Original Article

Efficacy of phentolamine combined with ambroxol aerosol inhalation in the treatment of pediatric severe pneumonia and its effect on serum IL-10 and CRP levels

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Background: The aim of the present study was to determine the therapeutic effect of phentolamine combined with Ambroxol aerosol inhalation on pediatric severe pneumonia and its effect on serum interleukin-10 (IL-10) and C-reactive protein (CRP) levels.

Methods: Eighty-five children with severe pneumonia treated in our hospital from November 2019 to November 2020 were selected as the research participants, and were divided into the routine group (n=41) and treatment group (n=44) according to odd and even admission numbers, respectively. Children in the first group received routine treatment, namely symptomatic treatment such as cough relief (e.g., expectorant) and defervescence, while those in the second group received phentolamine combined with Ambroxol aerosol inhalation. Clinical indexes of both groups before and after treatment were analyzed to determine the therapeutic effect of different treatment methods and serum IL-10 and CRP level changes.

Results: There was no significant difference in general clinical data between the 2 groups (P>0.05). The duration of cough, fever, abnormal lung sound and lung shadow, and hospitalization time in the treatment group was significantly shorter than those in the routine group (P<0.001). The total clinical effective rate in the treatment group was significantly higher than that in the routine group (P<0.05). Forced vital capacity and peak expiratory flow rate levels were higher in both groups after treatment (P<0.05), and these were higher in the treatment group compared with the routine group after treatment (P<0.05). Serum IL-10 and CRP levels at T1 (2 days after treatment), T2 (5 days after treatment), and T3 (7 days after treatment) in the treatment group were significantly lower than those in the routine group (P<0.001). The total incidence of adverse reactions in the treatment group was significantly lower than that in the routine group (P<0.05).

Conclusions: Phentolamine combined with Ambroxol aerosol inhalation can significantly improve the clinical symptoms of children with severe pneumonia, reduce the body's inflammatory response, and improve lung function safely.

Keywords: Phentolamine; ambroxol aerosol inhalation; pediatric severe pneumonia; serum interleukin-10 (IL-10); C-reactive protein (CRP)

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Introduction

Children are susceptible to pathogenic bacteria due to their low immunity and immature respiratory tract, which can trigger pneumonia (1,2). Pediatric pneumonia, a common respiratory disease with acute onset and rapid progression, often occurs in infants and young children due to genetic, environmental, nutritional, and other factors. If infants or children are not effectively treated, the disease can develop into pediatric severe pneumonia (3). Pediatric severe pneumonia is mainly characterized by ventilation dysfunction and fever symptoms (in the early stage), accompanied by hypoxemia, and has a high mortality rate. Therefore, it is important to treat the disease as soon as possible. At present, azithromycin and erythromycin are often used for antibacterial treatment in clinical practice, with unsatisfactory efficacy and obvious complications. Therefore, it is crucial to select proper anti-inflammatory drugs (4-6). Phentolamine is a non-selective α-receptor blocker that can induce lower blood pressure and vasodilation by blocking α1 and α2 receptors in blood vessels, and can enhance myocardial contractility. Specifically, it can improve cardiac function, accelerate vascular expansion, alleviate vascular resistance, and significantly reduce peripheral vascular resistance, thus effectively improving the clinical symptoms and signs of patients with pneumonia. At the same time, the alleviation of clinical symptoms promotes the improvement of inflammatory response to a certain extent, but the effect lasts for a short time. Ambroxol is a common drug to treat pediatric pneumonia by activating pulmonary surfactant and promoting the discharge of retained sputum. It is speculated that the combination of the 2 drugs can have a better therapeutic effect (7,8). At present, few studies have reported the therapeutic effect of the combination of phentolamine and ambroxol. In order to determine their efficacy, 85 cases of children with severe pneumonia diagnosed and treated in our hospital were selected as the research subjects, summarized as follows. We present the following article in accordance with the TREND reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-516/rc).

Methods

General information

Eighty-five children with severe pneumonia treated in our hospital from November 2019 to November 2020 were selected as the research participants, and were divided into the routine group (n=41) and treatment group (n=44) according to odd and even admission numbers, respectively. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013) (9). The study was approved by ethics committee of Yantai Mountain Hospital (No. 20190977) and individual consent for this retrospective analysis was waived.

Inclusion criteria

The inclusion criteria were as follows: (I) diagnostic criteria and clinical symptoms of severe pneumonia, including severe cough, expectoration, chest pain, dyspnea, wheezing, cyanosis, diffuse fixed rales in the lungs (mainly small vesicular sounds), and signs of diffuse infection in the lungs confirmed by chest CT; (II) no congenital heart disease; and (III) age 3–13 years.

Exclusion criteria

The exclusion criteria were as follows: (I) immune deficiency; (II) pulmonary tuberculosis; (III) liver and kidney dysfunction; (IV) unable to cooperate; and (V) allergic to the drugs used in the research.

Treatments

Children in the routine group received clinical routine treatment, including cough relief (e.g., expectorant), defervescence, anti-infection treatment, maintenance of acid-base balance, and other symptomatic treatment measures (10,11).

Children in the treatment group were treated with phentolamine combined with Ambroxol aerosol inhalation. The children received 0.5 mg/kg phentolamine (Bikang Pharmaceutical Xinyi Group Holding) mixed with 50 mL of 5% glucose injection 1–2 times each day. The children also received aerosol inhalation of Ambroxol hydrochloride (Shanghai Boehringer Ingelheim Pharmaceutical), 15 mg 1–2 times per day. Both groups were treated for 7 days to observe the therapeutic effect.

Observation indexes

The duration of clinical symptoms and hospitalization time were recorded and compared between the 2 groups. Clinical symptoms included cough, fever, abnormal lung noise, and lung shadow.

The curative effect of both groups after treatment was evaluated according to the following criteria. If the children's

Table 1 Comparison of general clinical data between the 2 groups

Items	Treatment group (n=41)	Routine group (n=44)	χ^2/t	P value
Sex, n (%)			0.021	0.886
Male	23 (56.10)	24 (54.55)		
Female	18 (43.90)	20 (45.45)		
Age (years)	7.42±2.31	7.37±2.36	0.099	0.922
Course of disease (days)	8.24±1.63	8.29±1.58	0.144	0.886
Body temperature (℃)	38.62±0.53	38.67±0.47	0.461	0.646
Dyspnea, n (%)			0.201	0.654
Yes	28 (68.29)	32 (72.73)		
No	13 (31.71)	12 (27.27)		
Loss of appetite, n (%)			0.031	0.859
Yes	25 (60.98)	26 (59.09)		
No	16 (39.02)	18 (40.91)		
Residence, n (%)			0.572	0.450
Urban area	22 (53.66)	20 (45.45)		
Rural area	19 (46.34)	24 (54.55)		

body temperature after 3 days of treatment returned to normal, and symptoms such as cough and expectoration disappeared, the children were cured. If the body temperature after 3 days of treatment returned to normal, and symptoms, such as cough and expectoration, were relieved, the treatment was markedly effective. If the body temperature after 3 days of treatment gradually returned to normal, and symptoms, such as cough and expectoration, were partially relieved, the treatment was effective. If the body temperature did not drop and clinical symptoms were not relieved, the treatment was ineffective. The total effective rate = (number of cured cases + number of markedly effective cases + number of effective cases) / total number of cases × 100%.

Pulmonary function indexes

A spirometer (RSFJ1000; Chengdu Risheng Electric) was used to detect changes in forced vital capacity (FVC) and peak expiratory flow rate (PEF) levels in both groups before and after treatment.

A total of 3 mL fasting venous blood was collected from children in both groups before treatment (T0), 2 days after treatment (T1), 5 days after treatment (T2), and 7 days after treatment (T3), and serum was collected after centrifugation. Enzyme-linked immunosorbent assay was used to determine interleukin-10 (IL-10) and C-reactive protein (CRP) levels in the serum samples. The kits were purchased from Shenzhen Ziker Biological Technology and used according to the manufacturer's instructions.

The incidence of clinical adverse reactions was recorded and compared between the 2 groups.

Statistical methods

All experimental data were statistically analyzed and processed using SPSS version 21.0 (IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). Count data were analyzed using χ^2-test and expressed as n (%). Measurement data were analyzed using t-test and expressed as $\bar{x}$±s. The difference was statistically significant when P<0.05.

Results

Comparison of general clinical data between the 2 groups

There were no significant differences in sex ratio, average age, average course of disease, average body temperature, dyspnea, loss of appetite, and residence of the patients between the 2 groups (P>0.05), indicating comparability, as shown in *Table 1*.

Table 2 Comparison of duration of clinical symptoms and hospitalization time between the 2 groups

Groups	n	Duration (days)				Hospitalization time
		Cough	Fever	Abnormal lung sound	Lung shadow	
Treatment group	41	5.23±1.42	4.53±1.38	9.62±1.36	8.41±2.31	7.24±3.15
Routine group	44	6.72±1.25	5.63±1.58	11.25±1.47	11.68±2.58	12.96±4.03
t		5.143	3.408	5.295	6.140	7.254
P value		0.000	0.000	0.000	0.000	0.000

Table 3 Comparison of clinical efficacy between the 2 groups

Groups	n	Cured, n (%)	Markedly effective, n (%)	Effective, n (%)	Ineffective, n (%)	Total effective rate
Treatment group	41	14 (34.15)	15 (36.59)	10 (24.39)	2 (4.88)	95.12% (39/41)
Routine group	44	9 (20.45)	14 (31.82)	12 (27.27)	9 (20.45)	79.55% (35/44)
χ^2						4.571
P value						0.033

Comparison of duration of clinical symptoms and hospitalization time between the 2 groups

The duration of cough, fever, abnormal lung sound, and lung shadow, and hospitalization time in the treatment group were significantly shorter than those in the routine group (P<0.001), as shown in *Table 2*.

Comparison of clinical efficacy between the 2 groups

The total clinical effective rate in the treatment group was significantly higher than that in the routine group (P<0.05), as shown in *Table 3*.

Comparison of pulmonary function indexes before and after treatment between the 2 groups

Both groups had higher FVC and PEF levels following treatment (P<0.05), and these levels were higher in the treatment group compared with the routine group after treatment (P<0.05), as shown in *Figures 1,2*.

Comparison of serum IL-10 and CRP level changes between the 2 groups at different time points

Serum IL-10 and CRP levels at T1, T2, and T3 in the treatment group were significantly lower than those in the routine group (P<0.001), as shown in *Figures 3,4*.

Comparison of therapeutic safety between the 2 groups

The total incidence of adverse reactions in the treatment group was significantly lower than that in the routine group (P<0.05), as shown in *Table 4*.

Discussion

A study (12) has confirmed that pneumonia is a lung inflammatory response caused by environmental or viral factors. Early clinical symptoms of pediatric pneumonia, such as mild cough, are not obvious, and are often ignored by parents, and can result in severe pneumonia (13-15). Clinically, pneumonia is divided into prolonged pneumonia, acute pneumonia, and chronic pneumonia, according to the course of the disease, while severe pneumonia is a more serious stage in the development of pneumonia. Children are prone to infection because of softer tracheal walls and narrower bronchi compared with adults, and are unable to resist the invasion of pathogens (16,17). If pathogens continue to invade other tissues, swelling of airway mucosa will occur, resulting in restricted ventilation function, and eventually severe pneumonia. In addition to the damage to the respiratory system of children, severe pneumonia also causes neurological, digestive, circulatory, and other dysfunctions, as well as cerebral edema, mental confusion, irregular respiratory rhythm, and even respiratory arrest (18-20).

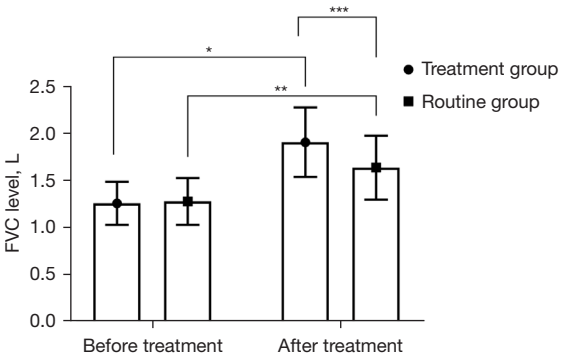

Figure 1 Comparison of forced vital capacity (FVC) levels before and after treatment between the 2 groups. FVC levels in the treatment group before and after treatment were 1.26±0.23 L and 1.91±0.37 L, respectively. FVC levels in the routine group before and after treatment were 1.28±0.25 and 1.64±0.34 L, respectively. *: t=9.644, P=0.000; **: t=5.528, P=0.000; ***: t=3.506, P=0.001.

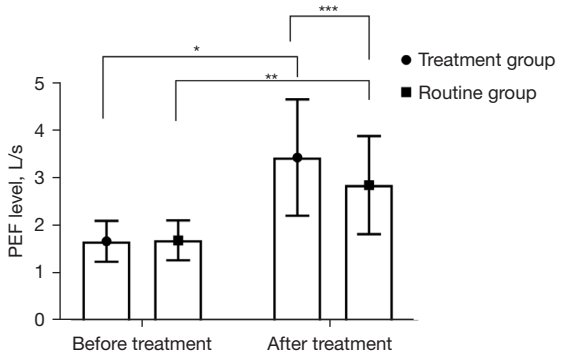

Figure 2 Comparison of peak expiratory flow rate (PEF) levels before and after treatment between the 2 groups. PEF levels in the treatment group before and after treatment were 1.68±0.43 and 3.44±1.22 L/s, respectively. PEF levels in the routine group before and after treatment were 1.70±0.42 and 2.86±1.03 L/s, respectively. *: t=8.742, P=0.000; **: t=6.708, P=0.000; ***: t=2.374, P=0.020.

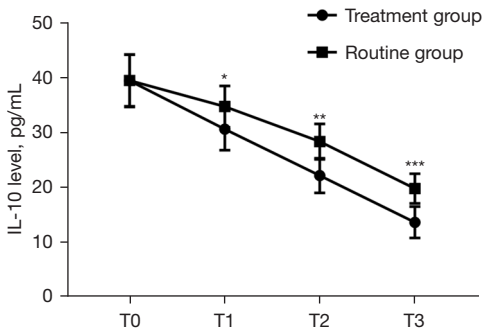

Figure 3 Comparison of interleukin-10 (IL-10) levels between the 2 groups at different time points. IL-10 levels in the treatment group at T0 (before treatment), T1 (2 days after treatment), T2 (5 days after treatment), and T3 (7 days after treatment) were 39.43±4.79, 30.62±3.84, 22.15±3.17, and 13.62±2.86 pg/mL, respectively. IL-10 levels in the routine group at T0, T1, T2, and T3 were 39.47±4.71, 34.71±3.76, 28.34±3.24, and 19.77±2.69 pg/mL, respectively. *: t=4.960, P=0.000; **: t=8.894, P=0.000; ***: t=10.216, P=0.000.

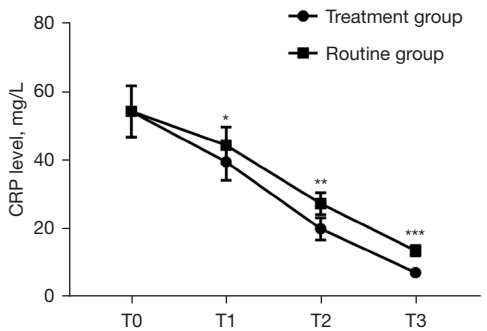

Figure 4 Comparison of C-reactive protein (CRP) levels between the 2 groups at different time points. CRP levels in the treatment group at T0 (before treatment), T1 (2 days after treatment), T2 (5 days after treatment), and T3 (7 days after treatment) were 54.32±7.52, 39.63±5.43, 20.07±3.26, and 7.32±1.45 mg/L, respectively. CRP levels in the routine group at T0, T1, T2, and T3 were 54.37±7.49, 44.47±5.28, 27.42±3.19, and 13.69±1.52 mg/L, respectively. *: t=4.166, P=0.000; **: t=10.503, P=0.000; ***: t=19.739, P=0.000.

Table 4 Comparison of therapeutic safety between the 2 groups

Groups	n	Gastrointestinal reaction, n (%)	Phlebitis, n (%)	Rash, n (%)	Abnormal liver function, n (%)	Total incidence
Treatment group	41	2 (4.88)	0 (0.00)	1 (2.44)	1 (2.44)	9.76% (37/41)
Routine group	44	3 (6.82)	4 (9.09)	3 (6.82)	2 (4.55)	27.27% (32/44)
χ^2						4.262
P value						0.039

Pneumonia is type of pulmonary edema, with congestion caused by a variety of pathogens. Its clinical symptoms include fever, expectoration, and dyspnea, as well as the shadow of inflammatory infiltration on lung X-ray (21,22). In the present study, both groups of children received basic treatment, including anti-infection, expectorant, and defervescence, while the treatment group additionally received phentolamine combined with Ambroxol aerosol inhalation. Phentolamine can effectively relieve spasm of bronchial smooth muscle in children, reduce airway resistance, improve ventilation function, and alleviate clinical symptoms, such as cough and lung moist rales. As a new mucolytic drug, ambroxol can effectively break the viscous polysaccharide fibers, weaken the adhesion of mucus, reduce the alveolar surface tension, affect the activity of respiratory enzymes in epithelial villi, and improve the mucociliary transport of respiratory mucosa. Phentolamine combined with ambroxol can play a good role in the dilation of bronchial smooth muscle, reduce venous pressure, improve pulmonary circulation, and enhance the curative effect by reducing myocardial oxygen consumption and reducing cardiac load. With a synergistic effect, their combination is more effective than the single drug treatment. As shown in *Table 2*, X-ray and clinical diagnosis of children showed that the duration of cough, fever, abnormal lung sound, and lung shadow in the treatment group was significantly shorter than those in the routine group ($P<0.001$), indicating that Ambroxol aerosol inhalation combined with phentolamine can effectively shorten the regression time of clinical symptoms in children. In addition, a previously published study (23) confirmed that severe pneumonia can cause disorders in body immune response in children, activate and release inflammatory factors into the blood, and induce respiratory tract inflammation. Inflammatory response is involved in the occurrence and development of the disease. After expansion, inflammatory response occurs throughout the body and in the lungs, with a large number of inflammatory factors in the alveoli. CRP and IL-10 are important inflammatory factors that can reflect the severity of infection in the body. CRP reduces inflammatory response by activating complement phagocytes and enhancing their role. Therefore, CRP levels are highly expressed in children with severe pneumonia. Serum IL-10 is a multifunctional cytokine that regulates and mediates the function of immune cells, and affects the occurrence of immune damage and inflammation. Therefore, serum IL-10 levels are highly expressed in children with severe pneumonia (24). After treatment, serum IL-10 and CRP levels in both groups decreased, and serum IL-10 and CRP levels at T1, T2, and T3 in the treatment group were significantly lower than those in the routine group ($P<0.05$). In their study, Nasser *et al.* found that, after children with severe pneumonia mycoplasma pneumonia were treated with azithromycin combined with phentolamine, CRP was 16.31±4.28 mg/L, which was significantly lower than 56.72±6.37 mg/L before treatment, suggesting that the combination of drugs can effectively inhibit bronchospasm, increase vascular permeability, reduce airway inflammation, and have a significant anti-inflammatory effect in children (25). In addition, the incidence of clinical adverse reactions in the treatment group was significantly lower than that in the routine group, demonstrating that phentolamine combined with Ambroxol aerosol inhalation not only improves the therapeutic effect on children with severe pneumonia but also has high safety.

In conclusion, phentolamine combined with Ambroxol aerosol inhalation not only effectively relieves the clinical discomfort symptoms of children with severe pneumonia but also reduces the inflammatory factor levels and controls disease development with high safety.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-21-516/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-21-516/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-21-516/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of

Yantai Mountain Hospital (No. 20190977) and individual consent for this retrospective analysis was waived.

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