

Original Article

Aerosol inhalation of ambroxol hydrochloride combined with terbutaline can promote recovery of children with severe pneumonia

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Received December 9, 2020; Accepted January 21, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Objective: This research aimed to investigate the clinical efficacy of aerosol inhalation of ambroxol hydrochloride combined with terbutaline on children with severe pneumonia, and to evaluate its influence on their immune function and inflammatory level. Methods: Totally 113 severe pneumonia children were included. Thereinto, 55 children in the control group (CG) were treated with terbutaline aerosol inhalation, while 58 in the research group (RG) were given ambroxol hydrochloride on the basis of the CG. Their symptom alleviating time, blood gas parameters, adverse reactions during treatment, clinical efficacy, immune function and inflammatory factors were compared. Results: The time of fever clearance time, disappearance of cough and pulmonary rates, chest shadow absorption and hospitalization of children in the RG were shorter than those in the CG. The combined treatment did not increase additional adverse reactions; instead, its effective rate was markedly higher than that in the CG. Further research found that after treatment, the arterial partial pressure of oxygen (PaO_2), oxygenation index (OI), CD4+ and CD4+/CD8+, and interleukin-10 (IL-10) levels were dramatically increased, while the arterial partial pressure of carbon dioxide (PaCO_2), C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-17 (IL-17) and CD8+ levels were obviously increased. In addition, these indexes of children in the RG were obviously better than those in the CG. Conclusion: Aerosol inhalation of ambroxol hydrochloride combined with terbutaline has a remarkable clinical efficacy on children with severe pneumonia, which can improve their immune function and reduce inflammatory reaction.

Keywords: Severe pneumonia, children, ambroxol hydrochloride, terbutaline, immune function, inflammatory level

Introduction

Pneumonia is the main infectious disease and cause of death of children aged 1-59 months [1]. Since 2000, although the mortality of pneumonia among children in the world has been greatly reduced, about 920,000 children under 5 years old still died of it in 2015 [2]. In pneumonia, 7-13% cases are severe enough to require hospitalization, and some serious cases even need to be transferred to pediatric intensive care unit (PICU) [3]. Severe pneumonia has acute onset and dangerous condition, which can cause respiratory distress, heart failure, multiple organ failure and other complications, and even death [4]. Thus, it is critical to treat children with severe pneumonia promptly and effectively.

In recent years, the clinical treatment of severe pneumonia in children mostly uses antiviral

and antibiotic drugs [5]. Immunodeficiency in children with severe pneumonia is mainly related to the production of pathogenic bacteria and excessive release of inflammatory factors [6]. There are some limitations in clinical medication. The effect of using only one drug may be poor, and most of them are intervened by comprehensive therapy [7]. Ambroxol hydrochloride, as an expectorant clinically, can promote the dissolution of viscous secretions and synthesize surface active substances. So, it is suitable for chronic and acute respiratory diseases accompanied by abnormal secretion of sputum and poor expectoration function [8]. Terbutaline is a kind of inhaled glucocorticoid preparation, which is an effective drug to control airway inflammation, and can suppress the release of inflammatory cells and reduce respiratory resistance [9]. A previous research has reported the application of ambroxol hydrochloride

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ride and terbutaline in airway diseases. For example, Liu *et al.* reported that the combined treatment of ambroxol hydrochloride and N-acetylcysteine could improve the immune function of children with bronchopneumonia and quickly relieve their clinical symptoms [10]. Doymaz *et al.* thought that the overall infusion of terbutaline was well tolerated in the treatment of acute severe asthma in children with no irreversible adverse reactions [11]. However, the application of aerosol inhalation of ambroxol hydrochloride combined with terbutaline in children with severe pneumonia and its effect on inflammatory response and immune function have not been studied.

In this research, we used these two drugs to treat severe pneumonia, and evaluated their clinical effects, adverse reactions and effects on inflammatory level.

Materials and methods

General data

This research was approved by the Ethics Committee of our hospital. Guardians of all children were informed of the experimental contents and an informed consent form was signed. Totally 113 severe pneumonia children admitted to Linyi Central Hospital from August 2017 to June 2020 were included. Inclusion criteria were as follows: After laboratory examination, the imaging diagnosis was severe pneumonia [12]; those were 1-14 years old. Exclusion criteria were as follows: those combined with other respiratory diseases, malignancies or other organ damage; congenital heart disease; children who were allergic to the drugs used; children who used bronchodilators, hormones and immunosuppressants 7 days before treatment.

Treatment methods

Totally 113 children were given anti-infection, antipyretic, expectorant, antitussive and balanced positive electrolyte symptomatic basic treatment. In the CG, 55 children were treated with terbutaline aerosol inhalation: 2 mL normal saline was fused with 2.5 g terbutaline (AstraZeneca AB, Sweden, H20140108), and aerosol inhalation was driven by oxygen, lasting for 10 min, twice a day. In the RG, 58 children were given ambroxol hydrochloride injection (Shijiazhuang Penghai Pharmaceutical Co.,

Ltd., China, H20153133), and 15 mg was mixed with 50 mL 10% glucose solution, and then given intravenous drip twice a day. All patients were treated for 2 weeks.

Efficacy evaluation

Shi *et al.* [13] evaluated the treatment efficacy of children. Specifically, results can be divided into the following three situations: cured: Children's symptoms and signs disappeared completely, and chest X-ray and blood routine examination were normal; improved: Children's symptoms and signs improved, and the shadow of chest X-ray examination was obviously absorbed; ineffective: Children's symptoms, signs and chest X-ray examination were not improved or even worsened. (cured + improved) cases/total cases \times 100% = total effective rate.

Outcome measures

The relief time of symptoms was observed, including fever clearance time, disappearance time of cough and pulmonary rales and chest shadow absorption. Their hospitalization time and adverse reactions during treatment were recorded. The arterial partial pressure of oxygen (PaO₂), the arterial partial pressure of carbon dioxide (PaCO₂) and oxygenation index (OI) were measured by PL2200 blood gas analyzer (Beijing Perlong New Technology Co., Ltd., China), and CD4+, CD8+ ratio and CD4+/CD8 in peripheral blood of children before and after treatment were measured by Attune NxT flow cytometry (Thermo Fisher Scientific (China) Co., Ltd.). The levels of c-reactive protein (CRP) (ZN2120-RHP), interleukin-6 (IL-6) (ZN2272-PIU), interleukin-10 (IL-10) (ZN2237-JLU) and interleukin-17 (IL-17) (ZN2248-DYW) in serum before and after treatment were tested by ELISA in the light of the kit instructions [14]; the kits were purchased from Beijing Bioeasy Biotechnology Co., Ltd. (China). Blank, reaction and standard holes were set up. Totally 50 μ L diluted standard substance and 50 μ L biotin-labeled antibody were added to the reaction and standard holes. After they were cultivated for 1 h and washed for 3 times, 80 μ L streptavidin was added and incubated continually for 30 min. After that, substrate was added and cultivated for 10 min, and 50 μ L stopping solution was added for color development in the dark. The levels of CRP, IL-6, IL-10 and IL-17 were

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Table 1. Baseline data of two groups of children

Clinical data	Control group (n=55)	Research group (n=58)	χ^2/t	P
Gender			0.191	0.662
Male	30 (54.55)	34 (58.62)		
Female	25 (45.45)	24 (41.38)		
Age (years)	3.62±1.71	3.57±1.85	0.149	0.882
Course of disease (d)	5.81±1.56	5.72±1.67	0.296	0.768
Place of residence			0.659	0.417
Cities	46 (83.64)	45 (77.59)		
Countryside	6 (16.36)	13 (22.41)		
Chest imaging lesions			0.597	0.742
Left lung	2 (3.64)	4 (6.90)		
Right lung	3 (5.45)	3 (5.17)		
Double lungs	50 (90.91)	51 (87.93)		
Electrolyte disturbance			0.051	0.822
No	39 (70.91)	40 (68.97)		
Yes	16 (29.09)	18 (31.03)		
Hyperpyrexia			0.140	0.708
No	19 (34.55)	22 (37.93)		
Yes	36 (65.45)	36 (62.07)		
Pant			0.090	0.764
No	25 (45.45)	28 (48.28)		
Yes	30 (54.55)	30 (51.72)		

determined by HBS-1101 enzyme-mark analyzer (NanJing DeTie Laboratory Equipment Co., Ltd., China).

Statistical methods

The research data were statistically analyzed via SPSS 24.0 (SPSS Inc., Chicago, IL, the States), and the pictures were drawn via GraphPad Prism 6. There were statistical differences when $P < 0.05$. The measurement data were represented as mean \pm SEM. The inter-group comparison was assessed via t-test, and the intra-group comparison before and after treatment was evaluated through paired-samples t test. The counting data were expressed by [n (%)]. The inter-group comparison was analyzed through Chi-square test; Fisher test was performed when theoretical frequency was less than 5.

Results

Baseline data

We collected and compared the clinical data of two groups of children. There was no difference

in baseline data of gender, age, course of disease and place of residence between the RG and the CG ($P > 0.05$) (**Table 1**).

Blood gas parameters of children before and after treatment

We observed the changes of blood gas parameters (PaO_2 , PaCO_2 and OI) before and after treatment. There was no marked change between the two groups before treatment ($P > 0.05$) (**Figure 1**). After treatment, PaO_2 and OI increased ($P < 0.001$), while PaCO_2 decreased ($P < 0.001$). What's more, PaO_2 and OI in the RG were higher than those in the CG ($P < 0.001$), and PaCO_2 was lower ($P < 0.001$).

Relief time of symptoms in children

During the whole treatment period, the disappearance time of clinical symptoms was observed. The fever clearance time, the disappearance time of cough and pulmonary rales, chest shadow absorption and hospital

stays in the RG were shorter than those in the CG ($P < 0.05$) (**Table 2**).

Adverse reactions

The adverse reactions of children during treatment were observed. In the CG, there were 2 cases of rash, 1 of pruritus and 1 of diarrhea, and the incidence of adverse reactions was 7.27% (**Table 3**). In the RG, there were 4 cases of rash, 2 of pruritus and 1 of diarrhea, and the incidence of adverse reactions was 12.07%. There was no remarkable difference in the incidence of adverse reactions between the two groups during treatment ($P > 0.05$).

Clinical efficacy of children

We compared the therapeutic effects of two groups of children. After treatment, 24 children in the CG were cured and 20 were improved, and the effective rate of treatment was 80.00%. In the RG, 39 cases were cured, 15 were improved, and the effective rate was 93.10%. Statistical analysis manifested that the effective rate of the RG was dramatically higher than that of the CG ($P < 0.05$) (**Table 4**).

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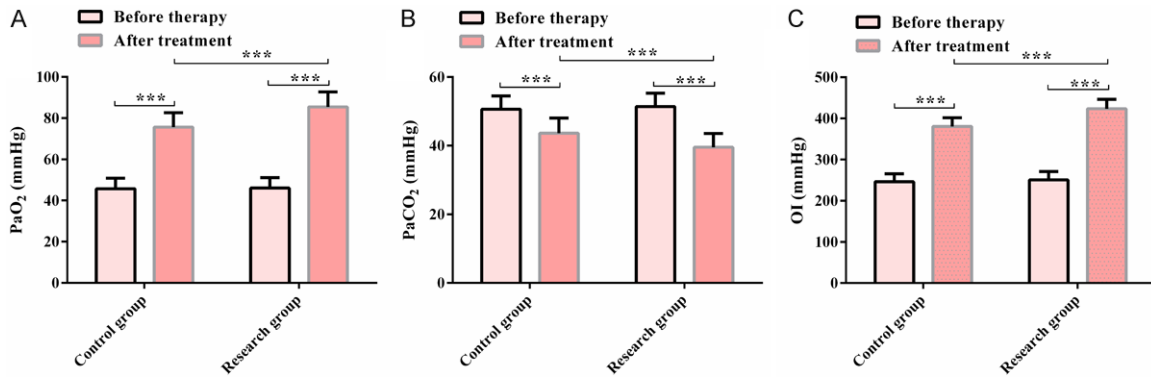


Figure 1. Changes of blood gas parameters of two groups of children before and after treatment. PaO₂ (A), PaCO₂ (B) and OI (C) are assessed via blood gas analyzer. After treatment, PaO₂ and OI increase, while PaCO₂ decreases. Furthermore, PaO₂ and OI in the RG are higher than those in the CG, and PaCO₂ is lower. Note: ***P<0.001.

Table 2. Comparison of disappearance time of symptoms between the two groups

Symptoms	Control group (n=55)	Research group (n=58)	χ^2	P
Fever clearance time (d)	5.02±1.15	4.17±0.94	4.312	<0.001
Disappearance time of cough (d)	6.13±1.96	5.31±1.73	2.361	0.020
Disappearance time of pulmonary rales (d)	6.51ppear	5.07ppear	4.844	<0.001
Chest shadow absorption	9.85t sha	8.08t sha	6.592	<0.001
Hospital stays (d)	11.45tal s	10.15tal s	4.484	<0.001

Table 3. Incidence of adverse reactions in two groups of children during treatment

Adverse reactions	Control group (n=55)	Research group (n=58)	χ^2	P
Rash	2 (3.64)	4 (6.90)	0.124	0.724
Pruritus	1 (1.82)	2 (3.45)	0.002	0.963
Diarrhea	1 (1.82)	1 (1.72)	0.001	0.970
Total incidence rate (%)	7.27	12.07	0.739	0.390

Table 4. Comparison of clinical efficacy of two groups of children

Treatment efficacy	Control group (n=55)	Research group (n=58)	χ^2	P
Recovery	24 (43.64)	39 (67.24)	-	-
Improved	20 (36.36)	15 (25.86)	-	-
Ineffective	11 (20.00)	4 (6.90)	-	-
Effective rate of treatment (%)	80.00	93.10	4.210	0.040

Changes of inflammatory factors in children before and after treatment

Before and after treatment, we detected the levels of CRP, IL-6, IL-10 and IL-17 in children's serum by ELISA. Before treatment, the levels of CRP, IL-6, IL-10 and IL-17 in serum of both groups had no marked change (P>0.05). After

treatment, the serum CRP, IL-6 and IL-17 levels decreased in varying degrees (P<0.001), while the serum IL-10 level increased (P<0.001). In addition, the serum CRP, IL-6, and IL-17 in the RG decreased, but IL-10 increased (P<0.001), which was different from that in the CG (P<0.001) (**Figure 2**).

Changes of immune function of children before and after treatment

We observed the changes of immune function indexes (CD4+, CD8+, CD4+/CD8+) before and after treatment. Before treatment, there was no obvious difference in peripheral blood between both groups (P>0.05). After treatment, CD4+ and CD4+/CD8+ in peripheral blood of children increased (P<0.001), while CD8+ decreased (P<0.001). Besides, CD4+ and CD4+/CD8+ in peripheral blood of children in the RG were higher than those in the CG

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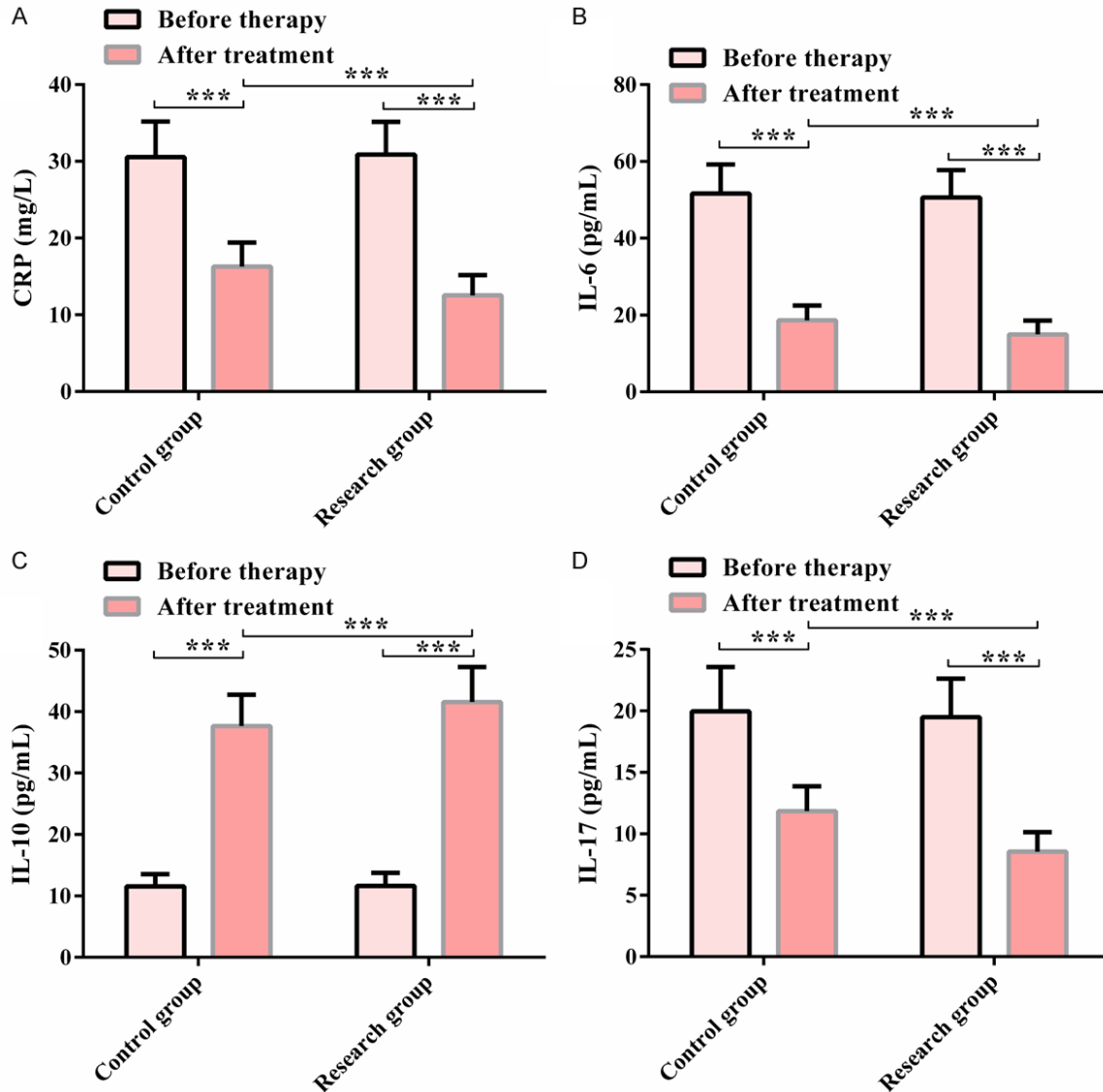


Figure 2. Changes of serum CRP, IL-6, IL-10 and IL-17 levels of children in both groups before and after treatment. After treatment, the serum CRP (A), IL-6 (B), and IL-17 (D) levels of the two groups decrease in varying degrees, but the serum IL-10 level increases (C). The serum CRP, IL-6, IL-17 levels in the RG decrease obviously, while IL-10 level increases ($P < 0.001$). Note: *** $P < 0.001$.

($P < 0.001$), and CD8⁺ was remarkably lower ($P < 0.001$) (Figure 3).

Discussion

Severe pneumonia is still a kind of infectious disease with high mortality in children, which can cause respiratory failure and lung injury, posing a great threat to their life and health [15]. In this research, we used aerosol inhalation of ambroxol hydrochloride combined with terbutaline to treat children with severe pneumonia, and achieved ideal efficacy. In addition,

the combined use of the two drugs can improve the immune function of children and prevent the excessive release of inflammatory factors.

Ambroxol hydrochloride is a common expectorant, which can reduce sputum and accelerate sputum excretion. It also has antioxidant capacity, preventing active groups from attacking lung tissue [16]. Terbutaline is often used in the treatment of airway diseases such as bronchial asthma, which can promote the relaxation of bronchial smooth muscle and enhance the activity of mucosal cilia [17]. After treating chil-

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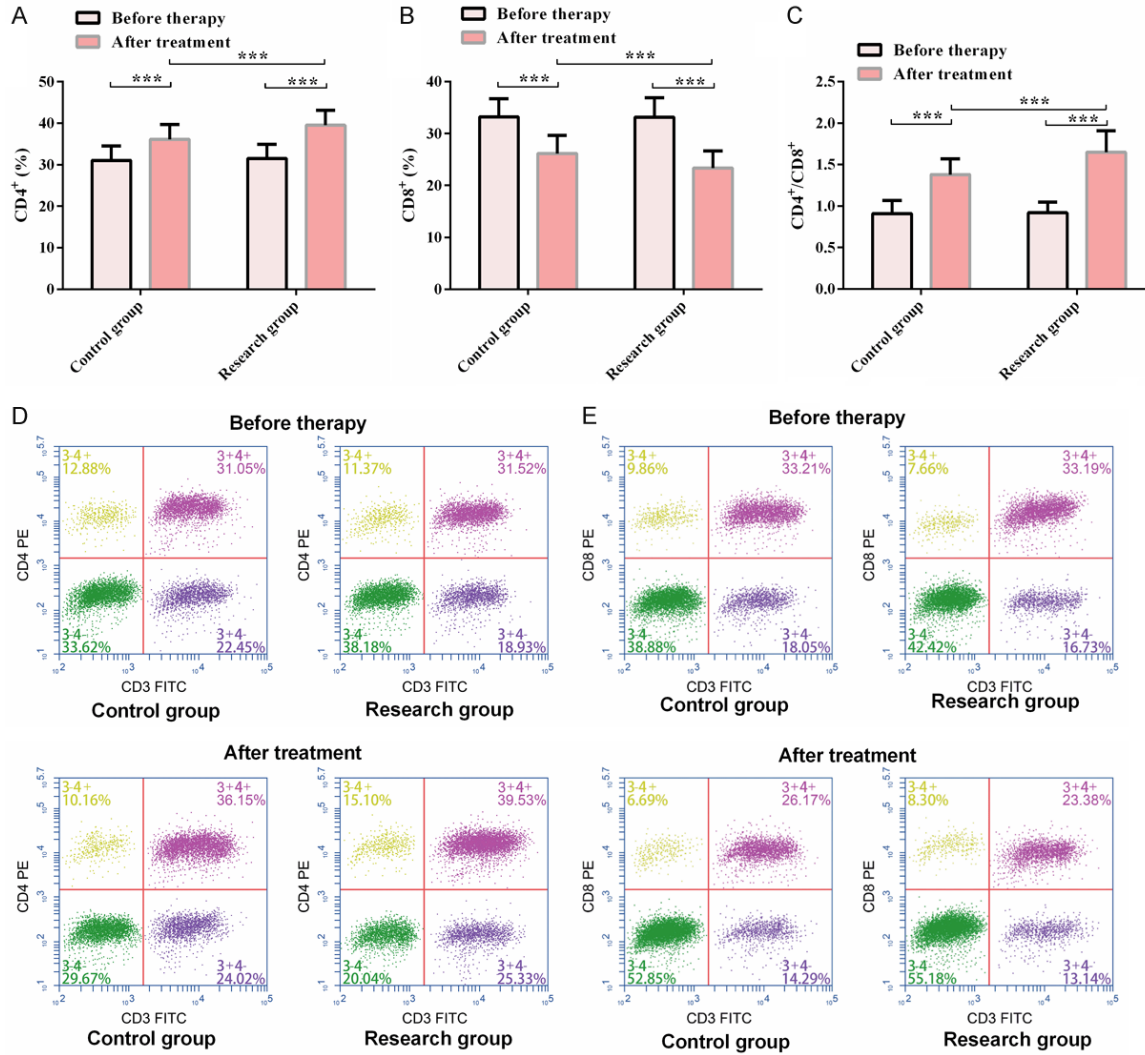


Figure 3. Changes of immune function indexes of children in both groups. The levels of CD4+ (A), CD8+ (B) and CD4+/CD8+ (C) are measured by flow cytometry. After treatment, CD4+ and CD4+/CD8+ in peripheral blood of children in both groups increase, while CD8+ decrease. Furthermore, CD4+ and CD4+/CD8+ in peripheral blood of children in the RG are higher than those in the CG, and CD8+ is markedly lower. Flow cytometry (D, E). Note: ***P<0.001.

dren with severe pneumonia with these two drugs, we found that they could quickly relieve the clinical symptoms of children, with an effective rate of 93.10%, improving the blood gas parameters and promote the recovery of illness. Paleari *et al.* reported [18] that ambroxol not only had strong anti-inflammatory, anti-oxidation and surface active substance synthesis activities, but also showed some antiviral and antibacterial activities, having a good therapeutic potential in children's respiratory diseases. While Wang *et al.* proposed [19] that the administration of atomized terbutaline and budesonide reduced the acute lung injury

caused by chlorine gas, and the combined treatment were more effective than using either drug alone. Similarly, we treated children with aerosol inhalation of terbutaline and ambroxol hydrochloride, achieving better efficacy. Additionally, the combined use of the two drugs did not increase much of the adverse reactions of children. Hence, it is safe.

Because children with severe pneumonia, their respiratory, circulatory and immune functions may not develop well, which will cause the risk of excessive release of inflammatory mediators, inhibits immune defense and aggravates

lung damage [20]. In the pathogenesis of severe pneumonia, the body can release a large number of inflammatory mediators, such as CRP, IL-6, and IL-17, which triggers inflammatory cascade reaction, causing secondary damage to lung tissue and systemic inflammatory reaction [21, 22]. L-10 has strong anti-inflammatory and immunosuppressive activities. Recently, its unique two-way immunomodulatory effect has become a research hotspot [23]. Previously, a report has shown that the immune function of the body can be obtained by detecting CD4+, CD8+ and other immune states [24]. Our further research revealed that aerosol inhalation of ambroxol hydrochloride combined with terbutaline can improve the immune function and suppress the inflammatory reaction in critically ill children. Similar to our research, Yang *et al.* thought that ambroxol treatment of neonatal pneumonia can improve lung function indexes and reduce the expression of inflammatory factors [25]. It may be because ambroxol hydrochloride has antioxidant effect that can reduce the release of less inflammatory mediators in children [26], and terbutaline can relieve bronchial smooth muscle and reduce airway resistance [27]. Combined use can reduce the inflammatory reaction of lung tissue and the high reactivity of airway, improving efficacy on children. Although our research signifies the feasibility of two drugs in treating children with severe pneumonia, there are still limitations. For one thing, it is not clear how ambroxol hydrochloride and terbutaline affect the lung function of severe pneumonia. For another, the mechanism of action in severe pneumonia animal model has not been studied. These shortcomings need to be further supplemented in the future.

Our research shows that aerosol inhalation of ambroxol hydrochloride combined with terbutaline has a remarkable clinical efficacy on children with severe pneumonia, thus improving their immune function and reducing inflammatory reaction.

Disclosure of conflict of interest

None.

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