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Research Article
Effects of Pulmonary Surfactant Dose Selection in Late Preterm Infants with Respiratory Distress Syndrome

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Abstract

Background and Objective: Pulmonary surfactant, a lipoprotein from type II alveolar epithelial cells, reduces alveolar surface tension, restores alveolar function and enhances oxygenation, but optimal dosage remains uncertain in clinical practice. This study investigated the impact of different doses of pulmonary surfactant (PS) on blood gas indices, cerebral oxygen metabolism and complications in late preterm infants with Neonatal Respiratory Distress Syndrome (NRDS). **Materials and Methods:** A retrospective analysis of clinical data from 105 late preterm infants with NRDS was conducted, which were divided into low-dose group (LDG) (n = 27, starting dose of 100 mg/kg), medium-dose group (MDG) (n = 48, starting dose of 200 mg/kg) and high-dose group (HDG) (n = 30, starting dose of 250 mg/kg) groups. The three groups were compared in terms of clinical efficacy, treatment duration, complications and developmental status during follow-up. **Results:** The total effective rate was significantly higher in the HDG than in the LDG ($p<0.05$). The duration of mechanical ventilation, oxygenation and hospitalization was shorter in the HDG than in the MDG and LDG and shorter in the MDG than in the LDG ($p<0.05$). The HDG had higher levels of PaO_2, PaO_2/FiO_2, SOD and GSH-Px than the MDG and LDG and lower levels of $PaCO_2$, MDA, IL-6, IL-8 and TNF-α. The MDG had higher levels of PaO_2, PaO_2/FiO_2, SOD and GSH-Px than the LDG and higher levels of FiO_2, SOD and GSH-Px than the LDG, while having lower levels of $PaCO_2$, MDA, IL-6, IL-8 and TNF-α ($p<0.05$). **Conclusion:** The PS can effectively improve blood gas indices and cerebral oxygen metabolism in late preterm infants with NRDS. The starting dose of 250 mg/kg PS is more beneficial than 100 and 200 mg/kg.

Key words: Respiratory distress syndrome, pulmonary surfactant, late preterm neonate, blood gas index, cerebral oxygen metabolism

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Neonatal Respiratory Distress Syndrome (NRDS) is a commonly occurring respiratory disease in preterm infants, primarily caused by a deficiency in pulmonary surfactant (PS). The NRDS is a significant cause of morbidity and mortality in preterm infants[1]. Epidemiological studies indicate that the incidence of NRDS in preterm infants ranges from 5.0 to 10.0%, with a higher incidence associated with younger gestational ages. The NRDS poses a serious threat to the life of the child[2]. Presently, specific drugs for the treatment of NRDS are lacking and exogenous supplemental PS and Continuous Positive Airway Pressure (CPAP) ventilation are the primary treatments. The CPAP involves giving positive end-expiratory pressure during intermittent positive pressure breathing. This technique increases functional residual capacity, maintains alveolar pressure at the end of expiration, dilates alveoli, reduces intrapulmonary shunts, prevents alveolar atrophy and improves the patient's ventilatory function[3,4]. However, clinical practice has shown that although single CPAP can improve the ventilation of children, it has a minimal effect on cerebral oxygen metabolism and blood gas indices. The CPAP can also induce a series of complications such as ventilator-associated pneumonia. Furthermore, the treatment effect in some children is not satisfactory. Therefore, additional treatment modalities need to be combined with CPAP therapy to enhance the efficacy. The PS is a complex lipoprotein produced by alveolar type II epithelial cells (AT2). The PS reduces alveolar surface tension, restores the expansion capacity of atrophied alveoli, protects pulmonary epithelial cells, improves pulmonary oxygenation and function and increases pulmonary compliance in children[5]. However, there is no clinical consensus on the optimal dose of exogenous PS. Furthermore, infants with NRDS have impaired cerebrovascular autoregulation. Inappropriately used drugs after birth can increase cerebrovascular load, induce cerebral circulatory disorders, affect cerebral oxygen metabolism and increase the risk of complications[6]. Thus, this study aimed to analyze the effects of different doses of PS on blood gas indices, cerebral oxygen metabolism and complications in late preterm infants with NRDS.

MATERIALS AND METHODS

Clinical data: A clinical data of 105 infants born between June 2019 and December 2020, who were admitted to the hospital with NRDS was collected. The infants consisted of 54 males and 51 females, with a mean gestational age of 35.66±1.02 weeks and weight of 2771.52±185.63 g. The mode of delivery was by cesarean section in 80 cases and by natural birth in 25 cases. All infants were between 34-37 weeks of gestational age. The infants were divided into three groups based on the different starting doses of bovine surfactant (PS) given: LDG (n = 27), MDG (n = 48) and HDG (n = 30).

Selection criteria: The inclusion criteria were: (1) Gestational age between 34-37 weeks, (2) Singleton pregnancy, (3) NRDS met the diagnostic criteria outlined in the Prevention and Treatment of NRDS - European Consensus Guidelines 2019 Edition[7] and confirmed by blood gas index examination, (4) Onset within 72 hrs after birth and (5) Complete clinical data. The exclusion criteria were: (i) Congenital heart disease, (ii) Air leak syndrome, (iii) Intrauterine infection before delivery and (iv) Apgar score[8] <4 at 5 min after birth.

Ethical consideration: Written informed consent from the subjects' guardians was obtained before trial entry. The trial was approved by the Medical Ethics Committee of Hainan Modern Women and Child's Hospital.

Methods: The infants received bovine surfactant (PS) treatment through tracheal intubation within 4 hrs after admission to the hospital. The starting dose of PS was 100 mg/kg in the LDG, 200 mg/kg in the MDG and 250 mg/kg in the HDG. If the first administration was ineffective, an equal dose of PS was added once every 12 to 24 hrs. After administration, a continuous positive airway pressure treatment device was used for nasal congestion (Somnetics International, Inc., No. 20152083010) for Continuous Positive Airway Pressure (CPAP) therapy. The oxygen concentration (FiO_2) was adjusted to 21-70%. The machine could be weaned off when the CPAP pressure was lower than 4-5 cm H_2O, the oxygen saturation (SaO_2) did not show any sign of decreasing and the infant did not show any symptoms of bradycardia or apnea.

Observation indexes

Baseline information: The baseline characteristics of the infants were collected, including their sex (male or female), mode of delivery (cesarean section or vaginal delivery), gestational age and birth weight.

Clinical effectiveness: After 12 hrs of treatment, the effectiveness of the treatment was evaluated according to the diagnostic criteria outlined in the Practical Neonatology[9] textbook. Markedly effective treatment was defined as the resolution of clinical symptoms and signs, normalization of chest X-ray and blood gas indexes and restoration of stable

spontaneous breathing. Effective treatment was defined as significant improvement in clinical symptoms and signs, reduction in the intensity of respiratory support, stable vital signs and improvement in chest X-ray and blood gas indexes. Ineffective treatment was defined as no improvement or worsening of clinical symptoms and signs and no significant improvement in chest X-ray and blood gas indexes.

Treatment duration: The duration of mechanical ventilation, oxygenation and hospitalization was recorded for all three groups.

Cerebral oxygen metabolism: Cerebral oxygen saturation (ScO_2) levels were measured using a near-infrared spectrometer, HEALITE II C (Lutronic Corporation, 20172267215), 5 min before, during and 5 min after treatment.

Blood gas indexes: Partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and the ratio of PaO_2 to fraction of inspired oxygen (FiO_2) were measured before treatment and 12 hrs after treatment using a blood gas analyzer (Nova Biomedical Corporation, 20162223109).

Oxidative stress: While 6 mL of fasting venous blood were collected from each of the three groups before and 12 hrs after treatment, respectively and then centrifuged at 3500 revolutions per minute for 10 min. Serum samples were collected and the levels of superoxide dismutase (SOD), malondialdehyde (MDA) and Glutathione Peroxidase (GSH-Px) were measured by spectrophotometry. The MDA was also measured by Thiobarbituric Acid Reactive Substance (TBARS) assay.

Inflammatory response: The levels of Interleukins (IL-6, IL-8) and Tumor Necrosis Factor-alpha (TNF-α) were measured using Enzyme-Linked Immunosorbent Assay (ELISA) before and 12 hrs after treatment in both groups. The ELISA kits were provided by Beijing Kaishiyuan Biotechnology Co.

Developmental status: At 24 months after treatment, the developmental status of the children was assessed using the Gesell Developmental Scale (Gesell)[10]. The scale includes five dimensions of infant language, fine motor skills, personal-social skills, gross motor skills and adaptive skills, each with a score ranging from 0 to 100. Higher scores indicate better developmental status.

Complications: The occurrence of complications during treatment was recorded, including intracranial hemorrhage, pneumothorax and necrotizing enterocolitis.

Statistical analysis: The statistical software used for data processing was SPSS25.0. For dose data ($\bar{\chi}\pm s$), One-way Analysis of Variance (ANOVA) was used for comparison between multiple groups, with the results expressed as F values and paired comparisons within each group were conducted using the least significant difference (LSD) t-test, with results expressed as t values. For count data, percentages were used and examined using the Chi-square (χ^2) test. Rank data were analyzed using the rank sum test. A statistically significant difference was considered when $p<0.05$.

RESULTS

Comparison of baseline data: There were no significant differences ($p>0.05$) in baseline characteristics, including gender, mode of delivery, gestational age and weight, among the three groups. These results were presented in Table 1.

Comparison of clinical efficacy: The HDG had a higher total effective rate than the LDG ($p<0.05$). However, there was no significant difference in the total effective rate between the HDG and the MDG ($p>0.05$). Table 2 displayed these results.

Comparison of treatment duration and ScO_2 at different time points in three groups: The HDG had shorter durations of mechanical ventilation, oxygenation and hospitalization than the MDG and LDG and the MDG had shorter durations than the LDG ($p<0.05$). The ScO_2 during the drug administration was higher than that 5 min before administration in all three groups ($p<0.05$). However, there was no statistically significant difference when comparing the ScO_2 among the three groups 5 min before administration, during administration and 5 min after administration ($p>0.05$). These results were presented in Table 3.

Comparison of blood gas indexes: Before treatment, there were no significant differences in the blood gas indexes among the three groups ($p>0.05$). After treatment, the PaO_2 and PaO_2/FiO_2 in all three groups were higher than those before treatment and $PaCO_2$ was lower than that before treatment ($p<0.05$). The HDG had higher levels of PaO_2 and PaO_2/FiO_2 than the MDG and LDG after treatment and the HDG had lower levels of $PaCO_2$ than the MDG and LDG. The MDG had higher levels of PaO_2 and PaO_2/FiO_2 than the LDG

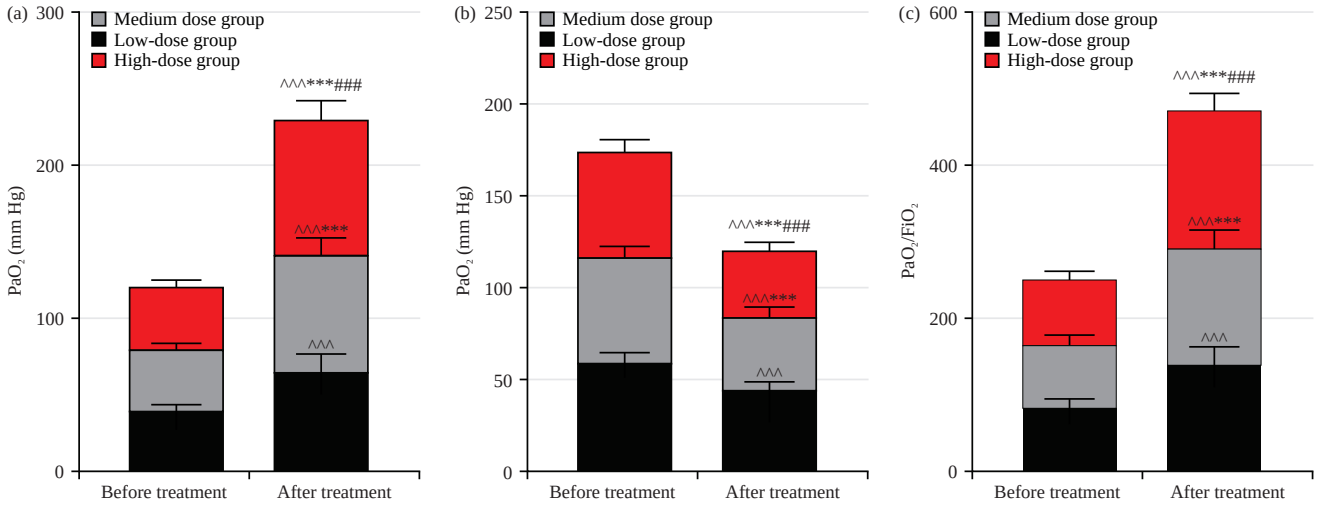

Fig. 1(a-c): Effect of dose selection of PS on blood gas indices in late preterm neonates with respiratory distress syndrome, (a) PaO_2, (b) $PaCO_2$ and (c) PaO_2/FiO_2

Compared with the low-dose group, ***p<0.001, compared with medium-dose group, ###p<0.00 and, compared within the same group before treatment, ^^^^p<0.001

Table 1: Comparison of baseline data

	Gender (cases (%))		Mode of delivery (cases (%))			
Group	Male	Female	Cesarean delivery	Natural birth	Gestational age/ ($\bar{\chi}\pm$s, weeks)	Body weight/ ($\bar{\chi}\pm$s, g)
Low-dose group (n = 27)	15 (55.56)	12 (44.44)	21 (77.78)	6 (22.22)	35.73±1.01	2770.25±198.63
Medium dose group (n = 48)	23 (47.92)	25 (52.08)	37 (77.08)	11 (22.92)	35.76±1.13	2768.69±176.39
High-dose group (n = 30)	16 (53.33)	14 (46.67)	22 (73.33)	8 (26.67)	35.59±1.26	2776.32±184.92

Table 2: Comparison of clinical efficacy n (%)

Group	Markedly effect	Effective	Ineffective	Total effective rate
Low-dose group (n = 27)	15 (42.86)	11 (31.43)	9 (25.71)	26 (74.29)
Medium dose group (n = 48)	20 (57.14)	11 (31.43)	4 (11.43)	31 (88.57)
High-dose group (n = 30)	27 (77.14)	7 (20.00)	1 (2.86)	34 (97.14)*

Compared with the low-dose group and *p<0.05

Table 3: Comparison of treatment duration and ScO_2 ($\bar{\chi}\pm$s)

				ScO_2 (%)		
Group	Duration of mechanical ventilation (d)	Oxygenation time (d)	Length of hospitalization (d)	5 min before administration	During administration	5 min after administration
Low-dose group (n = 27)	5.22±1.13	12.62±3.39	26.53±2.36	76.23±3.42	80.74±4.23***	77.01±3.55
Medium dose group (n = 48)	4.34±1.03*	10.86±3.15*	24.12±2.74***	77.23±3.32	81.16±4.19***	78.03±3.63
High-dose group (n = 30)	3.02±0.98***###	8.75±2.37***#	22.30±2.27***#	76.58±3.69	81.23±4.05***	78.32±3.53

Compared with the low dose group, *p<0.05, ***p<0.001, compared with medium dose group, #p<0.05, ###p<0.001 and compared with the 5 min before administration in same group, ***p<0.001

after treatment and the MDG had lower levels of $PaCO_2$ than the LDG (p<0.05). These results were presented in Fig. 1.

Comparison of oxidative stress indexes: Before treatment, there were no significant differences in the levels of oxidative stress indexes among the three groups (p>0.05). After treatment, the levels of SOD and GSH-Px in all three groups were higher than those before treatment and the levels of MDA were lower than those before treatment (p<0.05). The HDG had higher levels of SOD and GSH-Px than the MDG and LDG after treatment and the HDG had lower levels of MDA than the MDG and LDG. The MDG had higher levels of SOD and GSH-Px than the LDG after treatment and the MDG had lower levels of MDA than the LDG (p<0.05). These results were presented in Fig. 2.

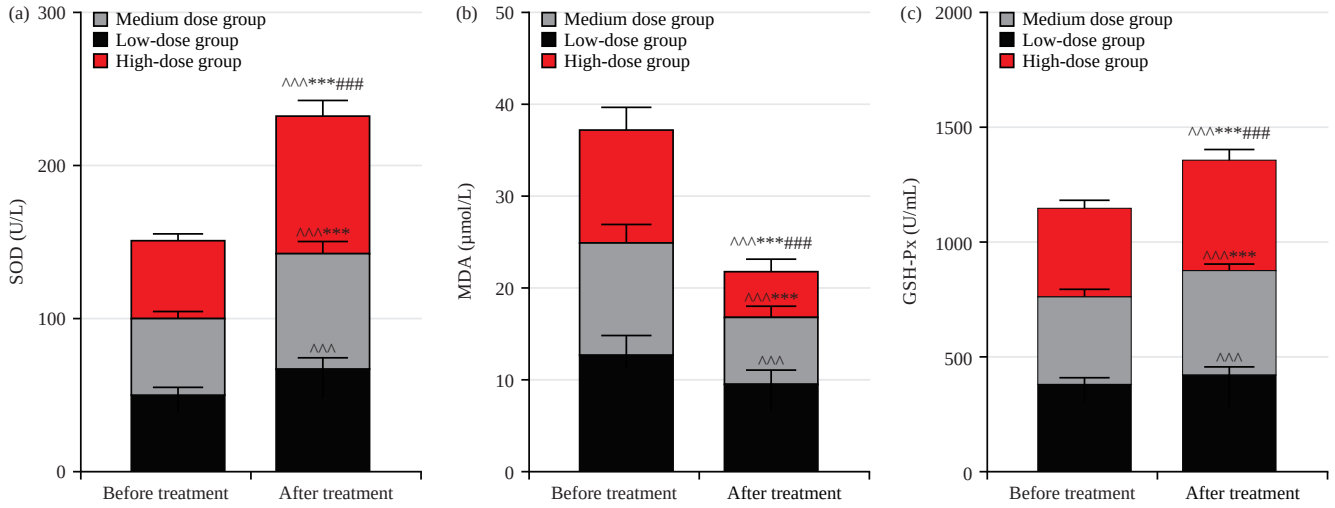

Fig. 2(a-c): Effect of dose selection of PS on oxidative stress indexes in late preterm neonates with respiratory distress syndrome, (a) SOD, (b) MDA and (c) GSH-Px

Compared with the low-dose group, ***p<0.001, compared with medium-dose group, ###p<0.001, compared within the same group before treatment and ^^^^p<0.001

Table 4: Comparison of inflammatory response ($\bar{\chi}\pm s$, ng/mL)

Time point	Group	IL-6	IL-8	TNF-α
Before treatment	Low-dose group (n = 27)	6.03±1.57	5.03±1.32	9.16±2.03
	Medium dose group (n = 48)	6.12±1.53	4.92±1.26	9.34±1.85
	High-dose group (n = 30)	5.86±1.68	5.08±1.35	8.86±2.11
After treatment	Low-dose group (n = 27)	4.36±1.03^^^^	3.54±0.86^^^^	6.54±1.52^^^^
	Medium dose group (n = 48)	3.16±0.84^^^^***	2.46±0.72^^^^^***	4.35±1.33^^^^***
	High-dose group (n = 30)	2.03±0.75^^^^***###	1.35±0.66^^^^^**###	3.03±1.02^^^^^**###

Compared with the low-dose group, ***p<0.001, compared with medium-dose group, ###p<0.001, compared within the same group before treatment and ^^^^p<0.001

Table 5: Comparison of Gesell scores ($\bar{\chi}\pm s$, points)

Group	Infant language	Fine-motor	Personal-social	Great-motor	Adaptation
Low-dose group (n = 27)	89.16±5.03	89.34±6.02	84.83±6.07	85.11±6.49	83.18±5.83
Medium dose group (n = 48)	90.32±5.14	87.95±6.23	85.09±5.33	84.83±5.84	84.63±4.36
High-dose group (n = 30)	91.28±5.32	88.26±7.28	84.18±5.87	85.66±3.36	85.57±5.64

Table 6: Comparison of complication rates n (%)

Group	Intracranial hemorrhage	Pneumothorax	Necrotizing colitis	Total
Low-dose group (n = 27)	2 (7.41)	4 (14.81)	2 (7.41)	8 (29.63)
Medium dose group (n = 48)	1 (2.08)	3 (6.25)	1 (2.08)	5 (10.41)
High-dose group (n = 30)	1 (3.33)	2 (6.67)	2 (6.67)	5 (16.67)

Comparison of inflammatory response indexes: Prior to treatment, there were no statistically significant differences (p>0.05) when comparing the levels of inflammatory response indexes among the three groups. Following treatment, the levels of IL-6, IL-8 and TNF-α decreased in all three groups compared to pre-treatment levels (p<0.05). Moreover, the HDG exhibited lower levels of IL-6, IL-8 and TNF-α than the MDG and LDG, while the MDG showed lower levels than the LDG (p<0.05) (Table 4).

Comparison of Gesell scores: There were no significant differences (p>0.05) in the infant and toddler language, fine motor, personal-social, gross motor and adaptive scores on the Gesell scale after treatment among the three groups (Table 5).

Comparison of complication rates among the three groups: When comparing the three groups, no statistically significant differences (p>0.05) were observed in the incidence of complications (Table 6).

DISCUSSION

Premature infants have insufficient production of PS due to immaturity and a lack of PS can lead to alveolar atrophy in preterm infants, causing dysfunction in pulmonary ventilation and air exchange, leading to NRDS[11]. The fetus begins to secrete PS at 18-20 weeks of gestation and gradually matures at 35-36 weeks. Despite late preterm infants having a higher gestational age than usual preterm infants, the amount of PS synthesis is still low, making them susceptible to NRDS[12]. Therefore, there is a need to actively explore clinical options to treat NRDS in late preterm infants. Currently, clinical treatment of NRDS mainly employs Continuous Positive Airway Pressure (CPAP) and supplemental exogenous PS, with CPAP being beneficial in increasing airway diameter and transpulmonary pressure, reducing airway resistance and promoting the restoration of spontaneous breathing[13]. However, CPAP cannot promote lung maturation by supplementing PS and the long-term treatment efficacy is limited. The PS can bind to alveolar type II cells and provide the material basis for endogenous PS synthesis, promoting lung maturation and improving clinical symptoms[14,15]. However, there is no uniform clinical standard for the optimal initial dose of PS and repeated use of PS has been observed clinically, increasing the risk of complications in infants[16].

Additionally, there is a molecular gap between exogenous and endogenous PS and whether exogenous PS can perform the same role on an equipotent basis requires further investigation. Thus, there is a clinical need to explore the effect of PS at different doses on the treatment of NRDS in late preterm infants. In this study, the HDG exhibited higher total clinical efficiency than the LDG and the duration of mechanical ventilation, oxygenation and hospitalization were shorter, with PaO_2 and PaO_2/FiO_2 being higher in the HDG compared to the MDG and LDG. The $PaCO_2$ was lower in the HDG compared to the MDG and LDG, indicating that high-dose PS can effectively improve the blood gas index, shorten the duration of mechanical ventilation and recovery time and improve clinical efficacy in late preterm infants with NRDS. The reason may be that normal alveoli have PS on their surface, synthesized by alveolar epithelial type II cells, which reaches its maximum synthesis between 22 weeks of gestation and birth, but preterm infants have low levels of PS due to incomplete lung development, leading to fetal hypoxia, damage to alveolar epithelial cells and triggering pulmonary atelectasis, inducing NRDS[17,18]. In contrast, exogenous PS can supplement the lack of PS in children with late preterm NRDS and PS can promote the adsorption and distribution of phospholipids to the alveolar air-liquid interface, promote the formation of a phospholipid monomolecular layer, thus reducing alveolar air-liquid interface tension, maintaining the relative stability of small and large alveoli and small airways, preventing small alveolar atrophy and large alveolar hyperinflation, thereby improving the blood gas index and promoting recovery[19,20]. The effect of PS treatment is significantly dose-dependent and high doses of PS can reduce alveolar tone faster and enhance the clinical effect.

The ScO_2 is a ratio of oxygen and oxyhemoglobin to deoxyhemoglobin in brain tissue blood, which can be assessed using near-infrared spectroscopy and effectively reflects brain tissue perfusion[21]. The present findings also demonstrated that ScO_2 was higher in all three groups during administration than 5 min before administration. However, there were no significant differences between the three groups in terms of ScO_2 at different time points and Gesell score at 24 months of follow-up. This suggests that different doses of PS have a minimal effect on brain oxygen metabolism in late preterm infants with NRDS and all doses can promote healthy child development. The reasons for this may be: (1) PS can maintain fluid balance between alveoli and capillaries, prevent an increase in intra-alveolar tissue fluid, promote lung fluid clearance and prevent pulmonary edema. Pulmonary ventilation may lead to changes in blood pressure, which can cause changes in ScO_2. Exogenous PS is a natural PS isolated from porcine or bovine lungs that is similar in composition to endogenous PS and can bind to alveolar type II cells to restore stable ScO_2 levels[22,23]. (2) When exhaling, the alveoli over-expand, PS molecules disperse and retraction force is enhanced, which can prevent alveolar over-expansion. When inhaling, the alveoli shrink, PS is denser and its effect is enhanced, which can reduce alveolar surface tension, avoid alveolar atrophy and improve clinical symptoms in children[24,25]. The study results also showed no significant difference in complication rates among the three groups, indicating that high-dose PS does not significantly increase the risk of complications in infants. However, further studies are necessary to investigate specific complications.

The pathogenesis of preterm NRDS involves oxidative, peroxidative and superoxidative reactions. In NRDS, oxygen free radicals increase, reducing the peripheral blood's ability to resist reactive oxygen radicals, aggravating cellular damage and even leading to apoptosis, thereby worsening the child's condition[26]. Therefore, reducing oxidative stress is crucial for improving the condition and prognosis of premature infants with NRDS. Additionally, the inflammatory response plays a significant role in the development of preterm NRDS[27]. Hypoxia-induced damage to cardiomyocytes in premature NRDS children results in the release of numerous enzymes

from cardiomyocytes into the bloodstream, activating inflammatory factors such as IL-6, IL-8, TNF-α and many others, leading to an inflammatory response. The inflammatory response damages the pulmonary vascular endothelium and alveolar epithelium, increases capillary permeability and leads to the release of neutrophils and other inflammatory factors, exacerbating the inflammatory response, causing an imbalance in the ratio of blood flow and ventilation in the lungs and aggravating hypoxia. Thus, reducing the inflammatory response is crucial for improving pulmonary function in premature infants with NRDS. The study results showed that after treatment, the levels of superoxide dismutase (SOD) and Glutathione Peroxidase (GSH-Px) were higher in the HDG than in the MDG and LDG and the levels of malondialdehyde (MDA), IL-6, IL-8 and TNF-α were lower than in the MDG and LDG. This indicates that high-dose PS can effectively reduce oxidative stress, inhibit the inflammatory response and promote physical recovery in premature infants with NRDS.

CONCLUSION

To summarize, the present study suggested that exogenous PS can effectively improve the blood gas parameters and cerebral oxygen metabolism in late preterm infants with NRDS. A starting dose of 250 mg/kg of PS appears to be more effective in promoting recovery and healthy development of the infants, compared to doses of 100 or 200 mg/kg. The use of high-dose PS does not appear to significantly increase the risk of complications. The mechanism of action may involve the reduction of oxidative stress and inhibition of inflammatory response. However, as this study is a retrospective analysis, some bias may exist in the data collection process. Therefore, future studies with larger sample sizes and longer follow-up periods are needed to further confirm these findings in a multicenter and prospective manner.

SIGNIFICANCE STATEMENT

This study assessed the effects of different doses of pulmonary surfactant (PS) on blood gas indices, cerebral oxygen metabolism and complications in late preterm infants with Neonatal Respiratory Distress Syndrome (NRDS). The results indicated that a starting dose of 250 mg/kg of PS was more effective in improving blood gas parameters and clinical outcomes compared to lower doses. The high-dose group exhibited higher total clinical efficiency, shorter durations of mechanical ventilation and hospitalization and improved blood gas indices. High-dose PS did not significantly increase the risk of complications. These findings underscore the potential of high-dose PS in enhancing treatment efficacy and promoting healthy development in late preterm infants with NRDS, while also suggesting mechanisms involving oxidative stress reduction and inflammatory response inhibition.

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