not provide or transform into a valid data. Finally, 22 studies were included in the meta-analysis (Figure 1), including 1178 CVA children treated with MKST+BUD and 1133 CVA children treated with BUD alone. The basic characteristics of the included 22 RCTs are shown in Supplemental Table I.[20-41]

Table I: Summarised results of included studies.

Indicators	No. of studies	Sample size	Effect size (95%CI)	Heterogeneity (%)	
				I^2	*P*
Comparison between joint group of MKST and BUD and BUD alone group before therapy					
FEV1	19	2012	0.01 (-0.07, 0.10)	0.0	1.000
FVC	15	1512	0.02 (-0.08, 0.12)	0.0	0.949
PEF	16	1664	-0.02 (-0.11, 0.08)	0.0	0.804
IgE	12	1259	0.13 (-0.01, 0.27)	35.9	0.103
TNF-α	12	1325	0.07 (-0.04, 0.17)	0.0	0.994
IL-8	4	613	-0.06 (-0.22, 0.10)	0.0	0.415
IL-6	4	276	0.03 (-0.20, 0.27)	0.0	0.861
IL-4	6	562	0.02 (-0.15, 0.18)	0.0	0.989
IL-10	2	245	0.00 (-0.25, 0.25)	0.0	0.379
hs-CRP	3	296	0.02 (-0.21, 0.25)	0.0	0.868
TGF-β1	4	376	-0.02 (-0.22, 0.18)	0.0	0.893
Comparison between, before, and after therapy in joint group of MKST and BUD					
FEV1	19	1028	2.77 (2.07, 3.46)	97.3	<0.001
FVC	15	778	2.54 (1.82, 3.27)	96.7	<0.001
PEF	16	850	2.27 (1.79, 2.75)	93.4	<0.001
IgE	12	652	-7.95 (-9.66, -6.25)	97.5	<0.001
TNF-α	12	675	-4.67 (-6.04, -3.31)	98.0	<0.001
IL-8	4	315	-8.18 (-11.46, -4.90)	98.0	<0.001
IL-6	4	138	-2.32 (-3.19, -1.44)	87.6	<0.001
IL-4	6	291	-5.25 (-6.07, -4.42)	82.6	<0.001
IL-10	2	123	-1.78 (-8.92, 5.36)	99.6	<0.001
hs-CRP	3	148	-2.06 (-4.15, 0.04)	97.9	<0.001
TGF-β1	4	188	-1.24 (-4.19, 1.71)	99.1	<0.001
Comparison between, before, and after therapy in BUD alone group					
FEV1	19	984	1.83 (1.34, 2.31)	95.2	<0.001
FVC	15	734	1.39 (0.93, 1.84)	93.6	<0.001
PEF	16	814	1.51 (1.13, 1.89)	91.0	<0.001
IgE	12	607	-4.93 (-6.14, -3.72)	97.4	<0.001
TNF-α	12	650	-2.78 (-3.76, -1.80)	97.6	<0.001
IL-8	4	298	-4.94 (-7.10, -2.79)	97.9	<0.001
IL-6	4	138	-1.37 (-2.18, -0.55)	89.2	<0.001
IL-4	6	271	-2.61 (-3.11, -2.10)	78.5	<0.001
IL-10	2	122	-0.67 (-3.92, 2.58)	99.1	<0.001
hs-CRP	3	148	-1.52 (-3.01, 0.02)	96.6	<0.001
TGF-β1	4	188	-0.40 (-2.94, 2.14)	98.9	<0.001

BUD = Budesonide; MKST = Montelukast; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity; PEF = Peak expiratory flow; TNF-α = Tumour necrosis factor-α; IL-8 = Interleukin-8; IL-6 = Interleukin-6; IL-4 = Interleukin-4; IL-10 = Interleukin-10; hs-CRP = Hypersensitive-C-reactive-protein; TGF-β1 = Transforming growth factor-β1.

Table II: Evaluation of publication bias and sensitivity analysis.

Index	Egger's regression		Duval and Tweedie's trim and fill		
	Intercept	*p*	Original effect size	Studies trimmed	Adjusted effect size
Comparison between before and after therapy in joint group of MKST and BUD					
FEV1	4.238	0.195	2.76 (2.07, 3.46)	7	1.52 (0.78, 2.26)
FVC	6.048	0.122	2.54 (1.82, 3.27)	6	1.41 (0.61, 2.21)
PEF	7.414	0.184	2.27 (1.79, 2.75)	1	2.04 (1.52, 2.56)
IgE	-13.212	0.001	-7.95 (-9.66, -6.25)	0	-7.95 (-9.66, -6.25)
TNF-α	-7.277	0.084	-4.67 (-6.04, -3.31)	0	-4.67 (-6.04, -3.31)
IL-4	-8.945	0.023	-5.25 (-6.07, -4.42)	0	-5.25 (-6.07, -4.42)
Comparison between before and after therapy in BUD alone group					
FEV1	5.878	0.119	1.83 (1.34, 2.31)	6	1.14 (0.61, 1.67)
FVC	9.207	0.115	1.39 (0.93, 1.85)	4	0.91 (0.39, 1.41)
PEF	0.936	0.839	1.51 (1.13, 1.89)	0	1.51 (1.13, 1.89)
IgE	-12.186	0.005	-4.93 (-6.14, -3.72)	0	-4.93 (-6.14, -3.72)
TNF-α	-9.209	0.012	-2.78 (-3.76, -1.80)	0	-2.78 (-3.76, -1.80)
IL-4	-5.016	0.346	-2.61 (-3.11, -2.10)	0	-2.61 (-3.11, -2.10)

BUD = Budesonide; MKST = Montelukast; FEV1 = Forced expiratory volume in one second; FVC = Forced Vital Capacity; PEF = Peak Expiratory Flow; TNF-α = Tumour Necrosis Factor-α; IL-4 = Interleukin-4.

Then, the quality of included RCTs was assessed using the Cochrane Handbook, and the procedure was mentioned in the methodology. All the included studies strictly followed the principle of randomisation. Additionally, this meta-analysis excluded patients who might have a chronic cough caused by other reasons, children with infectious diseases such as fever, sinusitis, pneumonia, and children allergic to the drugs. Therefore, all the included studies had no reporting bias that could damage the power of the analysis. Both biases were assessed as low-risk. The overall assessment of the remaining included RCTs considered to be at a low-risk of bias, demonstrating the good quality of this meta-analysis and the high credibility of the analysis (Figure 2).

A table was used to present the meta-analysis results on the comparison of the pre-treatment data of inflammatory levels and pulmonary function parameters between the two groups. The intergroup comparison results provided baseline data for the subsequent analysis. Further, the meta-analysis was conducted regarding the comparison of the pre-and post-treatment data of the combined group and the BUD alone group. The intragroup comparison results could indicate the degree of improvement, and which medication was effective for the treatment.

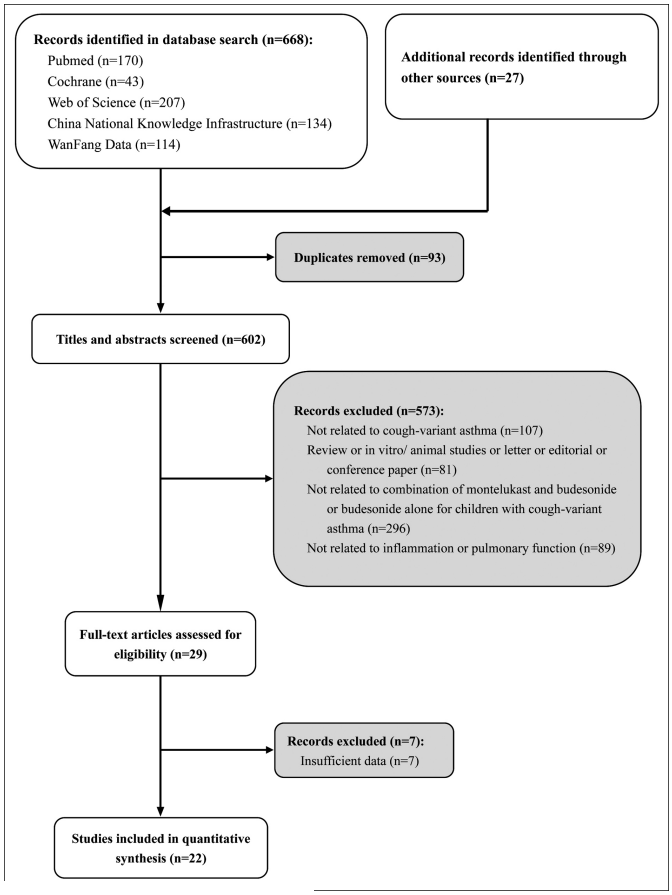

Figure 1: Study selection diagram.

From the results in Table I, there was no significant difference seen in the pulmonary function indicators, FEV1, FVC, and PEF between the MKST+BUD group and BUD alone group before the treatment (p >0.05). Also, no marked difference was found in the inflammation markers, IgE, TNF-α, hs-CRP, transforming growth factor-β1 (TGF-β1), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) between the two groups before the treatment (p >0.05, Table I).

The meta-analysis results showed that pulmonary function was significantly improved in children with CVA after combined treatment with MKST and BUD, and the differences were statistically significant (FEV1: SMD = 2.77, 95% CI: 2.07, 3.46; FVC: SMD = 2.54, 95% CI: 1.82, 3.27; PEF: SMD = 2.27, 95% CI: 1.79, 2.75; Table I). Similarly, all inflammation markers in the patients were decreased to different extents after the combination therapy; except for the IL-10, hs-CRP, and TGF-β1, where the decrease of the other markers were statistically significant (IgE: SMD = -7.95, 95% CI: -9.66, -6.25; TNF-α: SMD = -4.67, 95% CI: -6.04, -3.31; IL-8: SMD = -8.18, 95% CI: -11.46, -4.90; IL-6: SMD = -2.32, 95% CI: -3.19, -1.44; IL-4: SMD = -5.25, 95% CI: -6.07, -4.42; IL-10: SMD = -1.78, 95% CI: -8.92, 5.36; hs-CRP: SMD = -2.06, 95% CI: -4.15, 0.04; TGF-β1: SMD = -1.24, 95% CI: -4.19, 1.71; Table I).

Similarly, the meta-analysis results showed that the pulmonary function of CVA children was improved to varying degrees after BUD alone treatment.

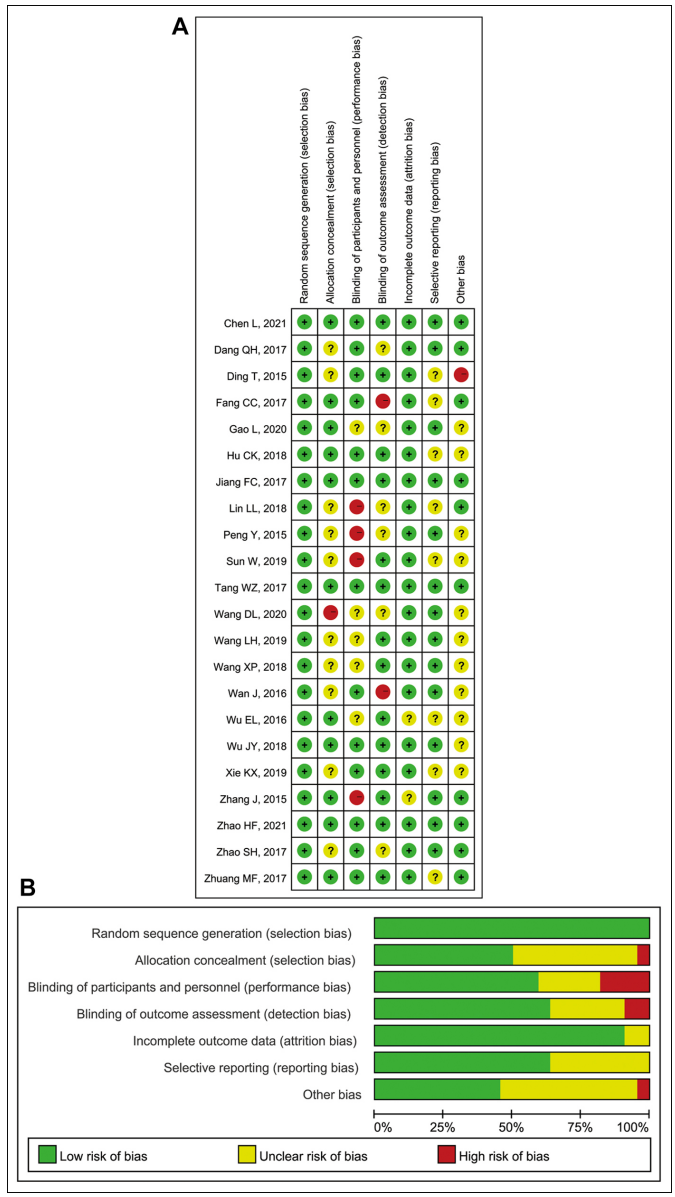

Figure 2: Review authors' judgements about each risk of bias item (A) Risk of bias summary (B) Risk of bias graph.

Additionally, the inflammatory level was correspondingly reduced; except for inflammatory markers IL-10, hs-CRP, and TGF-β1, the reduction in pulmonary function indicators and the other inflammatory markers were statistically significant (Table I).

This review and meta-analysis aimed to determine which of the two treatments was more effective for childhood CVA. Along with this purpose, the meta-analysis emphasised the changes in pulmonary inflammation and pulmonary function. The results showed that MKST+BUD could achieve better efficacy than BUD alone (Table I). However, it is also worth exploring that the pulmonary function indicators and inflammatory response indicators of the two treatment groups had strong heterogeneity, so the guiding significance of these indicators required further discussion.

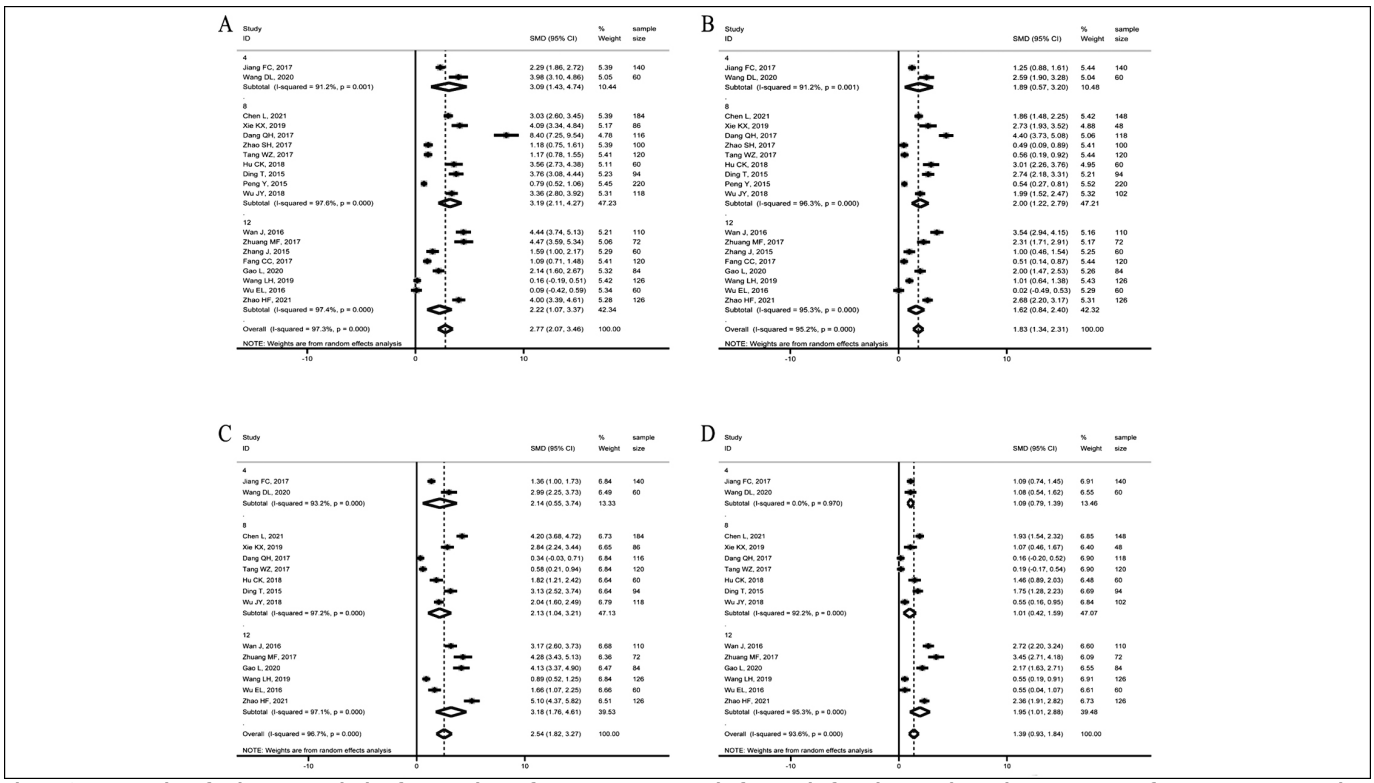

Figure 3: Forest plot of subgroup analysis of comparison of outcome measures before and after therapy dependant on course of treatment: A: FEV1 in combine group; B: FEV1 in control group; C: FVC in combine group; D: FVC in control group.

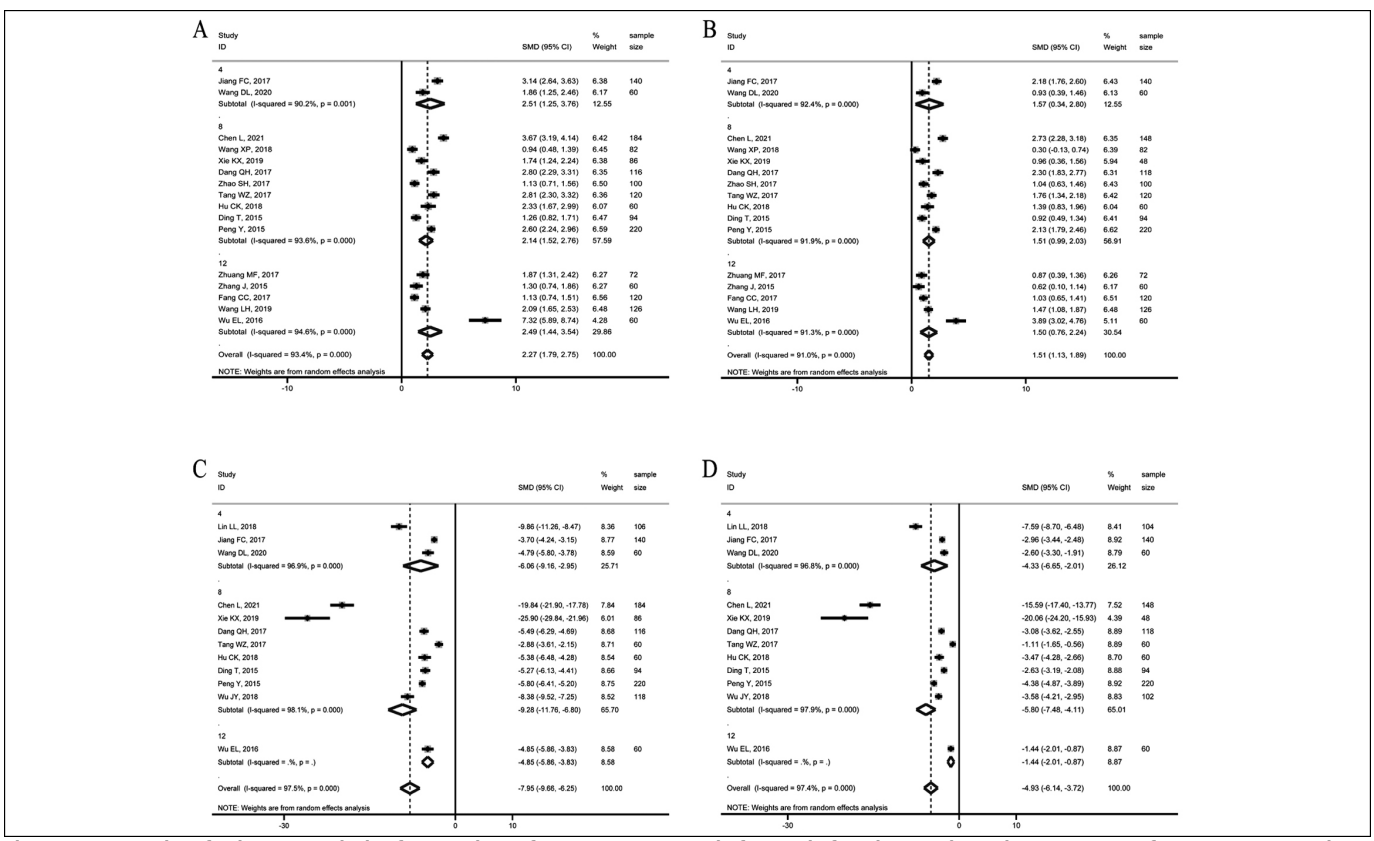

Figure 4: Forest plot of subgroup analysis of comparison of outcome measures before and after therapy dependant on course of treatment: A: PEF in combine group; B: PEF in control group; C: IgE in combine group; D: IgE in control group.

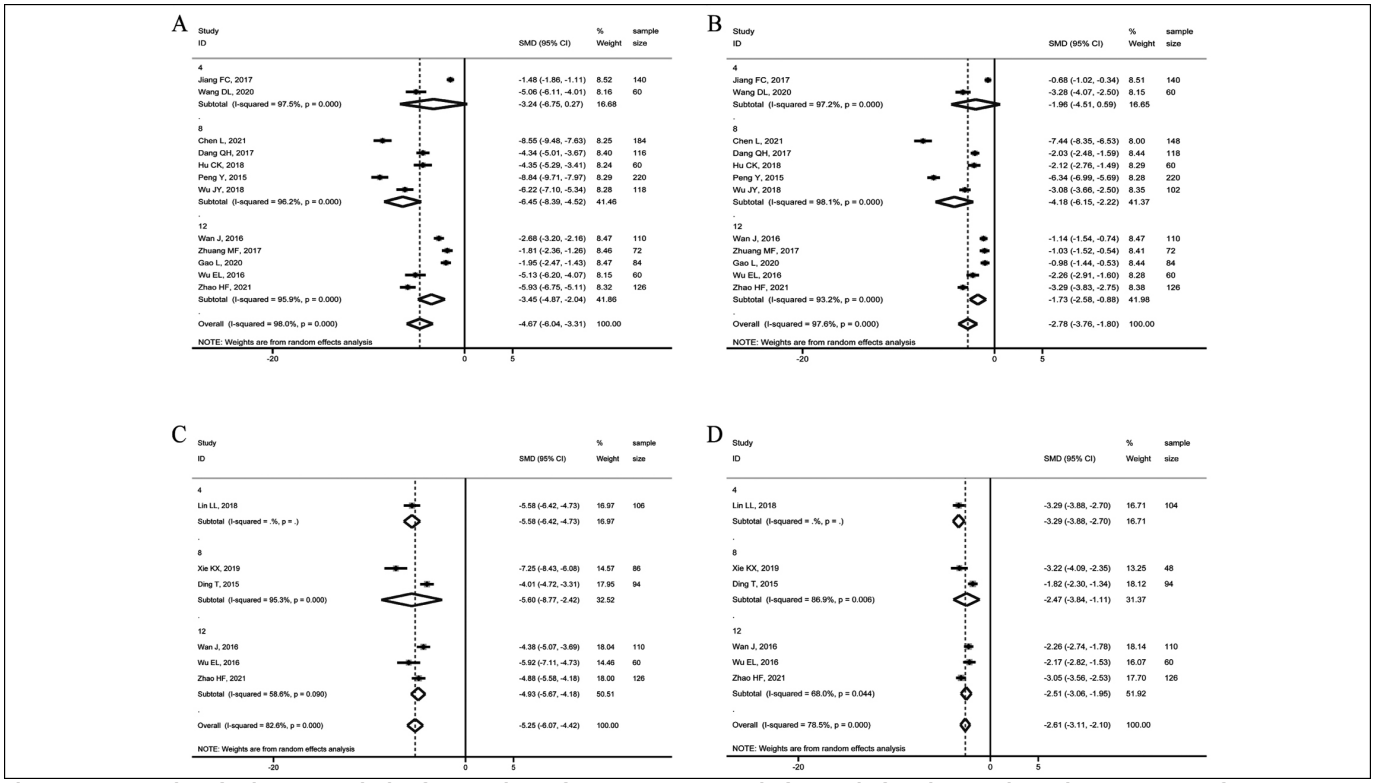

Figure 5: Forest plot of subgroup analysis of comparison of outcome measures before and after therapy dependant on course of treatment: A: TNF-α in combine group; B: TNF-α in control group; C: IL-4 in combine group; D: IL-4 in control group.

A subgroup analysis of FEV1, FVC, PEF, IgE, TNF-α, and IL-4 was performed, aiming to investigate whether the course of treatment was the source of heterogeneity. However, the analysis did not have a significant effect on reducing the heterogeneity of these indexes (Figures 3-5).

Affected by the studies with small sample size, the results showed a significant publication bias in IgE, TNF-α, and IL-4 of the MKST+BUD group, and in IgE and TNF-α of the BUD alone group using Egger's test ($p < 0.10$). No obvious publication bias was displayed in the other indicators (Table II). Duval and Tweedie's trim-and-fill method found that the findings of all indicators were robust, and no essential change was found observed before and after trimming and filling. Additionally, the effect size of each indicator in the MKST+BUD group was still more than those in the BUD alone group after trimming and filling, which was consistent with the conclusion of this meta-analysis and suggested a guiding significance (Table II).

DISCUSSION

CVA, a special type of asthma with chronic cough as the main clinical manifestation, is characterised by bronchial hyperreactivity, rapid and acute onset, easy recurrence, persistent cough, and respiratory tract infection.[42,43] CVA has a long course of disease and complex condition, causing various complications and bringing great physical and mental pain to children.[44] This disease may even lead to the death of children if left untreated in severe cases. At present, the drug therapy is mostly used to improve the clinical symptoms and pulmonary ventilation of children with CVA, and reduce their relapse.[45]

From the results of this meta-analysis, we could determine that both MKST+BUD therapy and BUD alone therapy could improve pulmonary function in children with CVA, but the former is more effective. Based on the effect sizes of meta-analysis, under the premise that there was no significant difference in the baseline level of pulmonary function in children with CVA in the two groups, it was observed that the effect sizes of pulmonary function indicators in the MKST+BUD group were higher than those in the BUD alone group. However, the high heterogeneity of pulmonary function parameters in the two groups creates some doubt about the above results. A further subgroup analysis based on the course of treatment revealed that the length of treatment was not the reason for the high heterogeneity. It might relate to the baseline characteristics of children like age and different administration of MKST and BUD in studies included for meta-analysis which cannot be explored in this study (Supplemental Table I). However, the good news is that Egger's test results showed no significant publication bias of the pulmonary function indicators, FEV1, FVC, and PEF in both groups. Duval and Tweedie's trim and fill test found that the effect sizes of all indicators were stable. Additionally, the effect size of each indicator in the MKST+BUD group was still greater than those in the BUD alone group after trimming and filling.

Supplemental Table I: Baseline characteristics of included studies for meta-analysis.

First author, year	No. of cases		Age (year, Joint / Contrl)	Course of treatment (week)	Detail of treatment
	Joint	Contrl			
Chen L, 2021[20]	92	74	6.7 ± 0.3 / 6.8 ± 0.3	8	Joint group: children received BUD aerosol at a dose of 0.8 mg and supplemented with 4 mg MKST chewable tablets when patient was ≤ 5 years, and 5 mg MKST chewable tablets when patient was 5 years old or older each time. Control group: children treated with BUD aerosol at a dose of 0.8 mg each time.
Wang XP, 2018[21]	41	41	6.2 ± 2.5 / 6.0 ± 2.8	8	Joint group: children received BUD aerosol (1mg, 3 times daily) and MKST chewable tablet (4mg, twice/day). Control group: children received BUD aerosol (1mg, 3 times daily).
Sun W, 2019[22]	56	56	7.5 ± 0.8 / 7.3 ± 0.5	8	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children > 6 years). Control group: children received BUD aerosol (1 mg/once, twice/day).
Lin LL, 2018[23]	53	52	10.1 ± 2.7 / 10.3 ± 2.9	4	Joint group: children received BUD aerosol (64 μg/once, twice/day) and additionally with MKST chewing tablet (10 mg/once, once/day). Control group: children received BUD aerosol (64 μg/once, twice/day).
Xie KX, 2019[24]	43	24	10. 7 ± 1.3 / 10.6 ± 1.2	8	Joint group: children received BUD aerosol (1 mg/once, once/6-8 h) and additionally with MKST chewing tablet (4 mg/once for children <5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (1 mg/once, once/6-8 h).
Jiang FC, 2017[25]	70	70	9.5 ± 2.7 / 9.8 ± 2.3	4	Joint group: children received BUD aerosol (0.5 mg/once, three times/day) and additionally with MKST chewing tablet (10 mg/once, twice/day). Control group: children received BUD aerosol (0.5 mg/once, three times/day).
Wan J, 2016[26]	55	55	4.3 ± 1.5 / 4.5 ± 1.3	12	Joint group: children received BUD aerosol (0.1 mg/once, three times/day) and additionally with MKST chewing tablet (4 mg/once, once/day). Control group: children received BUD aerosol (0.1 mg/once, three times/day).
Zhuang MF, 2017[27]	36	36	9.1 ± 2.3 / 8.7 ± 2.5	12	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once, once/day). Control group: children received BUD aerosol (1 mg/once, twice/day).
Dang QH, 2017[28]	58	59	4.2 ± 1.8 / 3.9 ± 1.6	8	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once, once/day). Control group: children received BUD aerosol (1 mg/once, twice/day).
Zhang J, 2015[29]	30	30	6.8 ± 3.3 / 6.9 ± 3.2	12	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once, once/day). Control group: children received BUD aerosol (1 mg/once, twice/day).
Wang DL, 2020[30]	30	30	7.4 ± 1.1 / 7.3 ± 1.0	4	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once, once/day). Control group: children received BUD aerosol (1 mg/once, twice/day).
Zhao SH, 2017[31]	50	50	10.6 ± 1.2 / 10.1 ± 1.5	8	Joint group: children received BUD aerosol (1 mg/once, once/6-8 h) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (1 mg/once, once/6-8 h).
Tang WZ, 2017[32]	60	60	4.1 ± 1.1 / 4.1 ± 1.1	8	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children < 6 years, 5 mg/once for children ≥ 6 years). Control group: children received BUD aerosol (1 mg/once, twice/day).
Hu CK, 2018[33]	30	30	5.3 ± 1.4 / 5.4 ± 1.2	8	Joint group: children received BUD aerosol (0.1 mg/once, twice/day for children < 7 years, 0.2 mg/once, twice/day for children > 7 years) and additionally with MKST chewing tablet (4 mg/once, once/day). Control group: children received BUD aerosol (0.1 mg/once, twice/day for children < 7 years, 0.2 mg/once, twice/day for children > 7 years).
Ding T, 2015[34]	47	47	6.2 ± 1.4 / 5.8 ± 1.9	8	Joint group: children received BUD aerosol (1 mg/once, once/6-8 h) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (1 mg/once, once/6-8 h).
Fang CC, 2017[35]	60	60	7.3 ± 2.8 / 7.5 ± 1.9	12	Joint group: children received BUD aerosol (1 mg/once, once/6-8 h) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (1 mg/once, once/6-8 h).
Gao L, 2020[36]	42	42	4.4 ± 1.6 / 4.5 ± 1.7	12	Joint group: children received BUD aerosol (0.5-1.0 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children <5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (0.5-1.0 mg/once, twice/day).
Wang LH, 2019[37]	63	63	6.9 ± 2.1 / 7.1 ± 2.2	12	Joint group: children received BUD aerosol (0.5 mg/once, twice/day for children < 6 years, 1 mg/once, twice/day for children > 6 years) and additionally with MKST chewing tablet (4 mg/once for children < 6 years, 5 mg/once for children ≥ 6 years). Control group: children received BUD aerosol (0.5 mg/once, twice/day for children < 6 years, 1 mg/once, twice/day for children > 6 years).
Wu EL, 2016[38]	30	30	5.1 ± 2.1 / 5.6 ± 2.1	12	Joint group: children received BUD aerosol (0.8 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (0.8 mg/once, twice/day).
Peng Y, 2015[39]	110	110	8.1 ± 0.9 / 8.2 ± 0.9	8	Joint group: children received BUD aerosol (0.2 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (0.2 mg/once, twice/day).
Zhao HF, 2021[40]	63	63	5.3 ± 1.0 / 5.2 ± 1.1	12	Joint group: children received BUD aerosol (1 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (1 mg/once, twice/day).
Wu JY, 2018[41]	59	51	5.1 ± 1.1 / 4.9 ± 1.2	8	Joint group: children received BUD aerosol (0.8 mg/once, twice/day) and additionally with MKST chewing tablet (4 mg/once for children < 5 years, 5 mg/once for children ≥ 5 years). Control group: children received BUD aerosol (0.8 mg/once, twice/day).

Joint = Combined treatment of budesonide and montelukast; Ctrl = Control; y = Year; BUD = Budesonide; MKST = Montelukast.

BUD, as a new generation of highly effective glucocorticoids, can block the metabolism of arachidonic acid to enhance the stability of membranes, reduce the synthesis and release the activity of sensitising mediators such as histamine. Also, BUD alleviates airway hyperreactivity by inhibiting the enzymatic reaction of antigen-antibody binding, reducing the synthesis and release of vasoexciter material, and inhibiting smooth muscle contraction.[46,47] Aerosol administration of BUD has high-absorption and availability and is well-tolerated by children. However, it has been reported that BUD cannot alleviate leukotriene-mediated organic inflammatory responses.[48] Leukotrienes are important inflammatory mediators that induce

CVA, and they can promote bronchial smooth muscle contraction and airway mucosal gland secretion, increase vascular permeability, and ultimately cause diseases.[49] MKST is a leukotriene receptor antagonist with high selectivity and specificity. MKST binds to leukotriene receptors to reduce bronchospasm and airway mucosal oedema and inflammatory cell infiltration and mucus secretion, thereby reducing airway hyperreactivity and symptoms of asthma and ultimately improving lung function. This meta-analysis results showed that the improvement of pulmonary function parameters, such as FEV1, FVC, and PEF, was more significant in children treated with MKST+BUD than in those treated with BUD alone.

Exacerbation of CVA is positively correlated with increased expression of inflammatory factors, and therefore attenuating inflammation and subsequent airway remodelling is vital for the clinical treatment of childhood CVA.[50] This meta analysis also showed that both treatments achieved a decrease in the levels of inflammatory cytokines IgE, TNF-α, IL-8, IL-6, and IL-4, but MKST+BUD was more effective. As with lung function indicators, inflammation markers also showed high heterogeneity, and the course of treatment was not a source of the high heterogeneity. Unfortunately, Egger's test results concluded that there was a significant publication bias in the markers IgE, TNF-α, and IL-4. According to the forest plots of these three parameters, the effect sizes in all studies showed a statistically significant decrease in inflammation levels in children (Figure 4 C and D, Figure 5 A-D). In addition, Duval and Tweedie's trim and fill sensitivity test also demonstrated that the effect sizes of the three indicators were stable. To a certain extent, this affirms that the results of the meta-analysis truly reflect the effect of the two treatments on children with CVA. MKST+BUD can inhibit the release of proinflammatory factors, accumulation and activation of inflammatory factors, and airway inflammatory response, to achieve the purpose of controlling asthma.[22] Meanwhile, this meta-analysis has also confirmed that IgE, TNF-α, IL-8, IL-6, and IL-4 were lower in the combined group than in the BUD group, indicating that MKST+BUD can compensate for their respective defects to play a synergistic role, thereby effectively reducing airway hyperreactivity, relieving chronic airway inflammation, and alleviating the condition of childhood CVA.

This study has some limitations. First, there is significant high heterogeneity among the studies, which may excessively exaggerate the effects of MKST+BUD on the improvement of pulmonary function and inflammation in children with CVA. Second, the identified studies are mainly conducted in China, so there are certain limitations in the extrapolation of the conclusion of this study.

CONCLUSION

This meta-analysis supports that, compared with BUD alone, MKST+BUD can receive better improvement of pulmonary function and reduction of inflammation in the treatment of children with CVA.

COMPETING INTEREST:

All the authors have no competing interest to declare.

AUTHORS' CONTRIBUTION:

WQX, WLO, LH: Critical revision of the manuscript.
WQX, WLO, LH: Significant contribution to the conception and design of the work.
WLO, LH: Manuscript drafting.
WQX, WLO, WMX: Records acquisition, data analysis, and interpretation of the data.
All authors have approved the final version of the manuscript to be published.

REFERENCES

1. Song W, Kim H, Shim J, Won HK, Kang SY, Sohn KH, *et al*. 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(3)**: 701-9. doi: 10.1016/j.jaci.2016. 11.037.
2. Li W, Ban C, Zhang J, Hu Y, Han B, Han B. Correlation study of cough variant asthma and mycoplasma pneumonia infection in children. *Pak J Pharm Sci* 2017; **30**: 1099-1102.
3. Zhu H, Zhang R, Hao C, Yu X, Tian Z, Yuan Y. Fractional exhaled nitric oxide (FeNO) combined with pulmonary function parameters shows increased sensitivity and specificity for the diagnosis of cough variant asthma in children. *Med Sci Monit* 2019; **25**:3832-8. doi: 10.12659/ MSM.913761.
4. De Diego A, Martínez E, Perpiñá M, Nieto L, Compte L, Macián V, *et al*. Airway inflammation and cough sensitivity in cough-variant asthma. *Allergy* 2005; **60(11)**:1407-11. doi: 10. 1111/j.1398-9995.2005.00609.x.
5. Chen X, Peng W, Wang L. Etiology analysis of nonspecific chronic cough in children of 5 years and younger. *Medicine (Baltimore)* 2019; **98**:e13910. doi: 10.1097/ MD.00000000 00013910.
6. Sirois P. Leukotrienes: One step in our understanding of asthma. *Respir Investig* 2019; **57(2)**:97-110. doi: 10.1016/ j.resinv.2018.12.003.
7. Niimi A. Cough, asthma, and cysteinyl-leukotrienes. *Pulm Pharmacol Ther* 2013; **26(5)**:514-9. doi: 10.1016/j.pupt.2013. 06.003.
8. Tagaya E, Kondo M, Kirishi S, Kawagoe M, Kubota N, Tamaoki J. Effects of regular treatment with combination of salmeterol/ fluticasone propionate and salmeterol alone in cough variant asthma. *J Asthma* 2015; **52(5)**:512-8. doi: 10.3109/ 02770903.2014.975358.
9. Akturk H, Karakoc-Aydiner E, Ozen A, Baris S, Akkoc T, Nadir Bahceciler N, *et al.* Predictive risk factors for relapse after cessation of inhaled corticosteroids in well-controlled childhood asthma. *Minerva Pediatr* 2017; **69(4)**:274-80. doi: 10.23736/S0026-4946.16.04244-4.
10. Al-Hamdani F. Comparative clinical evaluation of ketotifen and montelukast sodium in asthmatic Iraqi patients. *Saudi Pharm J* 2010; **18(4)**:245-9. doi: 10.1016/j.jsps.2010.07.001.

11. von Arnim U, Malfertheiner P. Eosinophilic esophagitis-treatment of eosinophilic esophagitis with drugs: Corticosteroids. *Dig Dis* 2014; **32(1-2)**:126-9. doi: 10.1159/000357089.
12. Wang X, Yang L, Zhou J. Montelukast and budesonide combination for children with chronic cough-variant asthma. *Medicine (Baltimore)* 2018; **97(30)**:e11557. doi: 10.1097/MD.0000000000011557.
13. Zhang Y, Wang H. Efficacy of montelukast sodium chewable tablets combined with inhaled budesonide in treating pediatric asthma and its effect on inflammatory factors. *Pharmazie* 2019; **74(11)**:694-7. doi: 10.1691/ph.2019. 9582.
14. Higgins J, Thomas J, Chandler J. Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019). 2019. Available from: training.cochrane.org/handbook/current.
15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4(1)**:1. doi: 10.1186/2046-4053-4-1.
16. Nyaga V, Arbyn M, Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; **72(1)**:39. doi: 10.1186/2049-3258-72-39.
17. Harris R, Deeks J, Altman D, Bradburn M, Harbord R, Sterne J. Metan: fixed- and random-effects meta-analysis. *Stata J* 2008; **8**:3-28. doi: 10.1177/1536867X0800 800102.
18. Egger M, Davey Smith G, Schneider M. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315(7109)**:629-34. doi: 10.1136/bmj.315.7109.629.
19. Duval S, Tweedie R. Trim and fill: A simple funnel plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; **56(2)**:455-63. doi: 10.1111/j.0006-341x.2000.00455.x.
20. Chen L, Huang M, Xie N. The effect of montelukast sodium plus budesonide on the clinical efficacy, inflammation, and pulmonary function in children with cough variant asthma. *Am J Transl Res* 2021; **13(6)**:6807-16.
21. Wang X, Yang L, Zhou J. Montelukast and budesonide combination for children with chronic cough-variant asthma. *Medicine (Baltimore)* 2018; **97(30)**:e11557. doi: 10.1097/MD.0000000000011557.
22. Sun W, Liu H. Montelukast and budesonide for childhood cough variant asthma. *J Coll Physicians Surg Pak* 2019; **29(4)**:345-8. doi: 10.29271/jcpsp.2019.04.345.
23. Lin L, Ou L. Effect of budesonide nasal spray combined with montelukast sodium tablets in the treatment of children with cough variant asthma and its influence on related factors. *Maternal Child Health Care China* 2018; **33**:2480-3. doi: 10.7620/zgfybj.j.issn.1001-4411.2018.11.27.
24. Xie K, Ma X, Ren H. Effect of budesonide combined with montelukast sodium on inflammatory response and symptom score in children with cough variant asthma. *Guizhou Med J* 2019; **43**:1394-6. doi: 10.3969/j.issn.1000-744X.2019.09.018.
25. Jiang F, Zhu W, Zheng S. Effect of budesonide combined with montelukast sodium on FeNO hS-CRP level in children with CVA. *Hebei Med* 2017; **23**:783-6. doi: 10.3969/j.issn.1006-6233.2017.05.023.
26. Wan J, Luo W, Zheng S, Zhang L. Observation on efficacy of budesonide combined with montelukast in treatment of cough variant asthma in children. *Evaluation Analysis Drug-use Hospitals China* 2016; **16**:1056-9. doi: 10.14009/j.issn.1672-2124.2016.08.019.
27. Zhuang M, Ma J, Yin R, Sheng F. Effect of montelukast on lung function in treatment of children with cough variant asthma. *J Clin Pulmonary Med* 2017; **22**:89-92. doi: 10.3969/j.issn.1009-6663.2017.01.025.
28. Dang Q, Zhao W. Influence of budesonide combined with montelukast on lung function and transforming growth factor-β1 of children with cough variant asthma. *Drug Evaluation Res* 2017; **40**:832-5. doi: 10.7501/j.issn.1674-6376.2017.06.21.
29. Zhang J, Sonf N, Gao N, Yang C, Lv H, Du B. Influence of montelukast combined with budesonide on serum transforming growth factor beta 1 and serum amyloid A in children with cough variant asthma. *Clin Focus* 2015; **30**:1273-9. doi: 10.3969/j.issn.1004-583X.2015.11.015.
30. Wang D. Effects of montelukast sodium combined with budesonide on lung function and symptom improvement time in children with cough variant asthma. *Chinese Remedies Clinics* 2020; **20**:84-6. doi: 10.11655/zgywylc 2020.01.032.
31. Zhao S. Effects of montelukast sodium combined with budesonide on symptom score, lung function and recurrence rate after 1 year in children with cough variant asthma. *Maternal Child Health Care China* 2017; **32**:4732-4. doi: 10.7620/zgfybj.j.issn.1001-4411.2017.19.47.
32. Tang W, Xu H, Xu J, Yan D. Effect of montelukast sodium combined with Budesonide suspension on respiratory function, IgE and EOS in children with cough variant asthma. *Chinese J Front Med Sci* 2017; **9**:134-8. doi: 10.12037/ YXQY.2017.12-30.
33. Hu C, Yang J, Jiang X, Zhang W. Effects of montelukast sodium combined with budesonide aerosol on lung function in children with cough variant asthma. *Guizhou Medical J* 2018; **42**:439-40. doi: 10.3969/j.issn. 1000-744X. 2018.04.022.
34. Ding T, Zhang S. Study on the clinical efficacy and safety of montelukast combined with budesonide in the treatment of cough variant asthma in children. *Med Recapitul* 2015; **21**:2637-41. doi: 10.3969/j.issn.1006-2084.2015.14.052.
35. Fang C, Yao H. Clinical analysis of montelukast sodium combined with budesonide in the treatment of children with cough variant asthma. *Maternal Child Health Care China* 2017; **32**:5935-7. doi: 10.7620/zgfybj.j.issn.1001-4411.2017.23.47.
36. Gao L. Effect of Montelukast sodium combined with budesonide on children with cough variant asthma. *Guizhou Med J* 2020; **2020**:937-8. doi: 10.3969/j.issn.1000-744X.2020.06.039.

37. Wang L, Li Y, Wang C. Effect of Montelast sodium combined with budesonide on airway remodeling in children with cough variant asthma. *Maternal Child Health Care China* 2019; **34**:2267-9. doi: 10.7620/ zgfybj.j.issn.1001-4411. 2019.10.30.
38. Wu E. Influence of montelukast combined with budesonide on pulmonary function and immunological function in infants with cough variant asthma. *J Clin Med Prac* 2016; **20**:91-4. doi: 10.7619/jcmp.201617028.
39. Peng Y, Wang C, Huang Y, Wang P, Zhao G. Clinical effect of montelukast sodium combined with budesonide on children with cough variant asthma and the effect of inflammatory factors. *Maternal Child Health Care China* 2015; **30**:5688-9. doi: 10.7620/zgfybj.j.issn. 1001-4411. 2015.32.67.
40. Zhao H. Clinical effect of montelukast sodium combined with budesonide in the treatment of children with cough variant asthma. *Chinese Remedies Clinics* 2021; **21**: 1713-5. doi: 10.11655/zgywylc2021.10.029.
41. Wu J. Effect of montelukast and budesonide on serum TNF-α and IgE in children with cough variant asthma. A*nhui Med Pharma J* 2018; **22**:750-753. doi: 10.3969/ j.issn.1009-6469.2018.04.046.
42. Chen L, Zeng G, Wu L, Zi M, Fang ZK, *et al.* Diagnostic value of FeNO and MMEF for predicting cough variant asthma in chronic cough patients with or without allergic rhinitis. *J Asthma* 2021; **58(3)**:326-33. doi: 10.1080/ 02770903.2019. 1694035.
43. Wang P, Shang E, Fan X. Effect of San'ao decoction with scorpio and bombyx batryticatus on CVA mice model via airway inflammation and regulation of TRPA1/TRPV1/ TRPV5 channels. *J Ethnopharmacol* 2021; **264**:113342. doi: 10. 1016/j.jep.2020.113342.
44. Zhu X, Tu J, Dai J. Clinical effect of fluticasone propionate, montelukast sodium and ketotifen in treatment of cough variant asthma in children. *Zhongguo Dang Dai Er Ke Za Zhi* 2019; **21**:393-8. doi: 10.7499/j.issn.1008-8830.2019. 04.017.
45. Sugawara H, Saito A, Yokoyama S, Tsunematsu K, Takahashi H. 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. doi: 10.1186/s12931-019-1005-2.
46. Acun C, Tomac N, Ermis B, Onk G. Effects of inhaled corticosteroids on growth in asthmatic children: A comparison of fluticasone propionate with budesonide. *Allergy Asthma Proc* 2005; **26(3)**:204-6.
47. Munch A, Bohr J, Miehlke S, Benoni C, Olesen M, Ost A, *et al*. Low-dose budesonide for maintenance of clinical remission in collagenous colitis: A randomised, placebo-controlled, 12-month trial. *Gut* 2016; **65(1)**:47-56. doi: 10.1136/gutjnl-2014-308363.
48. Crisafulli E, Guerrero M, Menéndez R, Huerta A, Martinez R, Gimeno A, *et al*. Inhaled corticosteroids do not influence the early inflammatory response and clinical presentation of hospitalised subjects with COPD exacerbation. *Respir Care* 2014; **59(10)**:1550-9. doi: 10.4187/respcare.03036.
49. Lotufo C, Yamashita C, Farsky S, Markus R. Melatonin effect on endothelial cells reduces vascular permeability increase induced by leukotriene B4. *Eur J Pharmacol* 2006; **534 (1-3)**:258-63. doi: 10.1016/j.ejphar.2006.01.050.
50. Urvasiev M, Ponomareva I, Bhar M, Glotov S. The cough variant asthma. *Ter Arkh* 2020; **92(3)**:98-101. doi: 10. 26442/ 00403660.2020.03.000404.