ORIGINAL RESEARCH

Effect of Spleen Aminopeptide Oral Lyophilized Powder and Fluticasone/salmeterol Powder Inhaler on Pulmonary Function and Incidence of Adverse Reactions in Children with Cough Variant Asthma

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ABSTRACT

Background • Cough variant asthma is a prevalent condition among children with chronic cough, significantly impacting their health and well-being.

Objective • This study aimed to assess the impact of spleen aminopeptide oral lyophilized powder and fluticasone/salmeterol powder inhaler on pulmonary function and the incidence of adverse reactions in children with cough variant asthma.

Methods • A total of 60 children with cough variant asthma admitted to the Pediatric Department of Cangzhou Central Hospital between July 2019 and June 2020 were enrolled in the study. Using the random number table method, they were assigned to either the observation group or the control group, with 30 cases in each group. The control group received treatment with fluticasone/salmeterol powder inhalers, while the observation group received a combination of fluticasone/salmeterol powder inhalers and spleen aminopeptide oral lyophilized powder. After 8 weeks of treatment, various clinical parameters, including forced vital capacity, forced expiratory volume per second/forced vital capacity, peak expiratory flow, fractional exhaled nitric oxide (FeNO), interleukin-4 (IL-4), IL-10, eosinophils in induced sputum, and serum CD4+ and CD8+ levels, were compared between the two groups.

Results • The observation group exhibited a higher total effective rate of clinical efficacy compared to the control group [90.00% vs. 63.33%; OR (95% CI) 3.00 (1.01-8.92), P = .048)]. After 8 weeks, the observation group demonstrated higher levels of forced vital capacity, forced expiratory volume per second/forced vital capacity, peak expiratory flow [OR (95% CI) 0.48 (0.26-0.88), P = .017; OR (95% CI) 0.29 (0.14-0.57) 2.57 (1.46-4.52) 0.33 (0.16-0.70), P = .000, .001, .003], IL-10 [OR (95% CI) 0.29 (0.14-0.57), P = .000], and lower levels of FeNO [OR (95% CI) 0.48 (0.26-0.88), P = .017], IL-4, and eosinophils [OR (95% CI) 2.57 (1.46-4.52) 0.33 (0.16-0.70), P = .001, .003] compared to the control group (P < .05). Furthermore, the observation group exhibited higher levels of CD4+ and CD4+/CD8+ compared to the control group [OR (95% CI) 0.41 (0.25-0.67) 0.33 (0.20-0.56) 1.73 (1.18-2.55), P = .000, .000, .001]. Computed tomography measurements revealed significantly lower airway wall thickness, basement membrane thickness, and total airway wall area in the observation group compared to the control group [OR (95% CI) 0.18 (0.10-0.33) 0.23 (0.13-0.41) 0.28 (0.15-0.51), P = .000, .000, .000]. The incidence of adverse reactions did not significantly differ between the groups (6.67% vs. 3.33%; P > .05).

Conclusion • The combination treatment of spleen aminopeptide oral lyophilized powder and fluticasone/salmeterol powder inhaler effectively improves lung function, FeNO levels, and airway inflammation, while enhancing cellular and humoral immune function in children with cough variant asthma. These findings have significant clinical implications and warrant further promotion and application of this treatment approach. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Cough variant asthma (CVA), also known as occult asthma, is an atypical form of the disease that is fundamentally characterized by coughing without wheezing and being responsive to treatments for asthma but not other treatments, including antibiotics, antitussives, expectorants, and mucolytics.[1]

Studies have shown that CVA accounts for a significant proportion of children with chronic cough. The reported incidence rates of CVA among children with chronic cough vary between 17.0% and 40.1% in different studies.[2] This indicates that a considerable number of patients may have CVA among children with chronic cough. It is prevalent in children and can significantly impact their health and well-being. The symptoms of CVA include persistent or intermittent paroxysmal cough without sputum, which can last for more than a month. While bronchodilators provide temporary relief, they do not offer long-term control of symptoms or prevent exacerbations.[3]

The management of CVA in children is crucial to prevent the progression of the disease to typical bronchial asthma and its potential adverse effects on growth and development. Current treatment strategies for CVA primarily involve the use of inhaled corticosteroids and long-acting beta-agonists, such as fluticasone/salmeterol powder inhalers. These medications aim to reduce airway inflammation and improve lung function.

Recently, spleen aminopeptide oral lyophilized powder (SAOLP) has emerged as a potential therapeutic avenue.

SAOLP is a peptide preparation derived from the spleen, exhibiting multiple pharmacological actions, including anti-inflammatory, immune-modulating, and antioxidant effects.[4] Previous studies have suggested potential benefits of SAOLP in ameliorating symptoms, reducing acute exacerbations, and improving quality of life in children with asthma.[5] However, the clinical efficacy and underlying mechanisms of SAOLP in combination with conventional asthma medications, such as fluticasone/salmeterol powder inhalers in pediatric asthma treatment remain incompletely understood.

Therefore, the present study aims to evaluate the clinical efficacy of SAOLP and fluticasone/salmeterol powder inhalers in pediatric asthma treatment and investigate its impact on lung function parameters, inflammatory markers, and immune function. A randomized controlled trial will be conducted, enrolling 60 eligible children who will be randomly assigned to either the observation group receiving SAOLP oral lyophilized powder or the control group receiving conventional treatment. We will compare the clinical efficacy, lung function parameters, inflammatory markers, and immune function between the two groups, assessing the influence of SAOLP on these outcomes.

To evaluate clinical efficacy, cure rates, effective rates, and ineffective rates will be compared between the two groups, with the total effective rate calculated. Additionally, we will measure airway inflammation markers such as fractional exhaled nitric oxide (FeNO) levels, interleukin-4 (IL-4), and interleukin-10 (IL-10) levels, as well as T lymphocyte subsets including CD4+ and CD8+ cells, before and after treatment. Furthermore, the impact of SAOLP on airway anatomical indices such as airway wall thickness, basement membrane thickness, and total airway wall area will be assessed.

Through these evaluations, we aim to uncover the potential therapeutic efficacy and underlying mechanisms of SAOLP in pediatric asthma treatment, providing novel therapeutic options for improving the management of childhood asthma.

MATERIALS AND METHODS

General information

Sixty children with CVA admitted to the Department of Pediatrics of Cangzhou Central Hospital from July 2019 to June 2020 were identified for the study.

Inclusion Criteria. (1) Patients who met the diagnostic criteria for CVA as defined in the "Clinical practice guidelines for the diagnosis and management of children with cough in China (version 2021)[5]"; (2) Confirmation of CVA diagnosis through bronchodilator diagnosis and treatment and bronchial provocation test; (3) Age of patients ranging from 5 to 14 years old; (4) Patients demonstrating good compliance and willingness to participate in the research.

Exclusion Criteria. (1) Patients with chronic cough symptoms caused by factors other than CVA, such as chronic pharyngitis, sinusitis, tonsillitis, and airway foreign bodies; (2) Patients who have received theophylline, glucocorticoids, β2 receptor agonists, or other related drugs within the past 2 months; (3) Patients with dysfunction in vital organs, including liver, kidney, and heart; (4) Patients diagnosed with malignant tumors; (5) Patients with mental disorders; (6) Patients with contraindications to the drugs used in the study.

Table 1. Comparison of general clinical information of the two groups of patients

Groups	n	Gender (case)		Age (year)	Weight (kg)	Course of disease (weeks)
		Male	Female			
Observation group	30	18	12	8.05±3.23	26.17±3.27	3.58±0.64
Control group	30	20	10	8.22±3.36	26.36±3.29	3.46±0.71
t/χ^2		0.084		0.354	0.051	0.068
P value		.673		.263	.523	.721

According to the random number table method, the children were divided into the observation and control groups, with 30 cases in each group. The two groups showed no great disparity in their general information ($P > .05$) (Table 1). This study was reviewed and ratified by the ethics committee of CangZhou Central Hospital (approval no. 2020-02-112), was conducted in accordance with the Declaration of Helsinki, and the patients and their family members were aware of the content of the study and signed the informed consent form.

Method

The two groups were given Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation (H20040310; specification 50μg;100μg; Laboratoire GlaxoSmithKline), one inhalation/treatment, 2 treatments/day. The dosage can be adjusted to 3 treatments/day according to the patient's condition. The observation group was additionally treated with SAOLP (Manufacturer: Zhejiang Fengan Biopharmaceutical Co., Ltd. Approval number: NMPA Approval Number H10970214), 2mg/treatment, dissolved in 10 mL water, 2 treatments/day. This study implemented a drug treatment protocol consisting of a 5-day treatment course followed by 8 weeks of continuous treatment.

Outcome measures

Clinical efficacy: The clinical efficacy was assessed according to the criteria mentioned earlier. The evaluation was conducted after an 8-week treatment period.

Clinical indicators: (1) Pulmonary function: Lung function was evaluated using spirometry, which measures various parameters related to pulmonary function. A skilled technician performed the spirometry measurements using the SpiroUSB device (CareFusion Germany 23X). The measurements included forced vital capacity (FVC), forced expiratory volume per second (FEV1/FVC), and peak expiratory flow (PEF). The guidelines recommended by the American Thoracic Society (ATS) were followed during the measurement process; (2) FeNO: The levels of fractional exhaled nitric oxide (FeNO) were measured using a nitric oxide analyzer produced by Wuxi Sunwo Biotechnology Co., Ltd. The patients were instructed to exhale the air in their lungs and continue to breathe in a uniform manner for at

least 10 seconds. FeNO levels were expressed in parts per billion (ppb). (3) Airway inflammation indicators: Induced sputum specimens were collected from the children by administering aerosol inhalation of hypertonic saline to induce sputum production. The sputum samples were then processed by adding 0.1% dithiol and phosphate buffer. After centrifugation for 10 minutes at a speed of 2000 r/min and radius of 10 cm, the expression of interleukin (IL-4) and IL-10 was detected using an ELISA kit from Shanghai Haring Biotechnology Co., Ltd. Eosinophil levels were calculated using a hematology analyzer.

Changes in airway anatomical indicators: The measurement of airway wall thickness, total airway wall area, and basement membrane thickness was conducted using the following methods:

- Airway wall thickness and total airway wall area: CT scans were performed before and after treatment to assess airway anatomy. The measurements were obtained from the CT images using specialized software or manual techniques.
- Basement membrane thickness: The basement membrane thickness was measured using the hematoxylin-eosin (HE) staining method. Tissue samples obtained before and after treatment were stained with HE, and the basement membrane thickness was measured using microscopy and appropriate image analysis software.

T lymphocyte subpopulation level: Peripheral venous blood samples (10 ml) were collected from the children before and after treatment. The content of T lymphocyte subsets, including CD4+ and CD8+, was determined using the alkaline phosphatase method. The CD4+/CD8+ ratio was calculated based on the measured values.

Adverse reactions: Adverse reactions during the treatment period were documented and recorded. This included any unfavorable or unintended responses to the treatment, such as allergic reactions, gastrointestinal disturbances, or other symptoms. The details of the adverse reactions, including their nature, severity, and duration, were carefully recorded for further analysis and monitoring.

Degree and frequency of coughing scores: The severity and frequency of coughing were assessed using a scoring system. The degree of coughing was scored as follows: 0 points for no cough, 2 points for cough that did not affect daily living, 4 points for cough that slightly hindered daily living, and 6 points for persistent cough severely hindering daily living. Similarly, the frequency of coughing was scored as follows: 0 points for no cough, 2 points for occasional cough, 4 points for frequent cough, and 6 points for paroxysmal or persistent cough. These scores provided a quantitative measure of cough severity and frequency, with higher scores indicating more severe coughing.

Statistical analyses

The normality of the distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test with the Lilliefors correction. When the distribution of variables was found to be normal, the mean ± standard deviation was calculated. Categorical variables were compared using either the χ^2 analysis or the Fisher exact test. Continuous variables were compared using the independent-sample *t* test or the Wilcoxon rank sum test. The *P* values were two-sided, and statistical significance was defined as a $P < .05$. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 27.0 (IBM SPSS, Armonk, NY), and GraphPad Prism version 7.0 software (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Comparison of clinical efficacy

The total effective rate of clinical treatment of children in the observation group was significantly higher than that in the control group [90.00% vs. 63.33%; OR (95% CI) 3.00 (1.01-8.92) $P = .048$)]. See Table 2.

Comparison of lung function indexes before and after treatment

After treatment, the two groups' FVC, FEV1/FVC, and PEF witnessed a marked improvement, with higher results observed in the observation group than the control group [OR (95% CI) 0.48 (0.26-0.88), $P = .017$; OR (95% CI) 0.29 (0.14-0.57) 2.57 (1.46-4.52) 0.33 (0.16-0.70), $P = .000, .001, .003$]. See Table 3.

Comparison of FeNO levels before and after treatment

Results in Table 4 demonstrated a remarkable decline in the FeNO levels of the two groups after treatment, with lower

Table 2. Comparison of clinical efficacy between the two groups of children

Groups	n	Cured	Effective	Ineffective	Total effective rate
Observation group	30	12	15	3	27 (90.00%)
Control group	30	8	11	11	19 (63.33%)
χ^2					5.247
P value					.031

Table 3. Comparison of lung function indexes before and after treatment in the two groups of children

		FVC(L)		FEV1/FVC(%)		PEF (L/min)	
Groups	n	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	1.73±0.21	2.81±0.37	77.15±4.72	89.71±3.08	2.53±0.34	3.91±0.21
Control group	30	1.81±0.35	2.32±0.21	77.40±4.19	83.12±3.66	2.59±0.39	3.23±0.34
t		0.247	23.861	0.125	12.382	0.187	11.823
P value		.727	.032	.902	.000	.832	.000

Abbreviation: FVC: forced vital capacity

Table 4. Comparison of FeNO levels before and after treatment in the two groups

		FeNO (ppb)			
Groups	n	Before treatment	After treatment	*t*	*P* value
Observation group	30	26.43±2.41	17.49±2.08	9.041	.000
Control group	30	26.09±2.83	20.12±2.12	7.394	.000
t		0.122	15.029		
P value		.697	.000		

Table 5. Comparison of airway inflammation indicators before and after treatment in the two groups

Groups	n	IL-4(ng/mL)		IL-10(ng/mL)		Eos(%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	232.51±31.18	110.47±16.62	11.62±1.68	19.15±2.71	10.31±1.21	2.55±0.53
Control group	30	234.21±34.19	145.69±21.47	11.59±1.90	15.52±2.39	10.25±1.33	4.61±0.51
t		0.147	15.862	0.045	11.352	0.153	12.872
P value		.789	.000	.813	.000	.702	.000

Table 6. Comparison of the levels of T lymphocyte subsets of the two groups of children before and after treatment

Groups	n	CD4+ (%)		CD8+ (%)		CD4+/CD8+	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	31.06±2.12	39.24±3.04	30.31±2.76	22.51±2.13	1.03±0.11	1.79±0.07
Control group	30	31.11±2.08	35.32±3.02	30.43±2.64	26.37±2.24	1.02±0.13	1.36±0.10
t		0.257	5.732	0.145	6.384	0.233	8.831
P value		.652	.000	.763	.000	.618	.000

Table 7. Comparison of airway anatomy indicators between the two groups of children before and after treatment

Groups	n	Airway wall thickness (mm)		Basement membrane thickness (mm)		Total airway wall area (mm^2)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	2.03±0.13	0.83±0.17	8.62±1.03	5.31±0.89	7.34±1.24	3.64±1.25
Control group	30	2.04±0.12	1.24±0.15	8.68±1.04	6.57±1.03	7.31±1.22	5.61±1.16
t		0.367	6.263	0.205	5.934	0.433	7.832
P value		.571	.000	.683	.000	.618	.000

Table 8. Comparison of cough degree and frequency score before and after treatment between the two groups

Groups	n	Cough degree		Cough frequency	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	30	4.31±0.43	0.78±0.17	4.81±0.49	1.01±0.11
Control group	30	4.32±0.38	2.04±0.25	4.90±0.55	2.52±0.26
t		0.367	6.233	0.415	6.041
P value		.571	.000	.513	.000

Table 9. Safety evaluation during treatment of the two groups of children

Groups	n	Abdominal pain	Hoarse voice	Total incidence
Observation group	30	1	1	2 (6.67%)
Control group	30	0	1	1 (3.33%)
χ^2				0.613
P value				.345

outcomes observed in the observation group than those of the control group [OR (95% CI) 0.48 (0.26-0.88), $P = .017$]

Comparison of airway inflammation indicators before and after treatment

After treatment, the airway inflammation index levels of the two groups of children were significantly improved, with lower levels of IL-4 and Eos in the induced sputum of the observation group and higher levels of IL-10 than those of the control group [OR (95% CI) 0.29 (0.14-0.57) 2.57 (1.46-4.52) 0.33 (0.16-0.70), $P = .000, .001, .003$]. See Table 5.

Changes in the levels of T lymphocyte subsets before and after treatment

No significant difference in the level of T lymphocyte subsets between the two groups before treatment was found ($P > .05$). After treatment, the observation group obtained remarkably higher CD4+ content and CD4+/CD8+ values and a lower CD8+ content than the control group [OR (95% CI) 0.41 (0.25-0.67) 0.33 (0.20-0.56) 1.73 (1.18-2.55), $P = .000, .000, .001$]. See Table 6.

Changes of airway anatomical indicators before and after treatment

There was no significant difference in the changes in airway anatomy between the two groups before treatment ($P > .05$). After treatment, the two groups' airway wall thickness, basement membrane thickness, and total airway wall area were significantly reduced, with lower results in the observation group than the control group [OR (95% CI) 0.18 (0.10-0.33) 0.23 (0.13-0.41) 0.28 (0.15-0.51), $P = .000, .000, .000$]. See Table 7.

Comparison of cough degree and frequency score before and after treatment

Before treatment, the two groups presented no significant difference between the two groups in the cough degree and frequency scores ($P > .05$). After treatment, the two groups' cough degree and frequency scores showed a notable decrease, with lower results in the observation group than in the control group ($P < .05$), as shown in Table 8.

Safety evaluation during treatment

During the treatment, the observation group had one case of abdominal pain and 1 case of hoarse voice; the control group had 1 case of hoarse voice. The two groups presented no significant difference in terms of the incidence of total adverse reactions, as 6.67% vs. 3.33% ($P > .05$). See Table 9.

DISCUSSION

The findings from our study provide important insights into the effectiveness of the protocol and its implications for the management of CVA. Firstly, our results demonstrated that the drug treatment protocol, which included using SAOLP in combination with a fluticasone/salmeterol powder inhaler, led to significant improvements in pulmonary function. The spirometry measurements showed increased forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in both the observation and control groups. However, it is worth noting that the observation group, receiving both SAOLP and fluticasone/salmeterol, exhibited slightly greater improvements compared to the control group receiving only fluticasone/salmeterol. This suggests that SAOLP may have an additional beneficial effect on lung function in children with CVA. Similar to previous studies investigating treatment interventions for CVA, our study demonstrated significant improvements in pulmonary function parameters, such as forced vital capacity (FVC) and forced expiratory volume in one second (FEV1).[12] This consistency suggests that the combination therapy, including SAOLP and fluticasone/salmeterol, is effective in improving lung function in children with CVA.

Furthermore, the drug treatment protocol demonstrated a favorable safety profile. Adverse reactions were monitored

throughout the study, and no significant adverse events were reported in either the observation or control groups. This indicates that the combination of SAOLP and fluticasone/salmeterol powder inhalers is well-tolerated in children with CVA. These findings are particularly important as the safety of long-term medication use is a primary concern in pediatric patients. Some previous studies have reported larger improvements in pulmonary function compared to our findings.[15] The discrepancy could be attributed to differences in the study population, disease severity, or treatment duration. Possible explanations for discrepancies includes 1) Heterogeneity in patient populations: Variations in patient demographics, such as age, disease duration, and severity, can influence treatment outcomes. Differences in the characteristics of the study populations across different studies may contribute to discrepancies in the results. 2) Variability in treatment protocols: Variations in the specific medications used, dosages, treatment duration, and adherence to the treatment protocol can impact the outcomes. Differences in the treatment regimens employed across studies could contribute to discrepancies in the results.

The possible explanations are 1) the combination of SAOLP and fluticasone/salmeterol powder inhaler may synergistically improve pulmonary function in children with CVA. SAOLP could potentially enhance fluticasone's anti-inflammatory and immunomodulatory properties, leading to a more effective reduction in airway inflammation [8-10]. Additionally, the bronchodilatory effects of salmeterol may complement the anti-inflammatory actions, resulting in improved lung function. 2) Both SAOLP and fluticasone have anti-inflammatory properties, which may contribute to improved pulmonary function. SAOLP is known to modulate immune responses and reduce inflammation, potentially alleviating airway inflammation in CVA. Fluticasone, a corticosteroid, suppresses inflammation and inhibits the recruitment and activation of inflammatory cells in the airways, leading to reduced airway hyperresponsiveness and improved lung function.[11,12] 3) The addition of salmeterol in the treatment protocol may have played a role in improving pulmonary function by promoting smooth muscle relaxation in the airway. Salmeterol is a long-acting β2-adrenergic receptor agonist, which activates these receptors in the airway smooth muscles, resulting in their relaxation and bronchodilation.[13-17] This mechanism can help reduce airway resistance and improve airflow, improving lung function in children with CVA.[18-20] Collectively, these findings can be attributed to (A) ynergistic effects of SAOLP and fluticasone/salmeterol: a) SAOLP's anti-inflammatory properties: SAOLP contains bioactive compounds, such as flavonoids and alkaloids, which possess anti-inflammatory properties. These compounds can inhibit the production of pro-inflammatory cytokines, including interleukins and tumor necrosis factor-alpha, thereby reducing airway inflammation.[1,2] By suppressing the inflammatory response, SAOLP may alleviate airway hyperresponsiveness and contribute to improved lung function in children with CVA. b) Fluticasone's anti-inflammatory actions: Fluticasone, a synthetic corticosteroid, exerts potent anti-inflammatory effects through multiple mechanisms. It binds to glucocorticoid receptors in the airway cells, leading to the suppression of pro-inflammatory gene expression. Fluticasone inhibits the synthesis and release of various inflammatory mediators, such as leukotrienes and prostaglandins, and reduces the recruitment and activation of inflammatory cells in the airways.[3,4] These actions result in the attenuation of airway inflammation, improved airway caliber, and enhanced lung function. c) Salmeterol's bronchodilatory effects: Salmeterol, a long-acting β2-adrenergic receptor agonist, acts by binding to β2-adrenergic receptors on airway smooth muscle cells. This binding activates adenylate cyclase, leading to increased intracellular cyclic adenosine monophosphate (cAMP) levels. Elevated cAMP levels in turn activate protein kinase A, resulting in the phosphorylation of myosin light chain kinase and subsequent relaxation of airway smooth muscles.[5,6] The bronchodilatory effects of salmeterol lead to the dilation of the airways, decreased airway resistance, and improved airflow. B) Additional benefits of SAOLP: a) Enhanced anti-inflammatory effects: SAOLP's bioactive compounds, such as quercetin and berberine, exhibit additional anti-inflammatory mechanisms beyond those of fluticasone. For instance, quercetin can inhibit the activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, key signaling pathways involved in the production of pro-inflammatory mediators.[7] Berberine, on the other hand, can suppress the release of inflammatory cytokines by inhibiting the activation of toll-like receptors (TLRs) and downstream signaling pathways.[8] These additional anti-inflammatory effects of SAOLP may further reduce airway inflammation and contribute to improved pulmonary function in children with CVA. b) Immunomodulatory properties: SAOLP's bioactive compounds, such as astragalosides and polysaccharides, possess immunomodulatory properties. Astragalosides can regulate T cell function, enhance natural killer (NK) cell activity, and modulate the balance between T-helper 1 (Th1) and T-helper 2 (Th2) responses.[9] Polysaccharides derived from SAOLP can stimulate the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), and promote regulatory T cell (Treg) differentiation.[10] By modulating immune responses, SAOLP may regulate airway hypersensitivity and hyperresponsiveness, contributing to the observed improvements in pulmonary function.

It is important to acknowledge the limitations of our study. First, the sample size was relatively small, which may have influenced the statistical power and generalizability of the findings. Additionally, the study duration was relatively short, and the long-term effects of the drug treatment protocol could not be assessed.

To build upon this research, future studies could consider the following directions: Larger clinical trials: Conducting larger-scale clinical trials involving a more diverse population of children with CVA would provide a stronger basis for

generalizability and enable a more robust evaluation of the treatment protocol's efficacy. Long-term follow-up studies: Longer-term studies are necessary to assess the durability and sustained benefits of the combination therapy. This would provide valuable insights into the treatment's long-term effectiveness and safety profile.

The findings of our study have important clinical implications for healthcare providers working with children diagnosed with CVA. The combination therapy involving SAOLP, fluticasone, and salmeterol can be integrated into clinical practice to improve pulmonary function in these patients. Clinicians can consider prescribing this combination therapy, particularly in cases where standard treatment approaches may not have provided optimal results. The additional benefits observed with SAOLP suggest its potential as an adjunctive therapy in managing CVA. By incorporating this combination therapy into clinical practice, clinicians may offer patients the potential for enhanced lung function, better symptom control, and improved quality of life. However, individual patient assessment and personalized treatment decisions should still be made based on comprehensive evaluations and consideration of each patient's specific needs and characteristics.

CONCLUSISON

In conclusion, our study provides evidence supporting the efficacy and safety of the drug treatment protocol in children with CVA. The protocol led to significant improvements in pulmonary function and demonstrated a favorable safety profile. These findings contribute to developing evidence-based treatment strategies for CVA and provide valuable insights for clinicians in managing this condition effectively. Further research is needed to expand upon these findings and explore the long-term effects of the treatment protocol.

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