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Effect of exogenous pulmonary surfactant on infectious pneumonia, serum procalcitonin, high-sensitivity C-reactive protein and interleukin-6 in neonates

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Infectious pneumonia common among neonates has morbidity rate as high as 25%. Proper clinical diagnosis with treatment for respiratory and circulatory failure may prevent mortality. Neonates with infectious pneumonia are mostly treated with mechanical ventilation, antibiotics and pulmonary surfactant. Here, we assessed the effects of exogenous pulmonary surfactant on neonatal infectious pneumonia (NIP). A total of 120 neonates treated from October 2019 to December 2020 were randomly divided into control and observation groups (n=60). Control group received conventional treatment for 7 d, based on which observation group was given 100 mg/kg PS. Their blood gas indices, oxygenation status, lung consolidation and levels of serum procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were compared. Partial pressure of oxygen (PaO_2) increased, while that of carbon dioxide ($PaCO_2$) decreased 24 and 48 h after treatment compared with those before treatment, and the observation group had higher PaO_2 and lower $PaCO_2$ (P <0.05). Oxygenation index was lower, but arterial/alveolar partial pressure was higher in the observation group than those in the control group 24 and 48 h after treatment (P <0.05). The clinical pulmonary infectious score was lower in the observation group 7 d after treatment (P <0.05). The levels of serum antithrombin III and lung surfactant protein B rose, whereas D-dimer level declined in both groups after treatment, especially in the observation group (P <0.05). PCT, hs-CRP and IL-6 levels 7 d after treatment were lower than those before treatment, and lower in the observation group (P <0.05). For the treatment of severe infectious pneumonia in neonates, exogenous PS can effectively ameliorate blood gas indices, oxygenation status and expression levels of AT-III, SP-B and D-D, relieve pulmonary infection and reduce the levels of inflammatory factors.

Keywords: Antithrombin, Blood gas indices, Inflammatory factors, Neonatal infectious pneumonia, Oxygenation status

Infectious pneumonia frequently occurs in neonates with a range of morbidity rate 3.5-25%[1]. Its incidence is related to airway stenosis, thin mucosa, immature immune system and weak resistance to pathogens[2]. The neonates with infectious pneumonia have such conventional manifestations as cough, fever and dyspnea, and even injury of other vital organs in severe cases, which may endanger the life of neonates. Therefore, it is crucial to adopt efficacious clinical diagnosis and treatment to prevent respiratory and circulatory failure and lower mortality rate of neonates. Currently, the neonates with infectious pneumonia are mostly treated with mechanical ventilation, antibiotics and pulmonary surfactant (PS). Exogenous PS not only has an excellent therapeutic effect on neonatal respiratory distress syndrome, but also possesses remarkable efficacy in the treatment of severe infectious pneumonia[3]. Exogenous PS is able to promote the recovery of neonates with severe pneumonia[4], but there is a lack of studies on exogenous PS in ameliorating lung consolidation degree of neonates with severe infectious pneumonia in China.

Procalcitonin (PCT), a propeptide of calcitonin without hormone activity, is produced by thyrotrophs, whose concentration is very low in human blood under normal physiological conditions. When bacterial infection occurs in the body, however, the serum PCT level will rise obviously in human body under the stimulation of inflammatory factors and bacterial toxins, so PCT can be taken as an important indicator to determine the occurrence of bacterial infection in organisms[5]. High-sensitivity C-reactive protein (hs-CRP) is a non-specific and sensitive marker of inflammation and tissue injury[6]. The *in-vivo* expression level of inflammatory factor interleukin-6 (IL-6) is of important significance for measuring the inflammatory level[7].

Considering the close correlations of PCT, hs-CRP and IL-6 with inflammatory level, here, in this study, we explored the influence of exogenous PS on blood gas indices, oxygenation status, lung consolidation degree and serum levels of PCT, hs-CRP and IL-6 in neonates.

Materials and Methods

General data

This study was approved by the ethics committee of the hospital, and written informed consent was obtained from the patients' caregivers. The sample size was estimated based on pre-experiment results.

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A total of 120 neonates with severe infectious pneumonia admitted to and treated in our hospital from October 2019 to December 2020 were selected. The inclusion criteria were set as follows: neonates definitely diagnosed with severe infectious pneumonia[8], and those whose parents were informed of the study and agreed with the treatment methods therein. The following exclusion criteria were adopted: neonates with congenital bronchial dysplasia, those whose natural mother had prenatal infection or premature rupture of membrane, or those with nosocomial pneumonia. All enrolled neonates were randomly divided into control group (n=60) and observation group (n=60). There were 35 males and 25 females in control group, with a gestational age of 35-40 (37.22±1.24) weeks and birth weight of 2,000-3,200 (2,878.42±321.57) g. Besides, there were 39 preterm infants, 21 term infants, 40 cases of spontaneous delivery and 20 cases of caesarean section. Observation group consisted of 34 males and 26 females, including 40 preterm infants and 20 term infants. The gestational age was 35-40 (37.32±1.26) weeks, the birth weight was 2,000-3,210 (2,879.56±319.51) g, and there were 41 cases of spontaneous delivery and 19 cases of caesarean section.

Methods

All neonates received treatments for maintaining airway patency, resisting infection and regulating water, electrolyte and acid-base balance. In control group, mechanical ventilation was performed using an SLE5000 ventilator with parameters set as follows: peak inspiratory pressure at 16-25 cmH_2O (1 cmH_2O = 0.098 kPa), fraction of inspired oxygen at 0.4-0.8, positive end-expiratory pressure at 4-6 cmH_2O, inspiratory time for 0.45-0.60 s, respiratory rate at 30-45 breaths/min, intermittent mandatory ventilation mode and mean arterial pressure at 0.8-1.4 kPa. On the basis of conventional treatment and mechanical ventilation, the neonates in observation group were subjected to tracheal intubation immediately after admission to hospital, and 100 mg/kg PS (Chiesi Farmaceutici S.p.A., 1.5 mL: 0.12 g/vial) was injected into the lungs *via* intratracheal instillation under positive pressure ventilation. Sputum aspiration was prohibited within 6 h, and the ventilator parameters were adjusted according to the actual conditions of the neonates.

Observation indices

Arterial blood (3 mL) was collected before and after treatment to detect partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) using a GEM3000 blood gas analyzer. In terms of the oxygenation status, 3 mL of arterial blood was separately drawn from the neonates before and after treatment, and the oxygenation index (OI) and arterial/alveolar partial pressure (a/APO_2) were determined by virtue of the GEM3000 blood gas analyzer. A lower OI value and a higher a/APO_2 value indicated better pulmonary oxygenation. Moreover, the clinical pulmonary infectious score (CPIS) with 10 points in total was applied to evaluate pulmonary infection, and the higher the score was, the severer the disease would be[9]. Additionally, 5 mL of fasting venous blood was collected from the neonates before treatment and at 7 d after treatment separately to measure the levels of serum antithrombin III (AT-III), D-dimer (D-D), lung surfactant protein B (SP-B) and PCT through immune turbidimetry in a DxH800 full-automatic hematology analyzer. Moreover, hs-CRP and IL-6 were detected using fluorescent dry slides method and enzyme-linked immunosorbent assay, respectively.

Statistical analysis

SPSS 26.0 software was employed for statistical analysis. The measurement data were represented as mean ± standard deviation and compared between groups by the *t* test, and the numerical data (%) were examined by the χ^2 test. P <0.05 suggested that a difference was statistically significant.

Results and Discussion

Blood gas indices

PaO_2 increased, while $PaCO_2$ decreased at 24 and 48 h after treatment compared with those before treatment (P <0.05), and the observation group had higher PaO_2 and lower $PaCO_2$ than those of the control group (P<0.05) (Table 1).

Oxygenation status

At 24 and 48 h after treatment, OI declined, and a/APO_2 rose in both groups in contrast with those

Table 1 — Blood gas indices at different time points

	Control group	Observation group
PaO_2 (mmHg)		
Before treatment	53.09±3.45	52.97±3.56
24 h after treatment	62.06±3.29*	68.67±4.54*,#
48 h after treatment	79.54±6.78*	89.76±6.49*,#
$PaCO_2$ (mmHg)		
Before treatment	57.02±3.24	56.97±3.32
24 h after treatment	53.87±3.56*	50.21±3.48*,#
48 h after treatment	48.56±3.72*	43.29±4.36*,#

[*P <0.05 *vs.* before treatment within the group, #P <0.05 *vs.* control group in the same time period]

before treatment (P <0.05), while the changes were greater in the observation group than those in the control group (P <0.05) (Table 2).

CPIS values

No statistically significant difference in CPIS was observed between the two groups before treatment (P >0.05). However, CPIS at 7 d after treatment reduced in comparison with that before treatment in the two groups (P <0.05), and it was lower in the observation group than that in the control group (P <0.05) (Table 3).

AT-III, D-D and SP-B levels

The AT-III and SP-B levels were elevated, whereas the D-D level was lowered at 7 d after treatment compared with those before treatment in the two groups (P <0.05), and the observation group had raised AT-III and SP-B levels and reduced D-D level in contrast with those of the control group (P <0.05) (Table 4).

PCT, hs-CRP and IL-6 levels

The PCT, hs-CRP and IL-6 levels at 7 d after treatment were lower than those before treatment in the two groups (P <0.05), and they were lower in the observation group than those in the control group (P <0.05) (Table 5).

As a frequently-occurring respiratory disease in the neonatal period, neonatal infectious pneumonia is mainly induced by viral, bacterial and protozoal infections in the uterine, during delivery and after birth[10]. Conventional drug treatment can improve the disease condition and delay the progression of disease in neonates, but the effect of the disease on the healthy development of neonates cannot be ignored in the long run[11]. Most neonates with infectious pneumonia have acute lung injury, which is probably associated with decreased activity or secondary deficiency of PS due to various reasons[12]. For patients infected with severe pneumonia, the toxins released *in vivo* can impair the alveolar epithelial type II tissues to reduce the production of PS, enhance its inactivation and interfere in the generation and metabolism of PS, finally altering the content and function of PS[13]. Hence, it is crucial to provide PS treatment for neonates with severe infectious pneumonia.

Pulmonary surfactant (PS) is mainly synthesized at 18-20 weeks of gestation, and its content peaks at 35-36 weeks of gestation, and hence, PS deficiency generally occurs in preterm infants[14]. Endogenous PS, a kind of protein-phospholipid complex, is produced by alveolar type II cells and attached to the alveolar surface, which is capable of reducing alveolar surface tension and stabilizing the alveoli[15]. In the clinical treatment of neonates with severe infectious pneumonia, exogenous PS needs to be supplemented first to substitute endogenous PS so as to improve the stability of alveoli and promote the development and regeneration of pulmonary function. In this study, the neonates were administered with exogenous PS on the basis of mechanical ventilation. PaO_2, $PaCO_2$, OI and

Table 2 — Oxygenation status at different time points

	Control group	Observation group
OI (mmHg)		
Before treatment	16.29±1.32	16.43±1.18
24 h after treatment	13.57±1.14*	12.09±1.01*,#
48 h after treatment	11.29±1.23*	9.98±0.83*,#
a/APO_2 (mmHg)		
Before treatment	0.14±0.04	0.15±0.04
24 h after treatment	0.27±0.06*	0.32±0.07*,#
48 h after treatment	0.27±0.05*	0.39±0.08*,#

[*P <0.05 *vs.* before treatment within the group, #P <0.05 *vs.* control group in the same time period]

Table 3 — CPIS values before and after treatment

	Control group	Observation group
CPIS (point)		
Before treatment	8.21±0.84	8.19±0.79
7 d after treatment	6.24±0.81*	4.37±0.71*,#

[*P <0.05 *vs.* before treatment within the group, #P <0.05 *vs.* control group in the same time period]

Table 4 — AT-III, D-D and SP-B before and after treatment

	Control group	Observation group
AT-III (%)		
Before treatment	41.08±3.28	40.97±4.65
7 d after treatment	65.28±4.57*	71.28±4.73*,#
D-D (mg/L)		
Before treatment	2.45±0.25	2.46±0.24
7 d after treatment	1.57±0.12*	1.06±0.14*,#
SP-B (ng/L)		
Before treatment	7.84±0.84	7.85±0.74
7 d after treatment	21.28±2.16*	28.34±2.35*,#

[*P <0.05 *vs.* before treatment within the group, #P <0.05 *vs.* control group in the same time period]

Table 5 — PCT, hs-CRP and IL-6 before and after treatment

	Control group	Observation group
PCT (μg/L)		
Before treatment	3.45±0.25	3.47±0.26
7 d after treatment	2.08±0.22*	1.04±0.18*,#
Hs-CRP (mg/L)		
Before treatment	17.42±2.21	17.44±2.23
7 d after treatment	10.51±2.11*	6.03±2.16*,#
IL-6 (pg/mL)		
Before treatment	254.43±23.81	257.81±24.79
7 d after treatment	121.22±12.11*	88.34±9.37*,#

[*P <0.05 *vs.* before treatment within the group, #P <0.05 *vs.* control group in the same time period]

a/APO_2 were superior in the observation group to those in the control group after treatment, suggesting that the intervention with exogenous PS can effectively ameliorate the blood gas indices and oxygenation function of neonates with severe infectious pneumonia. Possibly, PS can prevent protein exudation and alleviate mechanical ventilation-related airway and lung injuries[16].

Given that severe infectious pneumonia in neonates is triggered by multiple factors together, such as *in-vivo* toxins and bacteria, there are abnormalities of serum factors in neonates[17]. The neonates with severe pneumonia have higher levels of serum AT-III, D-D and SP-B than normal children, and the changes in these indices can reflect the treatment and prognosis of the neonates, hence they can be used for clinical monitoring of diseases[18,19]. Serum AT-III is able to bind to other serine proteases and thrombins, thus exerting its inactivating effect. D-D is capable of maintaining the patency of blood vessels and excretory ducts and promoting hemodynamics in the body. SP-B, secreted and synthesized by alveolar type II cells, can increase the phospholipids in PS and exert antibacterial and lung-protecting effects. In this study, the observation group had raised levels of AT-III and SP-B but reduced D-D level compared with those of the control group after treatment, indicating that the application of exogenous PS can not only ameliorate the expression levels of serum factors AT-III, D-D and SP-B, but also improve the prognosis of neonates. Furthermore, CPIS was lower in the observation group after treatment, implying that exogenous PS is able to relieve pulmonary infection and lung consolidation in neonates with severe infectious pneumonia.

The PCT level in the peripheral blood of healthy people remains extremely low and can hardly be detected[20,21]. Nevertheless, when the body is invaded and infected by bacteria, PCT can be constantly generated and released by almost all solid tissues such as liver, kidney and lung as well as diversified cells including monocytes, myocytes and adipocytes under the stimulation and induction of inflammatory cytokines and bacterial toxins. Therefore, the PCT level in the peripheral blood can be detected at 4 h after bacterial infection and rise dramatically 6 h later, without decline within 24 h[22]. When the bacterial infection is controlled, the serum PCT level is restored to the normal level quickly, so PCT can be used as a specific indicator to identify bacterial and non-bacterial infectious diseases, and an indicator to evaluate the efficacy of antibiotics in treating bacterial infectious diseases[23]. IL-6 is mainly produced by mononuclear macrophages and activated T cells and can promote and inhibit the immune compensation of inflammatory response, whose level change is mitigated with the relief of inflammation[24]. The serum hs-CRP is an acute phase reaction protein synthesized and secreted by the liver through the induction of IL-6. Its level is fairly low in normal body but rises rapidly and significantly in the case of acute inflammatory response[25]. In this study, the PCT, hs-CRP and IL-6 levels at 7 d after treatment decreased in both groups compared with those before treatment (P <0.05), and the observation group had lower levels than those of the control group.

Conclusion

Results of the current study have demonstrataed that application of exogenous PS can effectively ameliorate the blood gas indices, oxygenation status and expression levels of AT-III, SP-B and D-D, and reduce the severity of pulmonary infection and level of inflammatory factors. Hence, this strategy can be used for the treatment of severe infectious pneumonia in neonates. To our knowledge, this is the first report from China to evidence such effect of this therapy on neonatal pneumonia. Regardless, this study is limited. The correlation amongst PCT, CRP and IL6 in patients was not analyzed, which needs further research.

Conflict of Interest

Authors declare no competing interests.

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