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Control study of pulmonary surfactant combined with CPAP and BIPAP ventilation modes respectively in treatment of neonatal NRDS

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ABSTRACT

Objective: To analyze the differences in effect of pulmonary surfactant combined with CPAP and BIPAP ventilation modes respectively in treatment of neonatal NRDS. **Methods:** A total of 50 cases of children with neonatal respiratory distress syndrome (NRDS) born and receiving treatment in our hospital from August 2012 to January 2015 were selected as research subjects and randomly divided into observation group and control group, each with 25 cases. Control group received pulmonary surfactant combined with CPAP ventilation mode treatment, observation group received pulmonary surfactant combined with BIPAP ventilation mode treatment, and then differences in blood gas indicators and mechanical ventilation parameters, pulmonary artery pressure, endothelin and nitric oxide levels, blood coagulation and anticoagulation indicators and protein expression levels of CD24, TNF-α, IL-6 and IL-17A of two groups after treatment were compared. **Results:** PaO_2, PH value and oxygenation index of observation group after treatment were higher than those of control group, and $PaCO_2$, positive end-expiratory pressure, peak inspiratory pressure and inspired oxygen concentration were lower than those of control group; pulmonary artery pressure and EF-1 level of observation group after treatment were lower than those of control group, and NO level was higher than that of control group; PC, TPS and AT-Ⅲ levels of observation group after treatment were higher than those of control group, and D-D and vWF levels were lower than those of control group; protein expression of CD24 and IL-6 of observation group after treatment were lower than those of control group, and protein expression of TNF-α and IL-17A were higher than those of control group. **Conclusion:** Pulmonary surfactant combined with BIPAP ventilation mode treatment of children with NRDS can effectively optimize ventilation function and realize homeostasis, and it has active clinical significance.

1. Introduction

Neonatal respiratory distress syndrome (NRDS), also known as hyaline membrane disease, is caused by insufficient pulmonary surfactant and often occurs in premature infants whose gestational age is too small[1]. The main clinical manifestation of NRDS is progressive respiratory distress, exogenous pulmonary surfactant replacement and respiratory support are the main treatment methods, and how to choose the most reasonable way of respiratory support is closely associated with the final treatment outcome. Both bi-phasic positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) are currently common respiratory support ways of treating NRDS. BiPAP contains pressure support ventilation and continuous positive airway pressure under spontaneous breathing, can switch between different ventilation modes according to patients' spontaneous breathing frequency, and can improve patients' comfort during ventilation and reduce patient-ventilator asynchrony[2,3]. CPAP means that in the condition of spontaneous breathing in patients, a mask was used to put continuous positive pressure airflow into the airway, which is conducive to preventing airway collapse, increasing functional residual capacity and

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improving pulmonary compliance. At present, clinical choice of respiratory support modes for treatment of children with NRDS is controversial, so in the research, the differences in effect of pulmonary surfactant combined with CPAP and BIPAP ventilation modes respectively in treatment of neonatal NRDS were specifically analyzed, hereby reported as follows.

2. Information and methods

2.1. General information

50 cases of children with neonatal respiratory distress syndrome (NRDS) born and receiving treatment in our hospital from August 2012 to January 2015 were selected as research subjects and randomly divided into observation group and control group, each with 25 cases. Control group included 14 male cases and 11 female cases, the gestational age was 31-34 weeks, the average was (32.81±1.76) weeks and birth weight was (1.34±0.27) kg; observation group included 13 male cases and 12 female cases, the gestational age was 30-34 weeks, the average was (32.76±1.89) weeks and birth weight was (1.41±0.37) kg. Differences in baseline information between two groups were without statistical significant, $P>0.05$ and they were comparable.

2.2. Intervention methods

Both groups were given timely treatment of oxygen uptake, opening airway, keeping warm, correcting acid-base balance and regulating water-electrolyte imbalance, suitable tracheal catheter was chosen for intubation and they received ventilator support ventilation. Meantime they received pulmonary surfactant therapy, which was as follows: injecting curosurf 200 mg/kg into tracheal catheter in twice, and conducting manual ventilation for 1min after each injection. Observation group received BiPAP ventilation mode, adjusting high positive end-expiratory pressure (PEEPH) and high PEEP level time (TH) to make tidal volume reach 5-6 mL/kg. Control group received CPAP ventilation mode treatment, controlling flow rate 4-6 L/min and keeping inspired oxygen concentration at 30%-50%. During respiratory support, ventilation parameters were adjusted according to children's conditions and blood gas analysis results.

2.3. Observation indexes

After intervention, arterial blood was drawn from children, and blood gas machine was used to detect partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), PH value and oxygenation index. Mechanical ventilation parameters were recorded, including positive end-expiratory pressure (cmH_2O), peak inspiratory pressure (cmH_2O) and inspired oxygen concentration. Pulse ultrasonic Doppler diagnostic equipment was used to detect pulmonary artery pressure, which was reflected by the ratio of pulmonary arterial flow acceleration time (TPV) and right ventricular ejection time (RVET); radioimmunoassay was used to detect endothelin-1 (ET-1) level and nitrate reductase was used to detect nitric oxide (NO) level. Enzyme-linked immunosorbent assay was used to detect plasma protein (PC), total protein S (TPS) and D-dimer (D-D), and immunoturbidimetry was used to detect antithrombin Ⅲ (AT-Ⅲ) and von Willebrand Factor (vWF) levels. Real-time quantitative Weston-blot was used to detect protein expression of CD24, TNF-α, IL-6 and IL-17A in peripheral blood.

2.4. Statistical methods

SPSS 23.0 software was used for statistical analysis of above data, measurement data (Mean±SD) was by *t* test, count data was by *chi*-square test, and obtained results were considered to be statistically significant at a level of $P<0.05$.

3. Results

3.1. Blood gas indicators and mechanical ventilation parameters

After two groups received different intervention, mechanical ventilation data was recorded, arterial blood was drawn to detect blood gas indicators, and results showed that PaO_2, PH value and oxygenation index of observation group after treatment were higher than those of control group, and $PaCO_2$, positive end-expiratory pressure, peak inspiratory pressure and inspired oxygen concentration were lower than those of control group ($P<0.05$), shown in Table 1.

Table 1

Comparison of blood gas indicators and mechanical ventilation parameters between two groups after treatment

Groups	PaO_2 (kPa)	$PaCO_2$ (kPa)	PH value	Oxygenation index	Positive end-expiratory pressure	Peak inspiratory pressure	Inspired oxygen concentration
Observation group	11.92±1.17	5.41±0.47	7.35±0.16	66.71±5.95	3.12±0.29	14.39±1.32	39.72±3.59
Control group	9.21±0.87	7.62±0.69	7.20±0.11	43.59±4.05	4.76±0.85	19.11±1.78	56.81±5.04
t	6.982	7.129	5.281	9.204	6.172	8.374	7.923
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

3.2. Pulmonary artery pressure, endothelin and nitric oxide levels

After different respiratory support treatment, detection of pulmonary artery pressure as well as endothelin and nitric oxide levels in circulating blood of children showed that pulmonary artery pressure and EF-1 level of observation group after treatment were lower than those of control group, and NO level was higher than that of control group (P<0.05), shown in Figure 1.

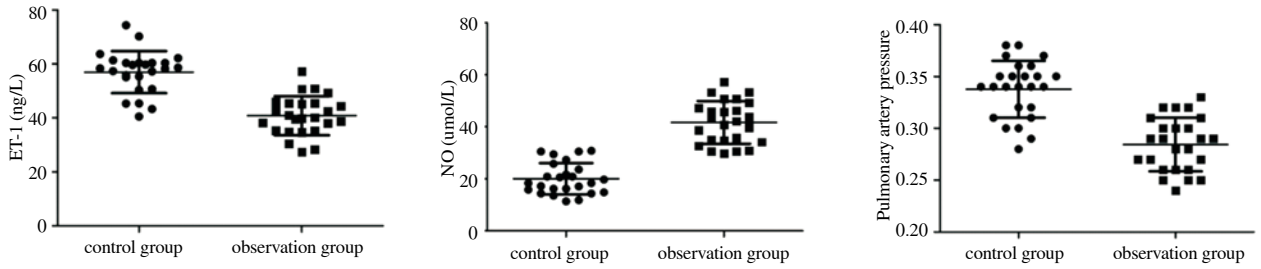

Figure 1. Comparison of pulmonary artery pressure, endothelin and nitric oxide levels after two groups received different treatment

3.3. Blood coagulation and anticoagulation indicators

There is widespread disorder of blood coagulation and anticoagulation indicator levels in children with NRDS, the levels change as the disease changes, and detection of blood coagulation and anticoagulation indicators through ELISA in the research showed that PC, TPS and AT-Ⅲ levels of observation group after treatment were higher than those of control group, and D-D and vWF levels were lower than those of control group (P<0.05), shown in Table 2.

3.4. Protein expression of CD24, TNF– α , IL–6 and IL–17A

Detection of protein expression of CD24 and related inflammatory factors through Weston-blot showed that protein expression of CD24 and IL-6 of observation group after treatment were lower than those of control group, and protein expression of TNF- α and IL-17A were higher than those of control group (P<0.05), shown in Figure 2.

Table 2

Comparison of circulating blood coagulation and anticoagulation indicator values between two groups after intervention

Groups	PC (g/L)	TPS (g/L)	D-D (mg/L)	AT-Ⅲ (mg/L)	vWF (%)
Observation group	2.31±0.19	20.37±1.89	0.27±0.02	152.28±13.47	189.36±15.48
Control group	0.92±0.07	15.82±1.34	0.69±0.05	98.55±8.45	215.23±18.94
t	6.495	7.124	5.483	7.928	6.384
P	<0.05	<0.05	<0.05	<0.05	<0.05

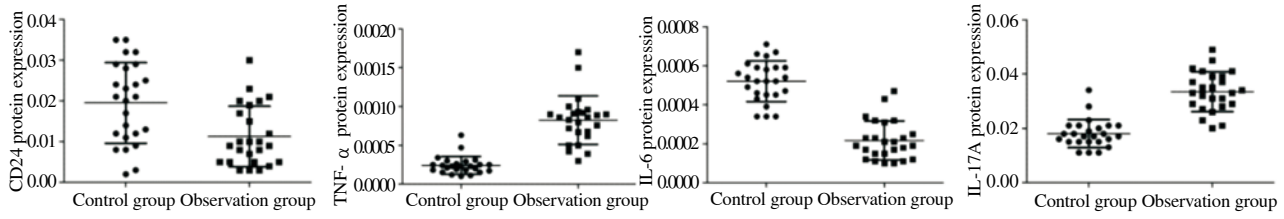

Figure 2. Comparison of protein expression of CD24, TNF- α , IL-6 and IL-17A in circulating blood between two groups after treatment.

4. Discussion

Neonatal respiratory distress syndrome (NRDS) is one of the important causes of neonatal asphyxia death and disability, and mostly occurs in premature infants whose gestational age is less than 35 weeks. Development of alveolar type Ⅱ cells in premature infants is immature, so the alveolar surface tension increases and pulmonary surfactant production is inadequate, which can gradually lead to decreased blood oxygen level and increased intrapulmonary shunt. Pulmonary surfactant has the role of preventing alveolar collapse, reducing pulmonary surface tension and so on, and application of exogenous pulmonary surfactant is expected to decrease alveolar surface tension and improve the present situation of poor oxygenation[4,5]. Effective ventilation treatment can promote the wide distribution and absorption of drugs and help to improve the effect of clinical treatment, but different choice of specific ventilation modes can lead to different treatment outcomes. Bi-phasic positive airway pressure (BiPAP) belongs to noninvasive ventilation mode, the essence is pressure support ventilation combined with positive end-expiratory pressure mode, it is the switching of two different continuous positive airway pressure ventilation according to the predesigned time frequency, the switching frequency is generally synchronized with patients' spontaneous breathing, and therefore, patients' spontaneous breathing is not restricted[6]. At present, BiPAP has been successfully used in treatment of acute respiratory distress

syndrome, respiratory failure and so on, and has obtained good results, but it is less applied in neonatal NRDS.

The first manifestation of neonatal NRDS is progressive dyspnea, and in cases of increased pulmonary artery pressure and right to left shunt, cyanosis in children is obvious and cannot be relieved by oxygen supply. Blood gas detection can show that there are seriously reduced partial pressure of oxygen, elevated partial pressure of carbon dioxide and poor oxygenation in children[7]. In the research, children received different modes of respiratory support, and then detection of blood gas indicators showed that PaO_2, PH value and oxygenation index of observation group after treatment were higher, and $PaCO_2$ value was lower, it indicated that BiPAP could maintain adequate gas exchange and improve pulmonary oxygenation in children during the entire respiratory cycle, and improvement of oxygenation could further promote the production of alveolar endogenous pulmonary surfactant, forming a virtuous circle. BiPAP belongs to flow trigger system, is the combination of pressure controlled ventilation and spontaneous breathing, improves children's comfort during ventilation and reduces patient-ventilator asynchrony, and is conducive to improving children's pulmonary compliance and oxygenation. BiPAP can effectively limit children's peak airway pressure and mean airway pressure, and under the ventilation mode, children's inspiratory flow rate can make peak airway pressure quickly reach its peak and maintain for a long time, which is conducive to rapid lung inflation and obtaining lower pressure of inflation[8,9]. Results of the research showed that positive end-expiratory pressure, peak inspiratory pressure and inspired oxygen concentration of observation group after respiratory support intervention decreased, and this is because that BiPAP allowed spontaneous breathing in any phase, played the double alveolar dilatation role of positive end-expiratory pressure and negative spontaneous breathing pressure, and reduced the injury of high airway pressure on lung function.

There is persistent pulmonary hypertension (PPHN) in most NRDS children, it is characterized by obviously increased pulmonary artery pressure and abnormal vascular reactivity, it can further aggravate hypoxemia, and severe cases can lead to children's bad response to oxygen uptake and vasodilator therapy[10]. Vascular tone and pulmonary circulation resistance of normal people are regulated by vasoactive substances, including endothelium-derived relaxing factor (EDRF) and endothelium-derived contracting factor (EDGF), nitric oxide (NO) is the main active component of EDFR and endothelin-1 (ET-1) is the main active component of EDGF, and their function will directly determine the pulmonary artery pressure and the subsequent treatment effect in NRDS children. ET-1 is produced by vascular epithelial cells and can cause durable vasoconstriction, under normal circumstances the vasoconstriction effect of endothelin is offset by relaxing factor produced by pulmonary vascular endothelial cells, and NO is the endogenous relaxing factor[11]. In the research, pulmonary artery pressure, ET-1 and NO levels of NRDS children were detected after treatment, and results showed that pulmonary artery pressure and EF-1 level of observation group after treatment decreased, indicating that pulmonary surfactant combined with reasonable mechanical ventilation mode could effectively optimize children's vascular relaxing and contracting factor levels, ultimately lower pulmonary hypertension and avoid complications and treatment difficulty caused by excessive pulmonary artery pressure.

Most NRDS children are with obvious bleeding tendency that mostly occurs in digestive tract and lungs, and severe cases may cause death in children. Studies have confirmed that there is abnormal anticoagulation and fibrinolytic system function in NRDS children, which plays an important role in disease development process. Both activated protein C (APC) and AT-Ⅲ are the physiological anticoagulants in blood system that are involved in the dynamic balance between anticoagulant and fibrinolytic system. AT-Ⅲ is combined with heparin or mucopolysaccharide to form active form that has the effect of inhibiting thrombin under physiological conditions, and in cases of NRDS, due to severe hypoxia and acidosis, vascular endothelial cell injury, pathological activation of coagulation pathway and so on can all cause that AT-Ⅲ combines with thrombinogen and form irreversible complexes, and the consumption increases, so AT-Ⅲ level dramatically decreases in NRDS children[12,13]. Plasma protein (PC) is the vitamin K-dependent plasma protein, its role in microcirculation has received more and more attention, and it relies on thrombin thrombomodulin (TM) complex to be activated into activated protein C to play its role. Total protein S (TPS) also acts as a cofactor to activate PC and play antagonistic effect, and study has confirmed that PC and TPS levels dramatically decrease in NRDS children, indicating that they are consumed when they antagonize thrombin. D-dimer (D-D) is specific cross-linked fibrin degradation product, the increase of it reflects the increase of thrombin in the body, and it is the specific indicator of hyperfibrinolysis. Von Willebrand Factor (vWF) is synthesized and secreted by vascular endothelial cells, and it is currently the sensitive indicator to reflect the damage of vascular endothelial cells. Increased vWF level mostly represents increased probability of thrombus and DIC in children. In the research, levels of anticoagulant and fibrinolytic parameters in children were detected after different treatment, and results showed that PC, TPS and AT-Ⅲ levels of observation group after treatment increased, and D-D and vWF levels decreased, indicating that pulmonary surfactant combined with BIPAP ventilation mode treatment could effectively reduce children's circulation hypercoagulable state.

NRDS is closely associated with pulmonary immaturity, inadequate synthesis of surfactant and so on. CD24 is a highly glycosylated

mucin that is mainly expressed in lymphocytes and granulocytes, and study in recent years has found that CD24 can be combined with ligand Siglec10 to negatively regulate NF- κ B signal by intracellular immunoreceptor Tyrosine-based inhibition motifs and block injury-related pro-inflammatory process. It is found in animal models with respiratory stress syndrome that the levels of inflammatory factors such as IL-6, TNF- α and IL-17A significantly increase[14]. In the research, levels of both CD24 and inflammatory factors were detected, and results showed that protein expression of CD24 and IL-6 of observation group after treatment decreased, and protein expression of TNF- α and IL-17A increased. CD24 can inhibit inflammatory response, NRDS children are in systemic inflammatory state before treatment, so CD24 expression reactively increases to fight inflammation, CD24 expression decreases when full oxygen uptake and other measures relieve the inflammatory state in children, so CD24 level can be used as an important molecular marker to judge systemic inflammatory state in children and its level is directly proportional to the severity of inflammatory response in children[15]. Literature has shown that levels of most inflammatory factors are affected by oxygen damage caused by oxygen uptake, levels of IL-6, MCP-1, TNF- α and so on in plasma may increase after continuous oxygen uptake, chemokines are inhibited when children are in hypoxic condition, so levels of above factors are lower before treatment and dramatically increase after treatment duo to good oxygen supply.

To sum up, it is concluded as follows: pulmonary surfactant combined with BIPAP ventilation mode treatment of children with NRDS can effectively optimize ventilation function and realize homeostasis, and it's worth popularization in clinical practice in the future.

References

[1] Solevag AL, Kann IC. N-BiPAP treatment in infants with respiratory distress syndrome: A population study. *Early Hum Dev* 2015; **91**(10): 577-581.

[2] Ricotti A, Salvo V, Zimmermann LJ, Gavilanes AW, Barberi I, Lista G, et al. N-SIPPV versus bi-level N-CPAP for early treatment of respiratory distress syndrome in preterm infants. *J Matern Fetal Neonatal Med* 2013; **26**(13): 1346-1351.

[3] Borowski KS, Clark EA, Lai Y, Wapner RJ, Sorokin Y, Peaceman AM, et al. Neonatal genetic variation in steroid metabolism and key respiratory function genes and perinatal outcomes in single and multiple courses of corticosteroids. *Am J Perinatol* 2015; **32**(12): 1126-1132.

[4] Hundalani SG, Richards-Kortum R, Oden M, Kawaza K, Gest A, Molyneux E. Development and validation of a simple algorithm for initiation of CPAP in neonates with respiratorydistress in Malawi. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**(4): F332-F336.

[5] Armanian AM, Badiee Z, Heidari G, Feizi A, Salehimehr N. Initial treatment of respiratory distress syndrome with nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure: a randomized controlled trial. *Int J Prev Med* 2014; **5**(12): 1543-1551.

[6] McAdams RM, Hedstrom AB, DiBlasi RM, Mant JE, Nyonyintono J, Otai CD, et al. Implementation of bubble CPAP in a rural ugandan neonatal ICU. *Respir Care* 2015; **60**(3): 437-445.

[7] Priyadarshi A, Quek WS, Luig M, Lui K. Is it feasible to identify preterm infants with respiratory distress syndrome for early extubation to continuous positive airway pressure post-surfactant treatment during retrieval? *J Paediatr Child Health* 2015; **51**(3): 321-327.

[8] Tagliaferro T, Bateman D, Ruzal-Shapiro C, Polin RA. Early radiologic evidence of severe respiratory distress syndrome as a predictor of nasal continuous positive airway pressure failure in extremely low birth weight newborns. *J Perinatol* 2015; **35**(2): 99-103.

[9] Iyer NP, Mhanna MJ. The role of surfactant and non-invasive mechanical ventilation in early management of respiratorydistress syndrome in premature infants. *World J Pediatr* 2014; **10**(3): 204-210.

[10] Lampland AL, Plumm B, Worwa C, Meyers P, Mammel MC. Bi-level CPAP does not improve gas exchange when compared with conventional CPAP for the treatment of neonates recovering from respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**(1): F31-F34.

[11] Martin S, Duke T, Davis P. Efficacy and safety of bubble CPAP in neonatal care in low and middle income countries: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2014; **99**(6): F495-F504.

[12] Daga S, Mhatre S, Borhade A, Khan D. Home-made continuous positive airways pressure device may reduce mortality in neonates withrespiratory distress in low-resource setting. *J Trop Pediatr* 2014; **60**(5): 343-347.

[13] Murki S, Deorari A, Vidyasagar D. Use of CPAP and surfactant therapy in newborns with respiratory distress syndrome. *Indian J Pediatr* 2014; **81**(5): 481-488.

[14] Moety GA, Gaafar HM, El Rifai NM. Can fetal pulmonary artery Doppler indices predict neonatal respiratory distress syndrome? *J Perinatol* 2015; **35**(12): 1015-1019.

[15] Borowski KS, Clark EA, Lai Y, Wapner RJ, Sorokin Y, Peaceman AM, et al. Neonatal genetic variation in steroid metabolism and key respiratory function genes and perinatal outcomes in single and multiple courses of corticosteroids. *Am J Perinatol* 2015; **32**(12): 1126-1132.