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Original Article

Safety and efficacy of ambroxol hydrochloride in combination with procaterol hydrochloride in pediatric pneumonia treatment and their effects on TNF-α, IL-6, and IL-18

Weiping Xiang, Ling Yao, Zhonggan Zhou

Department of Pediatrics, Tianjin Fifth Central Hospital, Tianjin 300450, China

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Abstract: Objective: This study aimed to investigate the safety and efficacy of ambroxol hydrochloride in combination with procaterol hydrochloride in treating pediatric pneumonia and their effects on plasma tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-18. Methods: A total of 86 children with pneumonia were selected and divided into group A (n=43) (received routine pneumonia treatment) and group B (received ambroxol hydrochloride treatment in combination with procaterol hydrochloride in addition to routine treatment). The general clinical data, related clinical symptoms, cough scores, and pulmonary function (FEV1 and FVC) and clinical efficacy of groups A and B were compared. The changes in plasma TNF-α, IL-6, and IL-18 levels were monitored using ELISA before and after treatment. Results: Cough disappearance time, wheezing disappearance time, defervescence time, and rale disappearance time in group B were shorter than those of group A ($P < 0.001$). Cough scores and IL-6 and IL-18 levels of both groups after treatment were lower than those before treatment, and those of group B were lower than group A after treatment ($P < 0.001$). TNF-α level of group B was lower than that of group A after treatment ($P < 0.001$). FEV1 and FVC of group B were higher than those of group A ($P < 0.001$). Notably, the effective rate of treatment of group B was higher than that of group A ($P < 0.05$). Conclusion: The combination of ambroxol hydrochloride and procaterol hydrochloride in pediatric pneumonia treatment showed better alleviation of pulmonary inflammation, better regulation of pulmonary function, and higher safety than routine pneumonia treatment.

Keywords: Ambroxol hydrochloride, procaterol hydrochloride, pediatric pneumonia, safety, efficacy

Introduction

Pneumonia is a common disease of the lungs, which is a part of the respiratory system [1]. Although the specific pathogenesis of pneumonia is complex, it is often induced by a variety of pneumonia-promoting pathogens. Due to incomplete self-development, imperfect immune system function, and poor resistance, the incidence of pneumonia in children is higher than that in adults [2]. The early clinical symptoms of pneumonia are not easy to detect. Unfortunately, the individual's condition is usually found to be aggravated once the symptoms manifest themselves, and serious cases even demonstrate a great threat to health and life [3]. Relevant studies have previously revealed that the serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-18 (IL-18) are closely related to the occurrence and development of pneumonia [4-6]. TNF-α is a very important regulator of the inflammatory reaction process. Together with other inflammatory cytokines, TNF-α activates and maintains the inflammatory reaction during lung cancer resection [7]. IL-6, is an inflammatory factor, and induces the inflammatory reaction in cells [8]. Thus IL-6-induced inflammatory reaction can lead to advanced lung injury and dysfunction due to various causes that are closely related to the occurrence and development of pneumonia [9]. Some studies have also shown that IL-18 levels are clearly increased during pneumonia and lung cancer resection [10].

Currently, the routine clinical treatment for pediatric pneumonia involves the administra-

tion of related glucocorticoids and other antibiotics. However, the overall clinical efficacy is poor due to weak autoimmune resistance and high recurrence in children [11]. Notably, choosing the right drug treatment can reduce the injury experienced by various organs from the inflammatory reaction, especially in children [12]. Therefore, this study explored the pulmonary function and clinical efficacy of ambroxol hydrochloride treatment in combination with procaterol hydrochloride in pediatric pneumonia and their effects on TNF-α, IL-6, and IL-18 levels in order to obtain better therapeutic effects.

Materials and methods

General data

In this study, 86 children with pneumonia, who were admitted to our hospital, were selected. Among them, 43 children (28 males and 15 females with an average age of (3.05 ± 0.58) years) that received routine pediatric pneumonia treatment were categorized into group A. Furthermore, 43 children (30 males and 13 females with an average age of (3.16 ± 0.44) years) that received ambroxol hydrochloride treatment in combination with procaterol hydrochloride, in addition to routine pediatric pneumonia treatment, were categorized into group B. The inclusion criteria required all patients to be admitted to our hospital and meet the diagnostic criteria for clinical pediatric pneumonia [13]. The exclusion criteria included patients with severe liver and kidney dysfunction, patients with coagulation dysfunction, patients who did not cooperate with the examination, and patients with cognitive and communication disorders. All the participants parents volunteered for the experimental procedure and informed consent was obtained from each participant's parent or guardian. The participants also cooperated with the medical staff to complete each relevant diagnosis and treatment. The study was approved by the Ethics Committee of the Tianjin Fifth Central Hospital.

Materials and methods

The children in groups A and B were administered with routine treatment for pediatric pneumonia. Briefly, the children were treated with anti-inflammatory drugs, anti-infectious drugs, vitamin C, cooling and so on after admission based on the specific conditions presented. Cefazolin and penicillin sodium were administered via intravenous drip and aminophylline was used to relieve or eliminate bronchospasm. This treatment lasted for 10 days. This study was approved by the Ethics Committee of Tianjin Fifth Central Hospital.

Next, the children in group B were treated with ambroxol hydrochloride in combination with procaterol hydrochloride based on the routine treatment. The dosage differed based on the age of the children. Ambroxol hydrochloride was administered orally, thrice a day, at 10 mg in children aged 3 months to 1 year, 15 mg from 2 to 3 years, and 30 mg for 4 years and over. Procaterol hydrochloride was also administered orally, thrice a day, at 12.5 μg in children aged under 5 years and 25 μg in children aged over 5 years. The drugs were administered continuously for 10 days.

Outcome measurements

Outcome measurements were made after one week of treatment. The general clinical data and related clinical symptoms, including cough disappearance time, wheezing disappearance time, defervescence time, and rale disappearance time, in groups A and B were compared. The cough scores of groups A and B before and after treatment were also compared. Symptom scores for the cough score standard were evaluated using the nimodipine method [14] i.e., (pre-treatment score - post-treatment score)/pre-treatment score × 100%. Furthermore, the changes in plasma TNF-α, IL-6, and IL-18 levels were monitored using ELISA before and after treatment. The pulmonary function (FEV1 and FVC) of groups A and B before and after treatment was also compared. Finally, the clinical efficacy after treatment was compared between groups A and B.

Statistical analysis

SPSS 17.0 software system (Beijing Bi Insight Information Technology Co., Ltd.) was used for all statistical analyses. The enumeration data between both groups was tested using the χ^2 test and expressed as [n (%)]. The measurement data was represented as (x ± s). Independent sample *t*-tests were used to compare data from both groups, and paired *t*-tests were used to compare data from both groups

Table 1. General clinical data

Group	Group A (n=43)	Group B (n=43)	t/X^2	P
Age	3.05 ± 0.58	3.16 ± 0.44	0.325	0.991
Gender			0.212	0.645
Male	28 (65.12)	30 (69.77)		
Female	15 (34.88)	13 (30.23)		
Average disease duration (d)	3.47 ± 1.00	3.28 ± 1.20	0.798	0.427
Whether anemia			0.534	0.465
Yes	30 (69.77)	33 (76.74)		
No	13 (30.23)	10 (23.26)		
Malnutrition			0.420	0.517
Yes	24 (55.81)	21 (48.84)		
No	19 (44.19)	22 (51.16)		
Immunocompromised			0.000	1.000
Yes	43 (100.00)	43 (100.00)		
No	0 (0.00)	0 (0.00)		
Family history of pneumonia			6.081	0.014
Have	1 (2.33)	8 (18.60)		
No	42 (97.67)	35 (81.40)		
Pathogen typing				
Bacterial	13 (30.23)	12 (27.91)	0.056	0.812
Viral	15 (34.88)	21 (48.84)	1.720	0.190
Mycoplasma pneumonia	15 (34.88)	10 (23.26)	1.410	0.235

Table 2. Time of disappearance of clinical symptoms associated with children in group A and group B

Group	Group A (n=43)	Group B (n=43)	t	P
Cough disappearance time	7.01 ± 1.43	3.04 ± 1.36	13.190	< 0.001
Wheezing disappearance time	7.20 ± 1.25	4.05 ± 1.62	10.090	< 0.001
Defervescence time	7.18 ± 1.44	3.95 ± 1.26	11.070	< 0.001
Rale disappearance time	6.82 ± 1.08	3.02 ± 1.17	15.650	< 0.001

before and after treatment. $P < 0.05$ was considered to be statistically significant.

Results

General clinical data of the 2 groups

No obvious difference was observed in the general clinical data between the 2 groups ($P > 0.05$; **Table 1**).

Relevant clinical symptoms of children in groups A and B

The cough disappearance time, wheezing disappearance time, defervescence time, and rale disappearance time of group A were (7.01 ± 1.43), (7.20 ± 1.25), (7.18 ± 1.44), and (6.82 ± 1.08) d, respectively. The cough disappearance time, wheezing disappearance time, defervescence time, and rale disappearance time of group B were (3.04 ± 1.36), (4.05 ± 1.62), (3.95 ± 1.26), and (3.02 ± 1.17) d, respectively. Notably, the cough disappearance time, wheezing disappearance time, defervescence time, and rale disappearance time of group B were shorter than those of group A ($P < 0.001$; **Table 2**).

Cough scores of groups A and B before and after treatment

The cough scores of group A before and after treatment were (5.23 ± 1.68) and (2.68 ± 1.42), respectively. The cough scores of group B before and after treatment were (5.42 ± 1.90) and (1.26 ± 0.23), respectively. No obvious difference was observed between the cough scores of the 2 groups before treatment ($P > 0.05$). However, the cough scores of both groups were lower after treatment when compared to those before treatment, with the cough score of group B after treatment being lower than that before treatment ($P < 0.001$; **Table 3**).

Changes in plasma TNF-α, IL-6, and IL-18 levels in groups A and B before and after treatment

Changes in plasma TNF-α levels in groups A and B before and after treatment: The plasma TNF-α levels of group A before and after treatment were (13.14 ± 2.15) and (7.02 ± 2.48) pg/mL respectively, while those of group B before and after treatment were (13.01 ± 2.47) and

Table 3. Cough scores before and after treatment in children in group A and group B

Group	Group A (n=43)	Group B (n=43)	t	P
Before treatment	5.23 ± 1.68	5.42 ± 1.90	0.491	0.625
After treatment	2.68 ± 1.42	1.26 ± 0.23	6.473	< 0.001
t	7.801	9.374		
P	< 0.001	< 0.001		

Table 4. TNF-α before and after treatment in children in group A and group B

Group	Group A (n=43)	Group B (n=43)	t	P
Before treatment	13.14 ± 2.15	13.01 ± 2.47	0.260	0.795
After treatment	7.02 ± 2.48	4.28 ± 1.99	5.651	< 0.001
t	5.207	8.580		
P	< 0.001	< 0.001		

Table 5. IL-6 before and after treatment in children in group A and group B

Group	Group A (n=43)	Group B(n=43)	t	P
Before treatment	48.39 ± 2.69	49.13 ± 1.06	1.678	0.097
After treatment	36.46 ± 2.16	28.49 ± 1.24	20.980	< 0.001
t	6.135	8.508		
P	< 0.001	< 0.001		

Table 6. IL-18 before and after treatment in children in group A and group B

Group	Group A (n=43)	Group B (n=43)	t	P
Before treatment	320.19 ± 58.29	319.45 ± 56.41	0.054	0.957
After treatment	302.18 ± 46.09	236.29 ± 39.08	7.150	< 0.001
t	7.542	9.014		
P	< 0.001	< 0.001		

(4.28 ± 1.99) pg/mL respectively. No obvious difference was observed between the plasma TNF-α levels of the 2 groups before treatment (P > 0.05). However, the plasma TNF-α levels of group B were lower than that of group A after treatment (P < 0.001; **Table 4**).

Changes in plasma IL-6 levels in groups A and B before and after treatment: The plasma IL-6 levels of group A before and after treatment were (48.39 ± 2.69) and (36.46 ± 2.16) ng/L respectively, while those of group B before and after treatment were (49.13 ± 1.06) and (28.49 ± 1.24) ng/L respectively. No obvious difference was observed between the plasma IL-6 levels of the 2 groups before treatment (P > 0.05). However, the plasma IL-6 levels of both groups were lower after treatment when compared to those before treatment, with the plasma IL-6 level of group B after treatment being lower than that of group A (P < 0.001; **Table 5**).

Changes in plasma IL-18 levels in groups A and B before and after treatment: The plasma IL-18 levels of group A before and after treatment were (320.19 ± 58.29) and (302.18 ± 46.09) pg/L respectively, while those of group B before and after treatment were (319.45 ± 56.41) and (236.29 ± 39.08) pg/L respectively. No remarkable difference was observed between the plasma IL-18 levels of the 2 groups before treatment (P > 0.05). However, the plasma IL-18 levels of both groups were lower after treatment when compared to those before treatment, with the plasma IL-18 level of group B after treatment being lower than that of group A (P < 0.001; **Table 6**).

Comparison of pulmonary function between groups A and B before and after treatment

The FEV1 values of group A before and after treatment were (1.26 ± 0.28) and (1.57 ± 0.23) respectively, whereas those of group B before and after treatment were (1.27 ± 0.28) and (1.99 ± 0.85) respectively. The FVC values of group A before and after treatment were (2.13 ± 0.15) and (2.50 ± 0.31) respectively, whereas those of group B before and after treatment were (2.12 ± 0.16) and (3.01 ± 0.46) respectively. No remarkable difference was observed between the FEV1 and FVC values of the 2 groups before treatment (P > 0.05). However, the FEV1 and FVC values of group B were higher than those in group A after treatment (P < 0.001; **Figure 1**).

Comparison of clinical efficacy after treatment in groups A and B

The effective treatment rate of group B was found to be higher than that of group A (P < 0.05; **Table 7**).

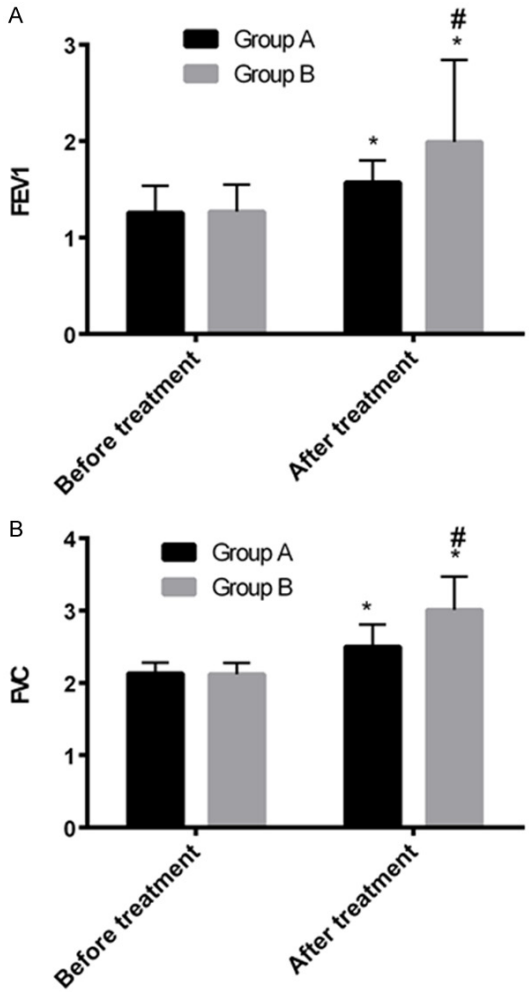

Figure 1. Comparison of pulmonary function between group A and group B before and after treatment. There was no obvious difference in FEV1 and FVC between the two groups before treatment ($P > 0.05$). * indicates that the FEV1 and FVC of the two groups after treatment were higher than those before treatment. # indicates that the FEV1 and FVC of group B after treatment were higher than those of group A ($P < 0.001$).

Discussion

The therapeutic effect of traditional medication on pediatric pneumonia is not only poor, but also greatly and negatively stimulates the body of children [15]. In recent years, studies on pneumonia medication have shown that ambroxol hydrochloride can effectively dilute respiratory sputum, promote the flow of respiratory secretion, keep the respiratory tract open, and alleviate adverse respiratory reactions in children with pneumonia [16]. Notably, ambroxol hydrochloride treatment in combination with procaterol hydrochloride, in addition to routine treatment, was also suggested to markedly improve the clinical efficacy of routine pneumonia treatment and accelerate recovery in children [17].

In this study, the clinical symptoms and cough scores of groups A and B were analyzed before and after treatment. The cough disappearance time, wheezing disappearance time, defervescence time, and rale disappearance time of group B were found to be shorter than those of group A. Furthermore, the cough scores of both groups after treatment were observed to be lower than those before treatment. Notably, the cough scores of group B after treatment were lower than those of group A. Previously, a study showed that ambroxol hydrochloride treatment in combination with procaterol hydrochloride, based on routine treatment, effectively improved clinical efficacy, alleviated symptoms and signs, shortened hospital stay, and promoted the rapid recovery of patients [18]. Ambroxol hydrochloride stimulates a mucus solubilizer in the bronchial glands, promotes pulmonary surfactants, and reduces the viscosity and accelerates the excretion of sputum and other secretions [19]. On the other hand, procaterol hydrochloride is a β2 receptor agonist that acts on bronchial smooth muscles and usually enlarges the bronchi [20]. A study on pneumonia medication further indicated that the combination of both drugs complemented each other's advantages and improved the clinical efficacy of pneumonia treatments [21]. Interestingly, in this study, the clinical cough, wheezing, rale disappearance, and defervescence time periods in children treated with ambroxol hydrochloride and procaterol hydrochloride were noticeably shortened and their cough scores were markedly lowered when compared to those in children who underwent routine treatment. Their clinical symptoms were also found to be in a better condition.

Next, changes in plasma TNF-α, IL-6, and IL-18 levels were analyzed in groups A and B before and after treatment. No remarkable difference in TNF-α, IL-6, and IL-18 levels was found between the 2 groups before treatment. However, TNF-α, IL-6, and IL-18 levels in both groups were lower after treatment when compared to those before treatment, with their levels being lower in group B when compared to

Table 7. Comparison of clinical efficacy between children in group A and group B after treatment

Group	Group A (n=43)	Group B (n=43)	X^2	P
Significant effect	30 (69.77)	20 (46.51)	-	-
Effective	12 (27.91)	15 (34.88)	-	-
Invalid	1 (2.33)	8 (18.60)	-	-
Total efficiency	42 (97.67)	35 (81.40)	6.081	0.014

those in group A after treatment. Previously, a study showed that excessive TNF-α initiated inflammation and facilitated lung injury via severe pneumonia. Although the proper secretion of TNF-α plays a protective role in the body, excessive TNF-α indirectly induces local inflammation, thereby leading to organ damage [22]. Another study confirmed that IL-6 was secreted by macrophages and neutrophils during the early stage of inflammation, which was closely related to the occurrence and development of other respiratory diseases such as asthmatic airway inflammation [23]. Furthermore, a previous study not only showed IL-6 and IL-18 upregulation in the bronchoalveolar lavage fluid (BALF) of asthmatic patients, but also showed a significant increase in IL-6 levels during severe pneumonia [24]. Therefore, TNF-α, IL-6, and IL-18 levels were observed to be downregulated more effectively with better alleviation of pulmonary inflammation in children who underwent ambroxol hydrochloride treatment in combination with procaterol hydrochloride, based on routine treatment. Finally, the lung function and clinical efficacy of treatments in groups A and B before and after treatment were compared. FEV1 and FVC values of group B were found to be higher than those of group A after treatment. The effective treatment rate of group B was also found to be higher than that of group A after treatment. Therefore, ambroxol hydrochloride treatment in combination with procaterol hydrochloride, in addition to routine treatment, demonstrated a better effect on improving pulmonary function and clinical efficacy in children with pneumonia. Moreover, a similar study demonstrated that the ambroxol hydrochloride and procaterol hydrochloride combination improved the clinical efficacy of treatments in patients with pneumonia [25]. There are certain limitations in these experimental results. Data reliability also needs to be further expanded to verify the sample size. Even though the study excluded patients with severe liver and kidney dysfunction, patients with coagulation dysfunction, patients who did not cooperate with the examination, and patients with cognitive and communication disorders, it is possible that the existence of some other factors were not taken into account.

In conclusion, the combination of ambroxol hydrochloride and procaterol hydrochloride demonstrated better alleviation of pulmonary inflammation, better regulation of pulmonary function, and higher safety in treating pediatric pneumonia. Therefore, this combination can improve the clinical efficacy of treatments in children with pneumonia to a certain extent and is worthy of wide clinical promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Weiping Xiang, Department of Pediatrics, Tianjin Fifth Central Hospital, Building 2, Century Golden Triangle, Yantai Road, Tanggu District, Binhai New Area, Tianjin 300450, China. Tel: +86-022-65575896; E-mail: xf9pkg@163.com

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