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Comparative study of synthetic and natural-source pulmonary surfactants in the treatment of neonatal respiratory distress syndrome in very low birth weight neonates

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Abstract: To compare synthetic and natural-source pulmonary surfactants (PS) for treating neonatal respiratory distress syndrome (NRDS) in very low-birth-weight neonates. A total of 113 neonates with NRDS were retrospectively divided into the natural-source PS group (NSPS, 63 cases) and the synthetic PS group (SPS, 50 cases). Oxygenation, ventilation, complications, efficacy and mortality were compared. Binary logistic regression analysis was performed using Statistical Package for the Social Sciences (SPSS) 23.0 to analyze the impact of PS type on the treatment of NRDS in very low birth weight neonates (VLBWIs). Additionally, the receiver operating characteristic curve (ROC) and the area under the curve (AUC) were calculated and evaluated to assess the association and closeness between PS type and the treatment of NRDS in VLBWIs. After treatment, NSPS group had higher arterial partial pressure of oxygen (PaO_2), lower arterial partial pressure of carbon dioxide ($PaCO_2$) and oxygenation index (OI). It also had shorter ventilation and hospital stay, lower pneumothorax, total-complication and mortality rates and higher effective rate. PS type correlated with complications and efficacy; the closeness (AUC) order was: clinical efficacy > complications. Natural-source PS in treating NRDS in very low-birth-weight neonates improves efficacy, optimizes blood gas, shortens treatment and reduces complications and mortality.

Keywords: Natural source; NRDS; Pulmonary surfactant; Synthetic; Very low birth weight neonates

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INTRODUCTION

Neonatal respiratory distress syndrome (NRDS) is one of the important causes of morbidity and mortality in very low birth weight infants (VLBWIs) (Shin *et al.*, 2024). VLBWIs refer to neonates with a birth weight of less than 1500 grams. Due to the immature development of various organ systems and imperfect physiological functions, this group faces numerous health risks and NRDS is one of the most common and severe conditions (Jang *et al.*, 2023).

The incidence of NRDS is closely related to the birth weight and gestational age of neonates. The lower the birth weight and the smaller the gestational age, the higher the incidence of NRDS. According to relevant statistical data, the incidence of NRDS can be as high as 80%-90% in neonates with a birth weight of less than 1000 grams. In VLBWIs with a birth weight of 1000-1500 grams, the incidence is also around 50%-70% (Wondie *et al.*, 2023). This high incidence seriously threatens the life and health of VLBWIs and brings a heavy burden to families and society.

Pulmonary surfactant (PS) can effectively reduce the surface tension of alveoli, maintain alveolar stability and improve oxygenation. It is currently a key measure for the treatment of NRDS (Guo *et al.*, 2023). Natural-source PS is predominantly extracted from animal lung tissues, most commonly bovine or porcine lungs. Its composition closely mimics the body's endogenous pulmonary surfactant, consisting of a complex mixture of phospholipids, such as phosphatidylcholine and phosphatidylglycerol and specific proteins like surfactant-associated proteins A, B, C and D. These components work in concert to enhance the surface-active properties, enabling more efficient alveolar stability and lung function restoration (Wang *et al.*, 2023). Synthetic PS, on the other hand, is produced through chemical synthesis processes. It typically contains synthetic phospholipids and may lack some of the protein components found in natural PS. Although it offers advantages such as well-defined composition, stable quality and no risk of infectious agent transmission, the absence of these proteins might potentially lead to differences in its therapeutic performance compared to natural PS (Walther and Waring, 2024).

Although both types of PS are widely used in clinical practice, comprehensive and systematic comparative studies on their use in the treatment of NRDS in VLBWIs are still relatively scarce. Past studies have often focused on the efficacy observation of a single type of PS or simply compared them in a relatively large sample of neonatal populations, lacking in-depth analysis of the special group of VLBWIs. Moreover, existing studies rarely comprehensively consider various factors such as the unique physiological characteristics of VLBWIs, the severity of the disease and the long-term effects of different treatment options.

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This study is the first to focus on this high-risk and special group of VLBWIs, aiming to comprehensively and systematically compare the effects of synthetic PS and natural-source PS in treating NRDS. Our comparison encompasses not only short-term treatment indicators like oxygenation improvement and mechanical ventilation time but also delves deep into the impact of the two types of PS on the long-term complication rate and mortality of these infants. Additionally, by integrating the physiological characteristics and disease progression of VLBWIs, this study will explore the underlying mechanisms of different types of PS, providing more targeted and precise guidance for clinical treatment. This research is expected to fill the existing research gap in this field, offering a scientific basis for further optimizing the treatment strategy for NRDS in VLBWIs, thus holding significant clinical practical significance and research value.

MATERIALS AND METHODS

A retrospective selection was made of 113 neonates with very low birth weight diagnosed with NRDS who were admitted to the hospital from January 2021 to June 2024. To enhance the scientific rigor of subject selection, a statistical model was utilized to stratify the potential candidates. Key factors such as gestational age, birth weight and initial severity of respiratory symptoms were incorporated into a logistic regression model. This model helped in estimating the likelihood of each neonate's inclusion based on the pre-defined criteria.

Gestational age between 24-34 weeks at birth, birth weight < 1500 g; Progressive dyspnea, groaning, cyanosis and other symptoms occurred after birth and chest X-ray examination showed typical NRDS manifestations (Lin *et al.*, 2024); The chest X-ray confirmed compliance with the clinical diagnostic criteria of NRDS (De Luca *et al.*, 2022); Treated with synthetic or natural-source PS. Neonates with severe congenital heart disease, chromosomal abnormalities, intracranial hemorrhage and other serious diseases; Incomplete clinical data.

Bioequivalence (BE) studies play a crucial role in evaluating the similarity of different therapeutic agents. In the context of treating NRDS with PS of synthetic and natural sources, understanding the concept of clinical endpoints in BE studies is essential. Clinical endpoints are observable and measurable outcomes that reflect the impact of treatment on the patient's condition. They serve as the basis for determining whether two formulations of a treatment, such as the two types of PS in this study, have comparable therapeutic effects. This study aims to define and measure relevant clinical endpoints to assess the BE of synthetic and natural-source PS in VLBWIs with NRDS."

Oxygenation indices

As key clinical endpoints in evaluating the treatment of NRDS, we recorded the arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and oxygenation index (OI) before treatment and at 12 h, 24 h and 48 h after treatment. OI = (inspired oxygen concentration × mean airway pressure × 100) / arterial partial pressure of oxygen (Huang *et al.*, 2024). These oxygenation-related parameters directly reflect the improvement of the neonates' respiratory function, which is a crucial aspect in determining the BE of the two PS treatments. A significant improvement in these oxygenation indices in both groups, with comparable magnitudes, would suggest similar therapeutic effects in terms of oxygenation.

Mechanical ventilation-related indices

The duration of mechanical ventilation and hospital stay is also an important clinical endpoint. Shorter mechanical ventilation time and hospital stay often indicate better treatment effects. By comparing these values between the synthetic and natural-source PS groups, we can assess whether the two PS are bioequivalent in promoting the recovery of neonates with NRDS. Reductions in these parameters in both groups, without significant differences between them, would support the BE hypothesis.

Occurrence of complications

Observing and recording the incidence of complications such as pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD) and intracranial hemorrhage is an integral part of evaluating the treatment effect. These complications are key clinical endpoints as they not only affect the prognosis of neonates but also reflect the safety and effectiveness of the treatment. The lower the incidence of these complications in both the synthetic and natural-source PS groups and the more similar the incidence rates between the two groups, the more likely it is that the two PS are bioequivalent in terms of preventing complications. The diagnostic criteria for pneumothorax are as follows: The shadow shown on the bedside chest X-ray is a thin, convex arc-shaped line. The area within the thin line is the compressed lung tissue and outside the thin line, there are no visible lung markings, while the lung transparency is significantly increased. If the pneumothorax area is large or it is a tension pneumothorax, the chest X-ray shows that the heart and mediastinum are displaced to the healthy side. The diagnostic criteria for BPD: Requiring oxygen therapy 28 days after birth (Kribs *et al.*, 2023). The diagnostic criteria for intracranial hemorrhage: Cranial ultrasound shows strong echo light masses in the trigone area, beside the anterior horn of the lateral ventricle on one or both sides/subependymal area/inside the lateral ventricle, in the brain parenchyma/parasagittal area. As the intracranial hemorrhage gradually decreases and is absorbed, the echo of the strong echo light mass gradually decreases and finally, it gradually liquefies to form a smaller cystic lesion. It can also cause the shift of the brain midline, with or without the dilation of one or both lateral ventricles.

Clinical efficacy evaluation criteria

The evaluation of clinical efficacy at 48 hours post-medication is a direct clinical endpoint for assessing treatment effectiveness (Yang *et al.*, 2021). By classifying efficacy into three grades—marked effect, effective, and ineffective—based on the neonates' symptoms, signs, and blood gas analysis results, we can compare the overall treatment effectiveness of the two types of PS. A higher effective rate (calculated as (the number of cases with marked effect + the number of cases with effective) / the total number of cases × 100%) in both groups, with no significant difference between them, would indicate BE in terms of overall clinical efficacy.

Marked effect: The child's clinical symptoms and signs are significantly improved, the respiratory rate returns to normal, the child is calm, the complexion is ruddy and the limbs are warm.

Effective: The neonate's clinical symptoms and signs are moderately improved; breathing is shallow and rapid, but the neonate remains calm, with perioral cyanosis, cool limbs, and an acceptable response. Ineffective: The child's clinical symptoms and signs show no obvious improvement, the blood gas analysis shows no improvement, or the condition worsens.

Mortality rate

Recording in-hospital mortality (i.e., death of neonates during hospitalization) is a crucial clinical endpoint. A lower mortality rate in both the synthetic and natural-source PS groups and a similar mortality rate between the two groups would suggest that the two PS are bioequivalent in terms of saving the lives of neonates with NRDS.

The baseline data of patients, including: gestational age, birth weight, 5-minute Apgar score, gender, mode of delivery, prenatal use of hormones, intrauterine infection, complicated with gestational diabetes, respiratory distress syndrome (RDS) grading, etc.

Treatment with synthetic PS: The synthetic PS used was Calf Pulmonary Surfactant for injection, manufactured by China Resources Shuanghe Pharmaceutical Co., Ltd, with the approval number H20052128 and a specification of 70 mg. After the diagnosis of NRDS, a dose of 70 mg/kg was slowly injected into the lungs through tracheal intubation under aseptic conditions. During the administration process, the vital signs of the neonates were closely monitored. For specific operational details, please refer to the instruction manual.

Treatment with natural-source PS: The natural-source PS used was Poractant Alfa Injection. It was extracted from pig lungs, manufactured by Chiesi Farmaceutici S.p.A., with the approval number H20080428 and a specification of 3 mL: 0.24 g. First, tracheal intubation was performed. This product was then administered at a dose of 100 mg/kg, delivered via tracheal instillation, and repeated if PaO_2 dropped below 90 mmHg (1 mmHg = 0.133 kPa).

Other treatment measures: Both groups of neonates received routine care, including warmth preservation, nutritional support, and anti-infective therapy. Mechanical ventilation was provided as needed according to the condition. The FABIAN HFO neonatal ventilator for infants and young children, manufactured by ACUTRONIC Medical Systems AG, was used for mechanical ventilation. Appropriate ventilation parameters were set according to the neonates' body weight and condition to maintain blood gas indices within the normal range.

To ensure balanced groups for a more valid comparison of the two types of pulmonary surfactants, a propensity score matching (PSM) approach, a type of statistical modeling, was employed. First, a comprehensive set of baseline variables including gestational age, birth weight, 5-minute Apgar score and presence of intrauterine infections was used to construct a logistic regression model. This model generated propensity scores for each neonate, representing the probability of receiving a particular type of PS treatment based on their baseline characteristics.

Based on the type of PS administered, the selected neonates were divided into the natural-source PS group (NSPS group) and the synthetic PS group (SPS group). After the PSM process, the balance of these covariates between the two groups was evaluated using standardized differences. This statistical modeling-based grouping method minimized the potential confounding effects of baseline differences, making the comparison of treatment outcomes more reliable.

SPSS 23.0 was used for statistical analysis. Continuous data (measurement data) were expressed as mean ± standard deviation (x±s). The independent samples t-test was used for inter-group comparisons and the repeated measures analysis of variance was used for comparing data at different time points between groups. Categorical data (count data) were expressed as number of cases (n) and percentages (%), and a chi-square test (χ^2 test) was used for between-group comparisons. Binary logistic regression was used to analyze the impact of PS type on the treatment of NRDS in VLBWIs. The receiver operating characteristic curve (ROC) and the area under the curve (AUC) were used to evaluate the association and closeness between PS type and the treatment of NRDS in VLBWIs. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In the context of BE assessment, comparable baseline characteristics among groups are of utmost importance as

they enable the attribution of treatment outcome differences to the treatments themselves rather than pre-existing disparities.

There were 63 cases in the NSPS group and 50 cases in the SPS group. There were no significant differences in baseline characteristics such as gestational age, birth weight, 5-minute Apgar score, proportion of male infants, proportion of spontaneous deliveries, proportion of prenatal hormone use, proportion of intrauterine infections, proportion of cases complicated with gestational diabetes and RDS grading between the two groups ($P > 0.05$) (Table 1).

Changes in oxygenation indices

Oxygenation indices serve as key clinical endpoints for evaluating the BE of PS treatments for NRDS. Before treatment, there were no statistically significant differences in PaO_2, $PaCO_2$ and OI between the two groups of neonates ($P > 0.05$). At 12 h, 24 h and 48 h after treatment, the PaO_2 in the NSPS group was higher than that in the SPS group, the $PaCO_2$ was lower than that in the SPS group and the OI was also significantly lower than that in the SPS group, with statistically significant differences ($P < 0.05$) (Fig. 1). For PaO_2 (between-group effect: F = 481.000; time effect: F = 82.3100; interaction effect: F = 10.4000; all $P < 0.001$), $PaCO_2$ (between-group effect: F = 112.200, time effect: F = 43.220, all $P < 0.001$; interaction effect: F = 5.019, $P = 0.002$) and OI (between-group effect: F = 60.780; time effect: F = 23.260, all $P < 0.001$; interaction effect: F = 4.826, $P = 0.003$) in both groups, there were trends of increase or decrease over time.

Mechanical ventilation-related indicators

The duration of mechanical ventilation and hospital stay are vital clinical endpoints that mirror the treatment effect and are relevant to BE. The mechanical ventilation time and hospital stay in the NSPS group were (6.24 ± 1.56) days and (21.31 ± 4.25) days, respectively, while those in the SPS group were (8.52 ± 2.61) days and (28.21 ± 3.22) days, respectively. The mechanical ventilation time and hospital stay in the NSPS group were both shorter than those in the SPS group and the differences were statistically significant (t = 5.761, 9.513; both $P < 0.001$) (Fig. 2).

Incidence of complications

The incidence of complications is a crucial clinical endpoint for assessing treatment safety and BE. In the SPS group, the incidence of pneumothorax was 11.11%, the incidence of pulmonary hemorrhage was 9.52% (6 cases), the incidence of BPD was 17.46% and the incidence of intracranial hemorrhage was 6.35%. In the NSPS group, the incidence of pneumothorax was 24.00%, the incidence of pulmonary hemorrhage was 14.00%, the incidence of BPD was 20.00% and the incidence of intracranial hemorrhage was 12.00%. There were statistically significant differences in the incidence of pneumothorax and the total incidence of complications between the two groups (pneumothorax: $\chi^2 = 5.628$, $P = 0.018$; the total incidence: $\chi^2 = 7.380$, $P = 0.007$). The NSPS group had a lower incidence of pneumothorax and total complications. There were no statistically significant differences in the incidences of other complications ($P > 0.05$) (Fig. 3).

Clinical efficacy

Clinical efficacy represents a direct clinical endpoint for evaluating treatment BE. In the NSPS group, 35 cases showed marked effect, 26 cases were effective and 2 cases were ineffective, with a total effective rate of 96.83%. In the SPS group, 22 cases showed marked effect, 19 cases were effective and 9 cases were ineffective, with a total effective rate of 82.00%. The total effective rate of the NSPS group was higher than that of the SPS group and the difference was statistically significant ($P < 0.05$) (Fig. 4).

Mortality rate

Mortality rate is a critical clinical endpoint. Four cases died in the NSPS group, with a mortality rate of 6.35%. Ten cases died in the SPS group, with a mortality rate of 20.00%. The difference in mortality rates between the two groups was statistically significant ($\chi^2 = 4.786$, $P = 0.029$) and the NSPS group had a lower mortality rate.

Impact of PS type on the treatment of NRDS in VLBWIs

Taking PS type (assigned values: 0 = natural-source PS, 1 = synthetic PS) as the independent variable and taking complications (assigned values: 0 = no occurrence, 1 = occurrence), clinical efficacy (0 = effective, 1 = ineffective) and death (0 = survival, 1 = death) as the dependent variables respectively, a binary logistic regression model was used to analyze the impact of PS type on the treatment of NRDS in VLBWIs. PS type was significantly correlated with the occurrence of complications in NRDS of VLBWIs. PS type was an independent influencing factor for the occurrence of complications. That is, for every one-unit increase in this type, the risk of complication occurrence increased by 2.917 times.

PS type had a significant impact on the clinical efficacy of NRDS in VLBWIs and was a positive influencing factor for clinical efficacy. For every one-unit increase in this type, the likelihood of ineffective clinical efficacy increased by 6.695 times. PS type was significantly correlated with the death of VLBWIs with NRDS and was an independent influencing factor for death. For every one-unit increase in this type, the risk of death increased by 3.687 times (Table 2).

After controlling for baseline variables such as gestational age, birth weight, 5-minute Apgar score, gender, mode of delivery, prenatal hormone use, intrauterine infection, complicated with gestational diabetes and RDS grading, PS type was still significantly correlated with the occurrence of complications, clinical efficacy and death in NRDS of VLBWIs (Tables 3-5).

Table 1: Baseline characteristics

Items	NSPS group (n=63)	SPS group (n=50)	t	*P*
Gestational age (weeks)	29.75±2.12	30.15±1.83	1.057	0.293
Birth weight (kg)	1.03±0.21	1.05±0.22	0.492	0.623
5-minute Apgar score (points)	9.19±0.64	9.29±0.57	0.865	0.389
Male (n, %)	32 (50.79)	23 (46.00)	0.256	0.613
Spontaneous delivery (n, %)	18 (28.57)	15 (30.00)	0.028	0.868
Prenatal hormone use (n, %)	22 (34.92)	19 (38.00)	0.114	0.735
Intrauterine infection (n, %)	18 (28.57)	13 (26.00)	0.093	0.761
Complicated with gestational diabetes (n, %)	16 (25.40)	13 (26.00)	0.005	0.942
Complicated with gestational diabetes (n, %)			0.395	0.941
Grade I	30 (47.62)	26 (52.00)		
Grade II	21 (33.33)	15 (30.00)		
Grade III	9 (14.29)	6 (12.00)		
Grade IV	3 (4.76)	3 (6.00)		

NSPS: natural-source pulmonary surfactant group; SPS: synthetic pulmonary surfactant.

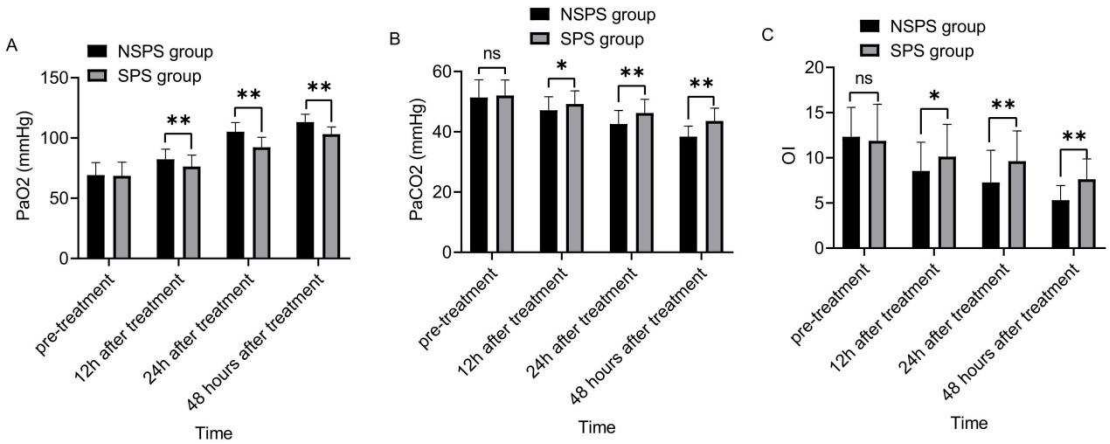

Fig. 1: Changes in oxygenation indices

NSPS: natural-source pulmonary surfactant group; SPS: synthetic pulmonary surfactant. (A) Arterial partial pressure of oxygen (PaO_2); (B) Arterial partial pressure of carbon dioxide ($PaCO_2$); (C) Oxygenation index (OI). ns: not significant ($P>0.05$); *$P<0.05$; **$P<0.001$.

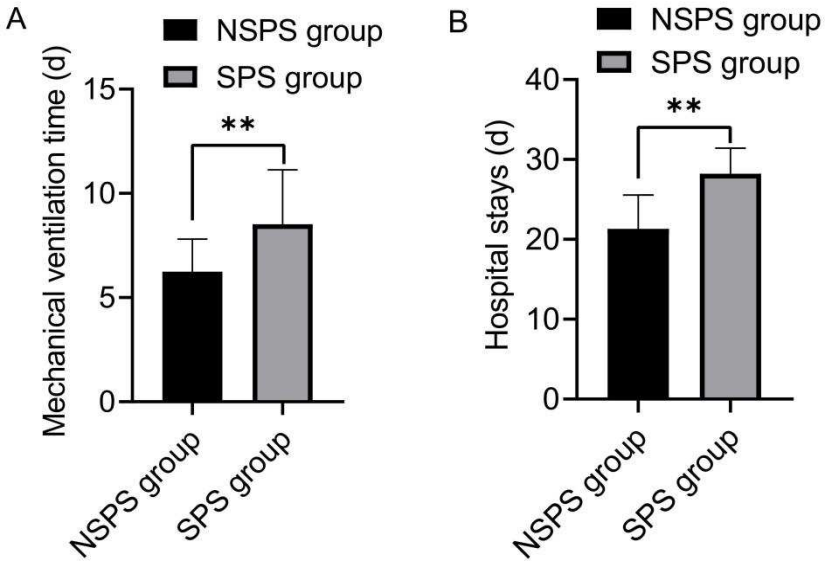

Fig. 2: Mechanical ventilation-related indicators

NSPS: natural-source pulmonary surfactant group; SPS: synthetic pulmonary surfactant. (A) Mechanical ventilation time; (B) Hospital stays. **$P<0.001$.

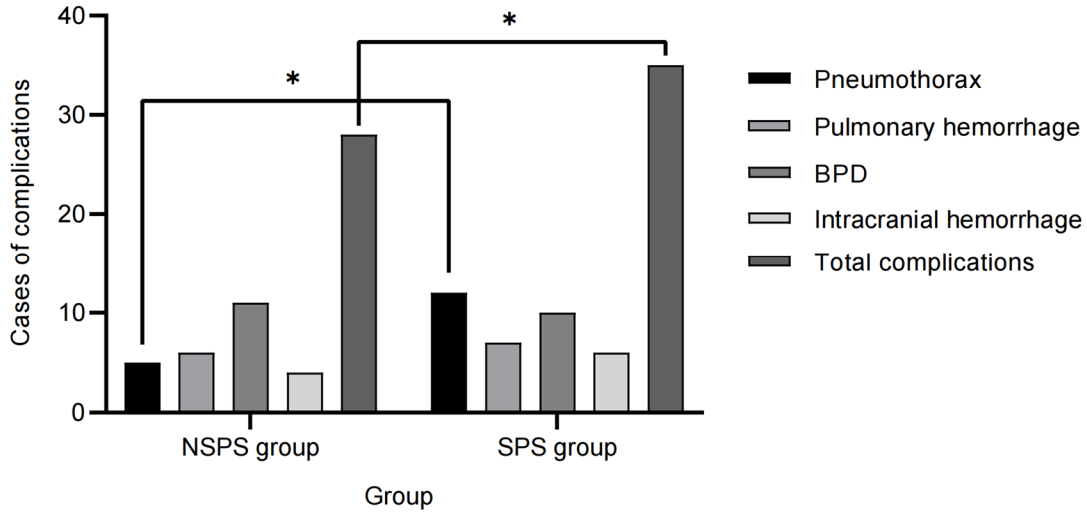

Fig. 3: Cases of complications
BPD: Bronchopulmonary dysplasia. NSPS: natural-source pulmonary surfactant group; SPS: synthetic pulmonary surfactant. *P < 0.05.

Table 2: Binary logistic regression analysis of the impact of PS type on the treatment of NRDS in VLBWIs

Variate	B	SE	Wals	P	OR
Complications	1.070	0.399	7.183	0.007	2.917 (1.333, 6.381)
Clinical efficacy	1.901	0.807	5.546	0.019	6.695 (1.376, 32.585)
Death	1.305	0.626	4.345	0.037	3.687 (1.081, 12.579)

PS: pulmonary surfactants; NRDS: neonatal respiratory distress syndrome; VLBWIs: very low birth weight infants; SE: standard error; OR: odds ratio.

ROC curve analysis
The ROC curve analysis showed that the PS type was closely associated with the complications and clinical efficacy of the treatment of NRDS in VLBWIs (P < 0.05). The order of closeness (AUC) was: clinical efficacy > complications (Table 6, Fig. 5).

DISCUSSION

In the treatment of NRDS in VLBWIs, the use of synthetic and natural-source PS has been a focus. This study systematically compared the two, providing insights into their performance, clinical value and mechanisms. Curosurf, a natural-source PS from bovine lungs, contains phospholipids, fatty acids and proteins. Its components mimic the body's own PS, reducing alveolar surface tension, maintaining alveolar stability and treating NRDS. The differences in efficacy between natural-source and synthetic PS are based on complex mechanisms.

Oxygenation improvement
Natural-source PS has advantages due to its unique composition. Proteins like SP-A, SP-B, SP-C and SP-D play key roles. SP-B and SP-C, with amphiphilic structures, insert into the alveolar air-liquid interface, reducing surface tension and maintaining alveolar patency at exhalation, thus enhancing oxygenation (Martínez-Calle *et al.*, 2021; Huang *et al.*, 2022). SP-A and SP-D, as part of the pulmonary immune defense, regulate the immune response, enhancing anti-infection ability and reducing the impact of inflammation on oxygenation (Avcibas *et al.*, 2024). In contrast, synthetic PS lacks some key proteins, leading to deficiencies in adsorption, spreading and immune regulation and a weaker oxygenation effect (Patel *et al.*, 2022).

Mechanical ventilation time and hospital stay
The advantages of the NSPS group in terms of mechanical ventilation time and hospital stay stem from its better oxygenation improvement effect. The rapid and effective enhancement of oxygenation enables the rapid recovery of the infants' respiratory function, allowing them to be weaned from mechanical ventilation at an earlier time (DiBlasi *et al.*, 2024). Shortening the mechanical ventilation time is crucial for reducing ventilator-related complications. During the mechanical ventilation process, due to the action of airway pressure, complications such as ventilator-associated pneumonia and barotrauma are likely to occur (Mandyam *et al.*, 2024). The natural-source PS, by optimizing oxygenation, reduces the need for high-pressure mechanical ventilation, decreases the risk of airway injury and infection and thus reduces the incidence of complications (Hernandez-Hernandez *et al.*, 2024).

Table 3: Binary logistic regression analysis of the impact of PS type on complications

Variate	B	SE	Wals	*P*	OR (95% CI)
PS type	1.325	0.46	8.297	0.004	3.761 (1.527, 9.262)
Gestational age (weeks)	-0.134	0.112	1.444	0.229	0.875 (0.703, 1.088)
Birth weight (kg)	0.097	0.527	0.034	0.854	1.102 (0.392, 3.098)
5-minute Apgar score (points)	0.294	0.288	1.042	0.307	1.342 (0.763, 2.362)
Gender	-0.763	0.444	2.95	0.086	0.466 (0.195, 1.114)
Mode of delivery	0.001	0.484	0	0.998	1.001 (0.388, 2.587)
Whether to use hormones	0.392	0.448	0.765	0.382	1.480 (0.615, 3.561)
Intrauterine infection	0.608	0.505	1.451	0.228	1.836 (0.683, 4.936)
Gestational diabetes	-0.202	0.48	0.177	0.674	0.817 (0.319, 2.094)
Complicated with gestational diabetes			7.292	0.063	
Grade I	1.057	1.002	1.113	0.291	2.878 (0.404, 20.506)
Grade II	2.021	1.062	3.624	0.057	7.547 (0.942, 60.473)
Grade III	2.33	1.177	3.918	0.048	10.275 (1.023, 103.183)

PS: pulmonary surfactants; SE: standard error; OR: odds ratio.

Table 4: Binary logistic regression analysis of the impact of PS type on clinical efficacy

Variate	B	SE	Wals	*P*	OR (95% CI)
PS type	2.287	1.001	5.215	0.022	9.844 (1.383, 70.084)
Gestational age (weeks)	-0.299	0.23	1.695	0.193	0.742 (0.473, 1.163)
Birth weight (kg)	-0.115	1.017	0.013	0.910	0.891 (0.121, 6.536)
5-minute Apgar score (points)	0.671	0.568	1.396	0.237	1.957 (0.643, 5.956)
Gender	-0.019	0.805	0.001	0.981	0.981 (0.202, 4.756)
Mode of delivery	-1.876	0.886	4.482	0.034	0.153 (0.027, 0.870)
Whether to use hormones	0.523	1.017	0.265	0.607	1.687 (0.230, 12.375)
Intrauterine infection	0.031	0.999	0.001	0.975	1.031 (0.146, 7.303)
Gestational diabetes	0.093	0.981	0.009	0.924	1.097 (0.160, 7.510)
Complicated with gestational diabetes			0.646	0.886	
Grade I	18.939	15244.62	0	0.999	1.68E+08
Grade II	18.417	15244.62	0	0.999	9.96E+07
Grade III	19.518	15244.62	0	0.999	3.00E+08

PS: pulmonary surfactants; SE: standard error; OR: odds ratio.

Table 5: Binary logistic regression analysis of the impact of PS type on mortality

Variate	B	SE	Wals	*P*	OR (95% CI)
PS type	2.646	0.914	8.381	0.004	14.103 (2.351, 84.613)
Gestational age (weeks)	-0.526	0.229	5.247	0.022	0.591 (0.377, 0.927)
Birth weight (kg)	1.923	1.074	3.208	0.073	6.845 (0.834, 56.175)
5-minute Apgar score (points)	-0.421	0.454	0.856	0.355	0.657 (0.269, 1.600)
Gender	0.298	0.69	0.187	0.666	1.347 (0.349, 5.204)
Mode of delivery	1.198	0.919	1.699	0.192	3.313 (0.547, 20.069)
Whether to use hormones	-0.251	0.748	0.113	0.737	0.778 (0.180, 3.367)
Intrauterine infection	-2.543	1.278	3.96	0.047	0.079 (0.006, 0.962)
Gestational diabetes	-1.28	0.945	1.834	0.176	0.278 (0.044, 1.773)
Complicated with gestational diabetes			1.614	0.656	
Grade I	-1.116	1.444	0.598	0.439	0.327 (0.019, 5.551)
Grade II	-0.322	1.546	0.043	0.835	0.725 (0.035, 15.014)
Grade III	-1.492	1.649	0.818	0.366	0.225 (0.009, 5.701)

PS: pulmonary surfactants; SE: standard error; OR: odds ratio.

Table 6: ROC curve analysis of the impact of PS type on treatment

Variate	AUC	SE	*P*
Complications	0.628 (0.524, 0.731)	0.053	0.020
Clinical efficacy	0.708 (0.559, 0.857)	0.076	0.024
Death	0.655 (0.559, 0.805)	0.076	0.061

ROC: receiver operating characteristic curve; PS: pulmonary surfactants; AUC: area under the curve; SE: standard error.

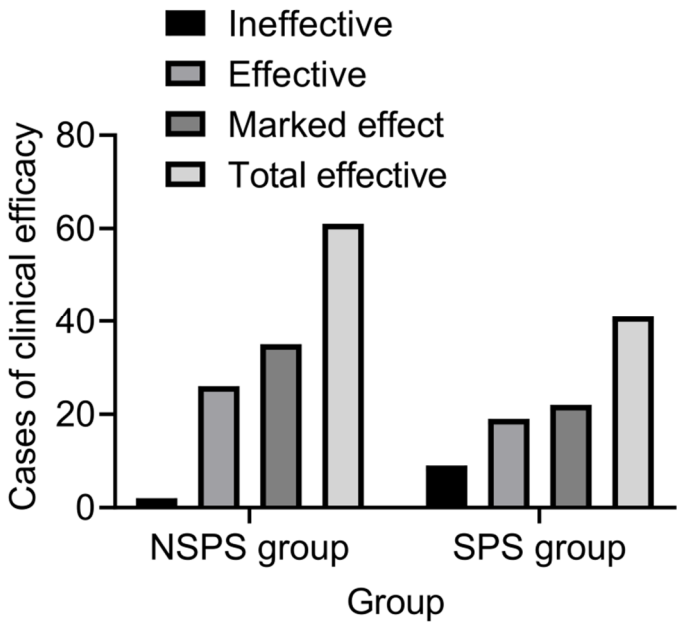

Fig. 4: Clinical efficacy
NSPS: natural-source pulmonary surfactant group; SPS: synthetic pulmonary surfactant.

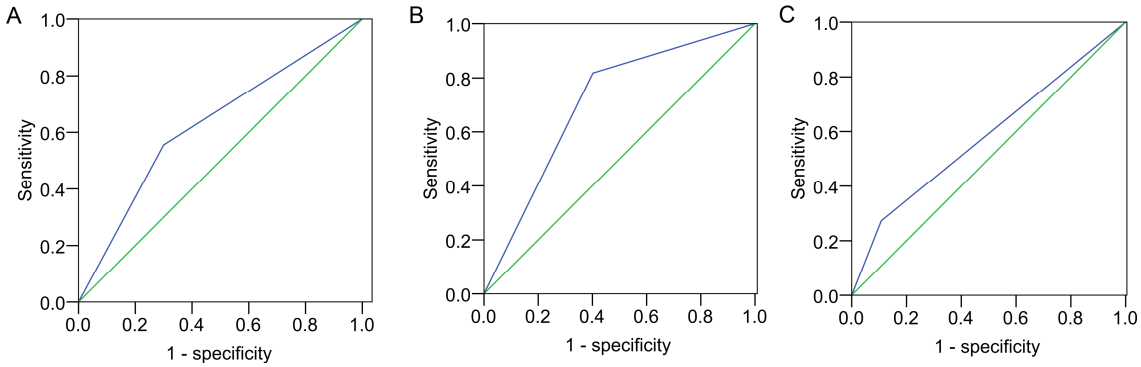

Fig. 5: Receiver operating characteristic curve (ROC) curves of the impact of pulmonary surfactants (PS) type on treatment
(A) Complications, (B) Clinical efficacy, (C) Mortality.

At the same time, a shorter hospital stay not only alleviates the economic burden on the infants' families but also reduces the risk of cross-infection during hospitalization, having a positive impact on the overall prognosis of the infants (Xu *et al.*, 2023).

Incidence of pneumothorax

Regarding the incidence of pneumothorax, the advantage of the NSPS group is also closely related to its ability to reduce alveolar surface tension. In NRDS infants, due to the lack of alveolar surfactant, the alveolar stability is poor. During the breathing process, the pressure fluctuation in the alveoli is relatively large, which easily leads to alveolar rupture and pneumothorax (Basheer *et al.*, 2022). The natural-source PS can more effectively reduce the alveolar surface tension, keep the alveoli stable during the breathing process, reduce the sharp changes in alveolar pressure, thereby reducing the risk of alveolar rupture and the occurrence of pneumothorax (Viitanen *et al.*, 2024).

Other complications

There were no significant differences in the incidence of pulmonary hemorrhage, BPD and intracranial hemorrhage between the two groups. These complications are caused by multiple factors. Pulmonary hemorrhage is related to coagulation, blood pressure and pulmonary vessel development (Katsoularis *et al.*, 2022). BPD involves prematurity, mechanical ventilation, infection and inflammation (Shin *et al.*, 2024). Intracranial hemorrhage is associated with cerebrovascular immaturity, blood pressure and hypoxic-ischemic injury (Sandoval Karamian *et al.*, 2022). PS type is not a decisive factor for these multi-factorial complications.

Clinical efficacy

Although PS plays a critical role in improving lung function, PS type is not a decisive factor for these complex, multifactorial complications. In terms of clinical efficacy, the NSPS group had a higher total effective rate and a lower mortality rate, which is a comprehensive manifestation of its advantages in aspects such as improving respiratory function and reducing complications. Natural-source PS has a component profile and mechanism of action that are more aligned with human physiological states, enabling it to more precisely correct the pathophysiological abnormalities of NRDS in neonates, provide more effective treatment for the infants and thus improve the quality of life and reduce the mortality rate (Kralovic-Kanjakova *et al.*, 2024).

Association between PS type and treatment outcomes

PS type is significantly associated with complications, clinical efficacy and mortality. Synthetic PS (coded as 1; natural-source PS coded as 0) was identified as a risk factor for complications. Its composition and structure differences from natural-source PS may affect its interaction with the alveolar surface, increasing complication risk (Sibrecht *et al.*, 2023). In terms of clinical efficacy, synthetic PS was associated with a 5.695-fold increased likelihood of treatment ineffectiveness, which is likely attributable to its relatively simplified component profile compared to natural-source PS (Possmayer, 2023). For mortality, each unit increase in synthetic PS increases the risk by 3.687 times, possibly due to adverse reactions or poor tolerance in VLBWIs (Li *et al.*, 2024). ROC curve analysis shows that PS type is closely related to complications and clinical efficacy, with clinical efficacy being more significantly affected. This helps clinicians select appropriate PS based on treatment goals.

Limitations

This study has certain limitations. The relatively small sample size may lead to bias in the research results, affecting the extrapolation and reliability of the conclusions. The limitation of a single-center study is that there are differences in treatment protocols and the basic conditions of infants in different regions and hospitals, which may affect the universality of the research results. In addition, only the short-term treatment effects were observed and the long-term effects of the two types of PS on the growth and development of infants were not evaluated. However, the long-term effects are crucial for a comprehensive understanding of the treatment effects and the formulation of scientific treatment strategies.

CONCLUSION

Natural-source PS has advantages in many aspects in the treatment of NRDS in VLBWIs. However, when choosing PS, clinicians need to comprehensively consider factors such as drug cost, accessibility and the individual conditions of infants to develop personalized treatment plans. In the future, long-term follow-up studies with larger sample sizes and multiple centers are needed to further explore the differences in efficacy and safety between the two types of PS, providing a more solid scientific basis for the treatment of NRDS.

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Authors' contributions

Jianjun Tang: Edited and refined the manuscript with a focus on critical intellectual contributions.

Tao Deng: Developed and planned the study, performed experiments and interpreted results.

Qijie Liu, Lina Zeng: Participated in collecting, assessing and interpreting the date. Made significant contributions to date interpretation.

Siyu Chen, Lanjuan Yang: Provided substantial intellectual input during the drafting and revision of the manuscript.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Chengdu Medical College, Chengdu Pidu District People's Hospital (HL-202006-D). All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that they have no conflict of interest. There are no financial, personal, or other relationships that could inappropriately influence the work presented in this manuscript.

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