Clinical observation of alveolar surface active substances in the treatment of neonatal respiratory distress syndrome at different periods

Han Han
Affiliated Hangzhou First People's Hospital,Zhejiang Uniwersity School of Medicine
Xiao-xia Li
Affiliated Hangzhou First People's Hospital,Zhejiang University School of Medicine
Xiang-hua Shuai
Affiliated Hangzhou First People's Hospital,Zhejiang University School of Medicine
Zhi-qun Zhang
Affiliated Hangzhou First People's Hospital,Zhejiang University School of Medicine
Jing Li
Affiliared Hangzhou First People's Hospital,Zhejiang University School of Medicine
Hui Lu (luhui6699@qq.com)
https://orcid.org/0000-0003-3420-4610

Research article

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Abstract

Background: Mechanical ventilation joint PS replacement therapy is an effective method in treatment of NRDS recognized, PS treatment of children with early can improve the oxygenation by increasing gas exchange area, but before FiO 2 to reduce the application of PS can cause local and/or systemic hemodynamic changes, making the use of PS has some potential problems, such as increasing the incidence of the IVH, PH, PDA and so on. SR rescue therapy can be divided into early treatment and delayed treatment, but the specific boundary point of the appropriate time period has not been clear. This paper aims to compare the efficacy differences of PS administration at different time periods and provide basis for the selection of clinical application period of PS. Methods: Case-control study . 135 children diagnosed with NRDS in neonatology department of our hospital. The patients were divided into two groups according to the use time of PS. Group A was applied within 3 hours after birth, and group B was applied 3 hours after birth. The changes of blood gas analysis parameter、mechanical ventilation time, incidence of complications, hospital stay and mortality were compared between the two groups. Results : The decrease of blood gas PaCO 2 in group A before and after treatment was more significant than that of group B ($P<0.05$), but the improvement of PaO 2 and OI in group B was better than that in group A ($P<0.05$). Although there were significant differences in birth weight between the two groups, there were no significant differences in the total duration of mechanical ventilation and mortality ($P>0.05$). Except PDA and BPD, there was no significant difference in the incidence of common complications between the two groups. Conclusion: PS treatment within 3 hours after birth can better improve ventilation, reduce the incidence of PDA. It can also help to reduce the death rate of high-risk children and the total duration of mechanical ventilation.

Background

Neonatal respiratory distress syndrome (NRDS) is one of the common diseases of premature infants. It occurs due to a lack of pulmonary surfactant (PS) synthesis and secretion. This results in immature lung development, manifested by extensive alveolar collapse and decreased lung compliance. Symptoms include progressive dyspnea, hypoxemia, respiratory failure, etc. Furthermore, the incidence and mortality in preterm infants are higher. Early alveolar surface active substance replacement therapy (SR) can improve oxygenation by increasing the gas exchange area, but it can also cause local and/or systemic hemodynamic changes, leading to some potential problems in the use of PS.SR rescue therapy can be divided into early treatment and delayed treatment, but the specific boundary point of the appropriate time period has not been clear. This paper aims to compare the efficacy differences of PS administration at different time periods and provide basis for the selection of clinical application period of PS. It is reported as follows:

Methods

1. General Information

In total, 135 premature infants with respiratory distress syndrome diagnosed by NICU in our hospital from January 2016 to December 2018 were enrolled. Inclusion criteria consisted of the following: (1) children who were born in the obstetrics and gynecology ward of our hospital; (2) gestational age: 28 to 36 weeks; (3) in line with the “Practical Neonatology” on the NRDS diagnostic criteria; (4) agreed to accept PS treatment. Exclusion criteria were as follows: (1) death within 6 hours after birth; (2) congenital organ defects or other comorbidities; (3) complicated with severe pneumonia, meconium inhalation syndrome, amniotic fluid inhalation and other diseases; (4) severe heart, liver and kidney disease comorbidities; (5) child born pneumothorax, intracranial hemorrhage or mediastinal emphysema and other diseases.

The legal guardians of all children in this study signed informed consent. Patients were divided into group A (<3h) and group B (>3h) according to PS administration time after birth. Group A included 69 patients, including 36 males and 33 females, with an average body weight of 1670±550g and an average gestational age 31.35±2.40 weeks. There were 66 cases included in group B, including 33 males and 33 females, with an average body weight of 2000 ± 500g, mean gestational age was 32.45 ± 2.04 weeks. The general data of the two groups were significantly different ($P>0.05$) except that the weight of group A was significantly lower than that of group B ($P<0.05$). (See Table 1)

2. Treatment Method:

After admission, the two groups of children were given warm, preventative bleeding, anti-infection and nutritional support treatment. Before the application of PS, nCPAP or SIMV mode respiratory support (or "mechanical ventilation" for short) was adopted. The parameters were set as follows: oxygen concentration 0.21-0.6, oxygen flow 6-10L/min, and end-respiratory positive pressure 4-8cmH_2O. The parameters were adjusted according to clinical manifestations, blood gas analysis and chest X-ray results. The PS dose was 200mg/kg, and the drug was rewarmed to room temperature before PS. After the respiratory secretions were completely removed, PS was slowly infused through the side hole of tracheal intubation with a sterile syringe after intubation, and the resuscitation balloon was used. Pressurized oxygen was given, so that PS could be evenly distributed in the lungs, and then connected to the ventilator to assist in ventilation. FiO_2 was down-regulated according to percutaneous oxygen saturation monitoring.

3. Observations

All patients underwent blood sampling from the radial artery. Blood gas analysis was performed before treatment and 12 h as well as 72 h after PS treatment. Changes in inhaled oxygen concentration (FiO_2) were also recorded. The incidence of nCPAP application or mechanical ventilation, the incidence of complications (BPD, intracranial hemorrhage, pulmonary hemorrhage, PDA, NEC, ROP), hospitalization days, and mortality were recorded and analyzed.

4. Statistical analysis

SPSS 22.0 software was used for statistical analysis of the data. Measurement data were expressed as mean number standard deviation (`x ± s), t-test was used for comparison between groups. Count data was expressed as a number of cases (composition ratio) [n (%)], and χ^2 test was used to compare differences between groups. The measurement parameters at each time point for each group were compared using repeated measures analysis of variance, $P < 0.05$ was considered statistically significant.

Results

Comparison of blood gas indexes and oxygen index OI (OI= PaO2 / FiO2) before and after treatment between the two groups of children is shown in table 2 .There was no significant difference in blood gas analysis parameters between the two groups before treatment (P>0.05). In both groups, after 12 hours and 72 hours of PS treatment, FiO_2 and $PaCO_2$ were significantly decreased, PaO_2 and OI significantly increased, both of which were significantly improved compared with that before PS treatment (P<0.05). The decrease of blood gas $PaCO_2$ in group A before and after treatment was more significant than that in group B (P<0.05), but the improvement of PaO_2 and OI in group B was better than that in group A (P<0.05). (See Table 2)

Comparison of treatment conditions between the two groups: although the oxygen treatment time of group A was significantly higher than that of group B (P<0.05), there was no significant difference in the mechanical ventilation time and length of stay between the two groups (P>0.05). (See Table 3)

The complications and deaths of the two groups were compared in Table 4. There was no significant difference in the incidence of intracranial hemorrhage, pulmonary hemorrhage, NEC and ROP during hospitalization between group A and group B (P>0.05). However, the incidence of BPD in group A was significantly higher than that in group B, and the incidence of PDA was significantly lower than that in group B (P<0.05). There was no significant difference in mortality between the two groups (P>0.05). (See Table 4)

Discussion

A large number of clinical studies have confirmed that early use of PS combined with ventilator assisted ventilation is an effective method for the treatment of NRDS [1, 2, 3], but there is no clear indication of the appropriate time limit point for the clinical application of PS. Prospective studies [4] have shown that FiO_2 is significantly reduced in children who received PS treatment earlier than 3 hours after PS administration, and the improvement in oxygenation was related to the increase of ventilation/perfusion (V/Q) caused by the rise of the functional residual gas (FRC). SR treatment changes lung function first by stabilizing the

alveoli with ventilation function, and then collecting a new gas exchange unit to improve FRC, increase the gas exchange area, and increase the V/Q, so as to improve gas exchange. This study showed that there was no significant difference in blood gas analysis parameters between the two groups before treatment. After 12 hours and 72 hours of PS treatment, FiO_2 and $PaCO_2$ in the two groups were significantly decreased, while PaO_2 and OI were significantly increased, both of which were significant improved compared with that before PS treatment ($P<0.05$). The decrease in blood gas $PaCO_2$ in group A before and after treatment was more significant than that in group B ($P<0.05$), but the improvement of PaO_2 and OI in group B was better than that in group A ($P<0.05$). General statistics of the two groups demonstrated that except that the birth weight of group A was significantly lower than that of group B ($P<0.05$), there was no statistically significant difference between the two groups. However, in group A with low body weight, the decrease of blood gas $PaCO_2$ was more significant than that in the group B after PS treatment.

An improvement in $PaCO_2$ also led to local and/or systemic hemodynamic changes which will affect the function and operation of other organs of premature infants. A previous study of bedside echocardiographic monitoring for children with NRDS found that systemic blood flow changes occurred in children 10 minutes after PS administration (including superior vena cava flow, right ventricular output, PDA diameter, and vhanges in blood flow in the foramen ovale) long before FiO_2 to reduce [5]. Although this hints in the clinical application of SR can improve the patient's lung ventilation and oxygenation, but after PS treatment, pulmonary vascular resistance decreased, pulmonary blood flow increased, PDA and body lung circulation pressure gradient increased, systemic blood flow and terminal organ perfusion decreased [6], which made PS potentially problematic, such as transient airway obstruction, bradycardia, decreased oxygen saturation, intracranial hemorrhage (IVH), pulmonary hemorrhage (PH), etc.

Pulmonary hemorrhage (PH), which is one of the complications of early death in children with NRDS during clinical treatment, is concerned with the risk of PH in preterm infants with RDS after SR. Premature infants with RDS after SR have an increased risk of PH. Possible causes include: vaginal delivery, low birth weight, low gestational age, male and PDA. After SR, the horizontal left to right shunt of the catheter will increase, and the pulmonary blood flow will increase rapidly, leading to high flow and high-pressure vascular bed injury, which is related to the occurrence of PH [7]. A recent summary also suggests that early indomethacin closure of PDA (3-12h postnatal) can reduce the incidence of PH in preterm infants at 30 weeks of gestational age [8]. In this study, it was shown that the incidence of PDA in group A treated with PS within 3 hours was significantly lower than that in group B, which made the incidence of PH in group A lower than that in group B despite the low birth weight. Thus, to some extent, the high mortality rate and hospitalization time of group A high-risk group with low body weight were avoided.

SR is also associated with changes in brain hemodynamics that may lead to intracranial hemorrhage (IVH) and periventricular white matter softening, but the mechanism of action is unclear[9]. Studies have shown that after surfactant replacement（SR）, child blood pressure, CBF and CBV change, $PaCO_2$ increases and EEG are inhibited [10]. $PaCO_2$ fluctuation can directly mediate brain injury by changing

cerebral blood flow, and interaction between high oxygen exposure and $PaCO_2$ fluctuation will increase the risk of BPD/death [11]. In addition, excessive lung inflation after PS treatment can also impede venous return and promote IVH in premature infants who lack autonomic regulation of cerebral blood flow [12]. In this study, two groups of children were treated with PS in a timely manner and strictly according to the clinical manifestations and blood gas analysis of the children, and the results of chest radiograph adjustment of ventilator assisted treatment ventilation parameters. There were no 3-4 degree intracranial hemorrhage complications, 1-2 There was no significant difference in the incidence of intracranial hemorrhage between the two groups (P>0.05). It should be said that there is a certain relationship with the reasonable control of the fluctuation of $PaCO_2$ and the avoidance of high concentration of oxygen inhalation.

Statistical results showed that there was no significant difference in the incidence of complications NEC and ROP between group A and group B (P>0.05). The increase in the incidence of NEC may have been due to systemic hemodynamic changes after SR, decreased circulating blood flow and terminal organ perfusion, decreased gastrointestinal blood flow, tissue hypoxia, etc. ROP occurs mainly with retinal dysplasia in premature infants and long-term elevation of oxygen levels. In this study, FiO_2 was significantly decreased in both groups A and B after treatment with PS, PaO_2 and OI were significantly increased, and significantly improved compared with PS before use (P<0.05). All these are beneficial to reduce the incidence of NEC and ROP. Although the duration of oxygen therapy in group A is relatively long, ROP can be effectively avoided as long as strict control is exercised to avoid high concentration of oxygen.

It is important to note that the incidence of BPD in group A was significantly higher than in group B (P<0.05). However, this does not prove that using PS earlier does not have any benefit in preventing the occurrence of BPD. Due to the fact that basic data analysis of the two groups of children showed that the birth weight of group A was significantly lower than that of group B (P<0.05), and the premature infants with low birth weight, especially those smaller than gestational age, were more likely to be congenital. The inevitable congenital disadvantages of poor bronchopulmonary development, weak respiratory muscle compensatory capacity, primary apnea, feeding difficulties and growth retardation are also a reality in preterm babies.

Limitations

There are several limitations to this research that should be noted. For example, the changes of systemic and local hemodynamic parameters before and after PS treatment in children also requires some objective ultrasound or imaging measurement data for analysis, and the changes of pulmonary compliance in children also need some pulmonary function monitoring for dynamic observation. More prospective studies are needed to determine the most appropriate surfactant administration time by combining different dosage forms of PS from different sources, different administration methods, and whether with other drugs create a synergistic treatment.

Conclusions

In summary, the early use of PS within 3 hours postpartum resulted in more significant improvement of blood gas PaCO2 and lower incidence of PDA in NRDS children. Though A group of children with congenital growth disadvantage is obviously low birth weight, but in the total duration of mechanical ventilation, overall length of hospital stay, mortality rate and PH, the IVH, NEC, ROP these will affect the long-term prognosis and quality of life in children with complications in group B with no significant difference, to a certain extent, reduce the treatment cost, improved the patient's disease prognosis.

Declarations

Ethics approval and consent to participate This study has been approved by the ethics committee of hangzhou first people's hospital.

Consent for publication All authors agree to publish.

Competing interests The authors declare that they have no conflict of interest.

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Authors' contributions Han Han and Hui Lu designed research, performed research, analyzed data, and wrote the paper. Xiao-xia Li conducted the analyses; Xiang-hua Shuai, Zhi-qun Zhang, and Jing Li provided the data; all authors contributed to the writing and revisions.

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Tables

Table 1. Comparison of general data between the two groups

Clinical data	Group A (n=69)	Group B (n=66)	statistic	P value
Gestational age (week)	31.35±2.40	32.45±2.04	t=1.661	0.104
Gender [n(%)]				
male	12(52.17)	11（50）	χ^2=0.021	0.884
Female	11(47.83)	11（50）		
Birth weight (Kg)	1.67±0.55	2.00±0.50	t=2.144	0.038
5min Apgar score	7.21±1.73	8.09±1.54	t=1.786	0.0812
Childbirth type [n(%)]				
Production	3(13.04)	0	χ^2=1.336	0.248
Cesarean section	20(86.96)	22(100)		
Whether twin pregnancy [n (%)]				
Single tire	20(86.96)	21(95.45)	χ^2=0.228	0.633
Twin	3(13.04)	1(4.55)		
Mother has diabetes [n (%)]				
Have	5(21.74)	4(18.18)	χ^2=0.089	0.766
No	18(78.26)	18(81.82)		

Table 2. Comparison of blood gas index and OI between the two groups before and after treatment

Time	PaO_2 (mmHg)		$PaCO_2$ (mmHg)		OI（PaO2/FiO2）	
	Group A	Group B	Group A	Group B	Group A	Group B
Before treatment	66.48±17.40	55.57±16.31	49.33±11.63	47.38±9.96	181.10±72.61	170.11±63.38
12h after treatment	67.43±15.49	66.44±15.90	40.22±6.27	39.21±5.14	298.12±83.78	289.70±85.89
72h after treatment	76.17±12.29	71.73±11.77	41.96±6.30	42.93±6.46	334.19±69.88	329.95±68.46
F	3.299	13.366	9.021	6.386	32.657	55.183
P	0.046	0.000032	0.00052	0.00379	0.00001	0.00001

Table 3. Comparison of treatment status between the two groups

Group	Number	Mechanical ventilation time (d)	Oxygen therapy time (d)	Hospitalization time (d)
Group A	69	6.17±7.98	17.06±21.36	30.96±16.54
Group B	66	4.04±2.05	4.91±7.30	21.50±11.38
t value	-	1.215	2.531	2.225
P value	-	0.231	0.015	0.031

Table 4 Comparison of complication rate and death between the two groups during treatment [case (%)]

Group	case	BPD	IVH	PH	PDA	NEC	ROP	death	
Group A	69	9（39%）	6（26%）	1（4.3%）	4（17.4%）		0	0	0
Group B	66	0	6（27%）	0	11（50%）	1（4.5%）	0	1（4.5%）	
X2 value	-	8.454	0.008	0.978	4.013	0.001	-	0.001	
P value	-	0.0036	0.9284	0.3226	0.0451	0.9821	1	0.9821	