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Original Article

Effect of pulmonary surfactant on the prevention of neonatal respiratory distress syndrome in premature infants

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Abstract: Objective: To investigate the effect of pulmonary surfactant on the prevention of neonatal respiratory distress syndrome (NRDS) in premature infants. Methods: A total of 216 premature infants in our hospital were selected. According to the guardian's choice, premature infants were grouped into treatment with pulmonary surfactant (PS) combined with nasal continuous positive airway pressure (NCPAP; the observation group) and treatment with NCPAP alone (the control group). The observation group was further divided into the young gestational age group (group A, 40 cases) and old gestational age group (group B, 74 cases), while the control group was divided into the young gestational age group (group C, 35 cases) and old gestational age group (group D, 67 cases). The incidence of NRDS, the first and second use of PS, the number of cases with mechanical ventilation, use of oxygen time, length of hospital stay and complications were observed. Results: The incidence of NRDS in the observation group was lower than that in the control group, but the first use rate of PS was higher than in the control group ($P<0.05$). The incidence of NRDS in group A was lower than that in the other three groups ($P<0.001$), while the mechanical ventilation rate in group C was higher than that in the other three groups ($P<0.001$). Use of oxygen time and length of hospital stay in groups A and C were higher than those in groups B and D ($P<0.001$). The mortality rate of group A was lower than that of group C ($P<0.05$). There was no difference in complications among patients with different gestational ages ($P>0.05$). Conclusion: Early use of PS can prevent the incidence of NRDS in preterm infants, significantly reduce the incidence of NRDS in neonates with young gestational age. It can also improve the survival rate of patients with young gestational age without increasing the incidence of complications.

Keywords: Preterm infant, pulmonary surfactant, prevention, neonatal respiratory distress syndrome, curative effect observation

Introduction

Neonatal respiratory distress syndrome (NRDS) is one of the most common diseases in preterm infants, which mainly occurs within 24 hours after birth, and becomes more serious and life-threatening at 48 hours [1]. NRDS has a high incidence and mortality rate, and it is an important factor affecting the life, and quality of life in premature infants [2]. The study also found that the younger the gestational age is and the smaller the birth weight is, the higher the incidence rate and the mortality rate of NRDS are [3]. Previous studies have found that the reason for the high incidence of NRDS in preterm infants is alveolar atrophy and collapse caused by the loss of pulmonary surfactant (PS) in preterm infants, which leads to the decline of lung compliance [4, 5]. The prevention and treatment principle of NRDS in preterm infants is to maintain normal pulmonary ventilation function. Nasal continuous positive airway pressure (NCPAP) is a common noninvasive breathing mode to maintain lung ventilation function. PS combined with NCPAP has a significant effect on the treatment of children with NRDS [6, 7]. Previous studies have suggested that PS preventive treatment should be carried out immediately after the birth of preterm infants with gestational age less than 32 weeks. Previous studies have shown that the incidence of NRDS in infants with a gestational age less than 28 weeks is as high as 60%, while the incidence of NRDS in infants with gestational age of 28-34 weeks is 30%, which is a bit lower than that in infants with gestational age less than 28 weeks. However, the incidence of NRDS was less than 5% in children with a gestational age of more than 34 weeks [8-10]. The 2013 European NRDS prevention and treatment guidelines proposed early PS treatment to prevent NRDS in high-risk preterm infants and did not recommend routine preventive treatment for all preterm infants [11]. Therefore, it is still controversial for the prevention of NRDS by PS in preterm infants. Based on this, this study observed the effect of early use of PS in preterm infants to prevent NRDS, in order to provide more evidence for clinical care.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of The Third People's Hospital of Haikou City. A total of 216 premature infants in The Third People's Hospital of Haikou City from January 2017 to June 2020 were selected and divided into the observation group (n=114) and the control group (n=102) according to the choice of the guardians for care. The infants in the control group were treated with NCPAP alone, while the infants in the observation group were treated with PS combined with NCPAP. The average gestational age of infants included in this study was 30.5±1.3 weeks, ranging from 28 weeks to 34 weeks. All the guardians of the premature infants included in our study signed the informed consent form.

Inclusion criteria

Conforming to the diagnosis of premature infants [12]. Singleton pregnancy; patients with gestational age between 28 and 34 weeks; without prenatal use of glucocorticoids; complete clinical data.

Exclusion criteria

Multiple pregnancies; patients with congenital heart disease; patients with genetic disease complicated with the cardiopulmonary disease; severe dyspnea after birth.

Methods

The control group was treated with NCPAP based on conventional treatment. NCPAP parameters were set as follows: FiO_2 concentration percentage (FiO_2) was 21-30%, oxygen flow was controlled at 6-8/min, the pressure was controlled at 6-8 cmH_2O. Mechanical ventilation was given if there were changes in the condition of patients after monitoring the development of the child's condition. The parameters of mechanical ventilation were: tidal volume 8-10 mL/kg, end-expiratory carbon dioxide ($ETCO_2$) 35-45 mmHg, respiratory rate 30-35 times/min, FiO_2 40%. If fetal distress symptoms occured during the treatment, or if FiO_2 was more than 30% to maintain SpO_2 at 90%, PS was given at 1.25-2.5 mL/kg. The medical solution was absorbed using sterile needles and syringes. Then the solution was directly dropped into the lower trachea through endotracheal intubation, or divided into two parts and dripped into the left and right main bronchus respectively. If FiO_2 was still not in the appropriate range after 6 hours, a second dose of PS was given.

Before NCPAP treatment in the control group, the observation group received PS (Casey pharmaceutical company, batch number: h2008-0428) 1.25-2.5 mL/kg first. The method of giving the medicine is described above. After extubation, NCPAP treatment parameters and follow-up mechanical ventilation parameters were the same as those of the control group. If FiO_2 needed increasing to maintain SpO_2 at 90%, a second PS treatment was given.

According to different gestational ages, the observation group was further divided into group A and group B, in which 40 cases were among the young gestational age group (28-30 weeks) and 74 cases were among the old gestational age group (31-34 weeks). The control group was divided into group C and group D, of which 35 cases were among the young gestational age group and 67 cases were among the old gestational age group.

Follow up methods: Outpatient follow-up or telephone follow-up were conducted every month, and the survival situation of the children in 3 months was recorded.

Observation index

Main outcome measures: The incidence of NRDS in the two groups and different gestational age groups were observed. The incidence of NRDS = the number of cases/the total number of cases * 100%. The diagnostic criteria of

Table 1. Comparison of general data in patients between the two groups ($\bar{x}$ ± sd)

Project	Observation group (n=114)	Control group (n=102)	χ^2/t	P
Gender (male/female)	70/44	65/37	0.124	0.725
Delivery mode (natural labour/cesarean section)	45/69	36/66	0.401	0.526
Gestational age (week)	30.7±1.4	30.4±1.3	1.646	0.101
Birth weight (g)	1,796.32±243.36	1,821.36±235.74	0.766	0.444
Neonatal Apgar score in one-minute	6.21±1.52	6.24±1.51	0.145	0.885
Neonatal Apgar score in five-minutes	7.12±1.85	7.06±1.78	0.242	0.809

NRDS [11]: (1) NRDS was diagnosed by clinical symptom assessment, blood gas analysis and X-ray examination. (2) Patients had typical clinical symptoms such as cyanosis, groan, dimples and shortness of breath. (3) Patients' arterial oxygen content/fraction of inspired oxygen is no more than 200 mmHg. (4) Chest X-ray examination showed infiltration of both lungs.

The first and second use of PS in two groups and different gestational age groups were observed.

The number of cases of mechanical ventilation, use of oxygen time and length of hospital stay of the two groups and different gestational age groups were observed.

Secondary outcome measures: The complications in the two groups and different gestational age groups were observed: apnea (AOP), pulmonary leakage, ventilator-associated pneumonia (VAP), bronchopulmonary dysplasia (BDP), intracranial hemorrhage (ICH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), extrauterine growth retardation (EUGR) [11]. The complications were recorded during the follow-up. Complication rate = number of incident cases/total cases * 100%.

Statistical methods

SPSS 17.0 was used to analyze the data. The continuous variables conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and those not conforming to normal distribution were expressed by M (P25, P75). The data conforming to a normal distribution and homogeneity of variance were tested by independent sample t test. A Paired sample t-test was used for intra-group comparison. One-way analysis of variance combined with the post-event Bonferroni test was used in the comparison between groups. The measurement data that did not conform to a normal distribution or the homogeneity of variance were compared by rank-sum test and expressed as Z. The count data were tested by the Pearson chi-square test, expressed as chi-square. Chi-square segmentation test were used for pairwise comparison between groups, and the test level is 0.0083. A logistic regression analysis was adopted. The occurrence of NRDS was taken as a dependent variable. Variables with differences in univariate analysis were selected. Gestational age, birth weight and PS use were regarded as independent variables, and the ward method was used to screen variables. The inclusion level was 0.05, and the exclusion level was 0.1. The risk of NRDS was expressed by an adjusted odds ratio (OR), and the difference was statistically significant when P<0.05.

Results

Comparison of general data between the two groups

There was no significant difference in general information of patients between the two groups (P>0.05), as shown in **Table 1**.

Comparison of the treatment process of patients between the two groups

The incidence of NRDS in the observation group was lower than that in the control group, but the first usage rate of PS was higher than that of the control group (P<0.05). There was no difference in the second use of PS, the number of cases of mechanical ventilation, the use oxygen time and the length of hospital stay (P>0.05). Further multivariate regression analysis showed that the usage of PS was a protective factor for NRDS. See **Tables 2-5**.

Comparison of the treatment process of patients among different gestational age groups

The incidence of NRDS in group A was lower than that in the other three groups (P<0.001),

Table 2. Comparison of treatment process in patients between the two groups ($\bar{x}$ ± sd)

Project	Observation group (n=114)	Control group (n=102)	χ^2/t	P
NRDS (%)	38 (33.33)	50 (49.02)	5.487	0.019
The first use of PS (%)	114 (100.00)	44 (43.14)	88.620	<0.001
The second use of PS (%)	5 (4.39)	8 (7.84)	1.138	0.268
Mechanical ventilation (%)	15 (13.16)	16 (15.69)	0.280	0.579
Using oxygen time (h)	89.36±2.51	88.89±3.47	1.149	0.252
Length of stay (d)	28.52±2.69	27.96±2.79	1.501	0.135

Note: NRDS: neonatal respiratory distress syndrome; PS: pulmonary surfactant.

Table 3. Univariate comparison among children with NRDS ($\bar{x}$ ± sd)

Project	Group with NRDS (n=88)	Group without NRDS (n=128)	χ^2/t	P
Gestational age (week)	29.9±1.1	30.9±1.4	4.768	<0.001
Birth weight (g)	1,703.81±254.23	1,902.12±221.45	6.058	<0.001
Use of PS (n)	38	76	5.478	0.019

Note: NRDS: neonatal respiratory distress syndrome; PS: pulmonary surfactant.

Table 4. Independent variable assignment table of influencing factors of the occurrence of NRDS

Factors	Independent variables	Assignment
Gestational age	X1	Gestational age ≤30 weeks =1, Gestational age >30 weeks =0
Birth weight	X2	Birth weight ≤1500 g =1, Birth weight >1500 g =0
Early use of PS	X3	Without early use of PS =1, Early use of PS =0

Note: NRDS: neonatal respiratory distress syndrome; PS: pulmonary surfactant.

Table 5. Multivariate regression analysis was performed according to whether NRDS occurred in children

Factors	β	SE	Wald value	OR (95% CI)	P
Use of PS	-0.276	0.072	13.283	0.743 (0.634-0.878)	0.004

Note: NRDS: neonatal respiratory distress syndrome; OR: odds ratio.

and the rate of mechanical ventilation in group C was higher than that in the other three groups (P<0.001). The oxygen use time and length of hospital stay in groups A and C were higher than those in groups B and D (P<0.001), respectively. See **Table 6**.

Comparison of complications after treatment in patients between the two groups

There was no significant difference in complications between the two groups (P>0.05), as shown in **Table 7**.

Comparison of complications in patients among different gestational age groups

There was no significant difference in complications among different gestational age groups (P>0.05). See **Table 8**.

Comparison of survival rate of patients between the two groups

There was no difference in the survival rate of patients between the two groups (P>0.05), as shown in **Table 9**.

Comparison of survival rate of patients among different gestational age groups

The mortality rate of newborns with young gestational age in group A treated with PS combined with NCPAP was lower than that of newborns in group C treated with NCPAP (P<0.05). The mortality rate of newborns in group C treated with NCPAP was higher than that of newborns with large gestational age in group D (P<0.05). See **Table 10** and **Figure 1**.

Discussion

NRDS is a frequent clinical disease of premature infants, and its pathogenesis is complex. Studies have shown that children with NRDS have pathological changes such as pulmonary edema and atrophy and arteriovenous intrapulmonary shunts, which lead to the decrease of

Table 6. Comparison of treatment process among patients with different gestational age ($\bar{x}$ ± sd)

Project	Group A (n=40)	Group B (n=74)	Group C (n=35)	Group D (n=67)	χ^2/F	P
NRDS (%)	8 (20.00)***,###,@@@	30 (40.54)	19 (54.29)	31 (46.27)	10.363	0.014
The first use of PS (%)	40 (100.00)###,@@@	74 (100.00)###,@@@	17 (48.57)	27 (40.30)	88.620	<0.001
The second use of PS (%)	2 (5.00)	3 (4.05)	4 (11.43)	4 (5.79)	2.390	0.496
Mechanical ventilation (%)	4 (10.00)###	11 (14.86)###	13 (37.14)@@@	3 (4.48)	20.737	<0.001
Using oxygen time (h)	90.89±2.49***,@@@	88.51±2.18###	91.27±3.22@@@	87.82±3.04	19.450	<0.001
Length of stay (d)	30.85±2.71***,@@@	27.38±1.73###	31.77±2.41@@@	27.91±1.92	50.591	<0.001

Note: A: the young and middle gestational age group in the observation group; B: the middle and old gestational age group in the observation group; C: the young and middle gestational age group in the control group; D: the middle and old gestational age group in the control group. Compared with Group B, ***P<0.001, compared with Group C, ###P<0.001, compared with Group D, @@@P<0.001. NRDS: neonatal respiratory distress syndrome; PS: pulmonary surfactant.

Table 7. Comparison of complications after treatment in patients between the two groups (n, %)

Project	Observation group (n=114)	Control group (n=102)	χ^2	P
AOP	38 (33.33)	35 (34.31)	0.023	0.879
Pulmonary leakage	5 (4.39)	3 (43.14)	0.315	0.575
VAP	5 (4.39)	5 (4.90)	0.032	0.857
BDP	2 (1.75)	3 (2.94)	0.335	0.563
ICH	5 (4.39)	5 (4.90)	0.032	0.857
NEC	3 (2.63)	2 (1.96)	0.107	0.743
ROP	2 (1.75)	0 (0.00)	1.806	0.179
EUGR	5 (4.39)	5 (4.90)	0.032	0.857
Total incidence	65 (57.02)	58 (56.86)	0.001	0.982

Note: AOP: apnea; VAP: ventilator associated pneumonia; BDP: bronchopulmonary dysplasia; ICH: intracranial hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; EUGR: ectopic growth retardation.

Table 8. Comparison of complications among patients with different gestational age (n, %)

Project	Group A (n=40)	Group B (n=74)	Group C (n=35)	Group D (n=67)	χ^2	P
AOP	14 (35.00)	24 (32.43)	12 (34.29)	23 (34.33)	2.017	0.569
Pulmonary leakage	2 (5.00)	3 (4.05)	2 (5.71)	1 (1.49)	3.139	0.371
VAP	3 (7.50)	2 (2.70)	2 (5.71)	3 (4.48)	3.011	0.390
BDP	1 (2.50)	1 (1.35)	1 (2.86)	2 (2.99)	3.208	0.361
ICH	2 (5.00)	3 (4.05)	2 (5.71)	3 (4.48)	1.710	0.635
NEC	1 (2.50)	2 (2.70)	1 (2.86)	1 (1.49)	1.825	0.609
ROP	1 (2.50)	1 (1.35)	0 (0.00)	0 (0.00)	3.325	0.251
EUGR	2 (5.00)	3 (4.05)	3 (8.57)	2 (2.99)	1.710	0.635
Total incidence	26 (65.00)	39 (52.70)	23 (65.71)	35 (52.24)	5.896	0.117

Note: A: the young and middle gestational age group in the observation group; B: the middle and old gestational age group in the observation group; C: the young and middle gestational age group in the control group; D: the middle and old gestational age group in the control group. AOP: apnea; VAP: ventilator associated pneumonia; BDP: bronchopulmonary dysplasia; ICH: intracranial hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; EUGR: ectopic growth retardation.

lung gas diffusion capacity, blood perfusion ratio and ventilation imbalance [13, 14]. It was reported that the occurance of NRDS was closely related to the absence of PS, and some studies suggested that the loss of PS led to the increase of alveolar tension and the decrease of pulmonary gas diffusion function [15]. Therefore, it is believed that PS combined with NCPAP is effective in the treatment of children with NRDS [16, 17]. Sun et al found that early use of PS has a good effect on the prevention of NRDS in preterm infants, and other studies have shown that the prevention of NRDS in preterm infants is safe and effective [18, 19]. It

Table 9. Comparison of survival rate of patients between the two groups (n, %)

Project	Observation group (n=114)	Control group (n=102)	χ^2	P
Survival	109 (95.61)	94 (92.16)	1.138	0.268
Death	5 (4.39)	8 (7.84)		

Table 10. Comparison of survival rate of children with different gestational age (n, %)

Project	Group A (n=40)	Group B (n=74)	Group C (n=35)	Group D (n=67)	χ^2	P
Survival	39 (97.50)	70 (94.59)	29 (82.86)	65 (97.01)	8.970	0.030
Death	1 (2.50)$^{\#}$	4 (5.41)	6 (17.14)$^{@}$	2 (2.99)		

Note: A: the young and middle gestational age group in the observation group; B: the middle and old gestational age group in the observation group; C: the young and middle gestational age group in the control group; D: the middle and old gestational age group in the control group. Compared with Group C, $^{\#}P<0.05$, compared with Group D, $^{@}P<0.05$.

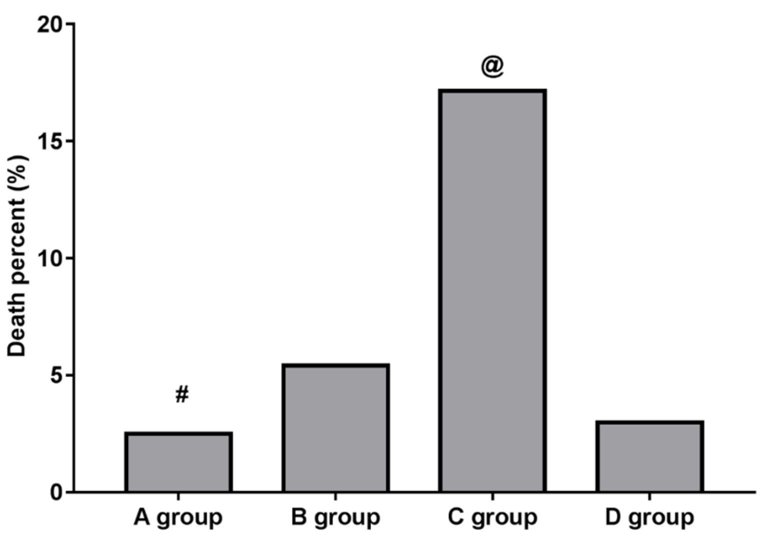

Figure 1. Comparison of mortality rate of children with different gestational age. A: the young and middle gestational age group in the observation group; B: the middle and old gestational age group in the observation group; C: the young and middle gestational age group in the control group; D: the middle and old gestational age group in the control group. Compared with group C, $^{\#}P<0.05$, compared with group D, $^{@}P<0.05$.

has been proven that the treatment with PS can reduce the use of oxygen time and mechanical ventilation time, which is conducive to the recovery of children [20]. This study also showed that the use of PS combined with NCPAP in preterm infants can reduce the incidence of NRDS, which is consistent with the above results. In this study, we further studied the prevention effect for NRDS in patients of different gestational ages. It was found that PS had a significant effect on preventing NRDS in young gestational age children, which can significantly reduce the incidence of NRDS, while the incidence of NRDS in young gestational age children without PS prevention in the early stage was significantly increased, which reflected the value of early application of PS in the prevention of NRDS. This study also showed that the use of oxygen time and length of hospital stay of young gestational age children were longer than those of old gestational age children, which may be attributed to the underdevelopment of young gestational children who need a longer time for treatment. For young gestational age children, early use of PS can maximize its role. PS mainly functions in the alveoli, which can effectively improve alveolar compliance, thus improving the children's ventilation and oxygenation function, and can protect the alveoli and capillaries from damage and reduce the fluid leakage in the pulmonary alveoli, to reduce lung injury [21, 22].

In terms of complications of the treatment, because PS needs endotracheal intubation for complete infusion, which is an invasive operation, the incidence of complications will increase [23]. A randomized controlled trial including the early use of PS combined with NCPAP and selective use of NCPAP according to the individual situations of children has shown that early use of PS can reduce the mechanical ventilation ratio in children and reduce the incidence of bronchopulmonary dysplasia and pulmonary air leakage [24]. However, it was found that both of the treatments can reduce the mortality and the incidence of pulmonary complications [25]. In this study, we found that there was no significant difference in complications between the two treatments, which was consistent with the results of previous studies. Therefore, this study suggests that PS combined with NCPAP will not increase the incidence of complications, which is safe and feasible. A six-month follow-up was conducted to observe the prognosis of the patients. Among them, the mortality of children with young gestational age using PS combined with NCPAP was the lowest, suggesting that the early use of PS in children with young gestational age is of great significance to improve the prognosis, because the use of PS immediately after birth can effectively reduce lung injury and the occurrence of NRDS [26].

The sample size of this study is small. Besides, it is a non-randomized controlled study and a single-center study. A multi-center randomized controlled study can be further conducted. The follow-up time of this study is short. We can further increase the follow-up time to observe the effect of early PS application on the long-term prognosis of children.

In conclusion, early use of PS can prevent the incidence of RNDS in preterm infants, significantly reduced the incidence of NRDS in young gestational age children without increasing the incidence of complications, and improved the survival rate of young gestational age children.

Disclosure of conflict of interest

None.

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