

Original Article

Comparison of the efficacy and safety of bovine lung phospholipid and poractant alfa injections in the treatment of neonatal hyaline membrane disease with continuous positive airway pressure

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Received September 1, 2018; Accepted October 8, 2018; Epub March 15, 2019; Published March 30, 2019

Abstract: Objective: The aim of this study was to investigate and compare the efficacy and safety of bovine lung phospholipid and poractant alfa injections in the treatment of neonatal hyaline membrane disease with continuous positive airway pressure. Methods: A total of 136 newborns with neonatal hyaline membrane disease were selected as research objects and were analyzed, retrospectively. The newborns were divided into group A (66 newborns treated with bovine lung phospholipid injections combined with continuous positive airway pressure) and group B (70 newborns treated with poractant alfa injections combined with continuous positive airway pressure), with different treatment methods for each group. The two groups were compared regarding arterial blood gases (PH value, arterial partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$), artery partial pressure of carbon dioxide (PaCO_2)), vital signs (respiratory, heart rate, mean blood pressure, and pulse oxygen saturation (SpO_2)), before treatment, at 12 hours and 24 hours after treatment, complications (infection, pneumothorax, bronchopulmonary dysplasia, retinopathy, and brain injury), hospitalization time, treatment cost, and survival. Results: Clinical data of the newborns and pregnant women between the two groups showed no statistical differences (all $P>0.05$). The two groups showed no differences in respiration, heart rate, mean blood pressure, and SpO_2 before treatment and 24 hours after treatment (all $P>0.05$). At 12 hours after treatment, the two groups showed no differences in heart rate and mean blood pressure (both $P>0.05$), while group B showed significantly higher respiratory frequency and $\text{SpO}_2\%$ than group A ($P=0.002$, $P=0.001$). Before treatment and at 24 hours after treatment, group A and group B showed no statistical differences in PH value, $\text{PaO}_2/\text{FiO}_2$, PaCO_2 , and positive end-expiratory pressure (PEEP) (all $P>0.05$), while group A showed a significantly lower PH value than the normal value. At 12 hours after treatment, compared with group B, group A showed a significant increase in PH value and $\text{PaO}_2/\text{FiO}_2$, while showing significant lower PaCO_2 and PEEP (all $P<0.05$). Compared with group B, group A showed a significant increase in incidence of complications, which was statistically significant ($P=0.001$). Compared with group A, group B showed a significant decrease in hospitalization time and treatment costs ($P=0.037$, $P=0.041$). Finally, a K-M survival curve was drawn based on 6 months of follow-up. It showed that group A and group B had no statistical differences in survival ($P>0.05$). Conclusion: Bovine lung phospholipid and poractant alfa injections showed few efficacy differences. However, poractant alfa injections have greater application value and are worthy of clinical promotion, due to advantages in safety, hospitalization time, and treatment costs.

Keywords: Bovine lung phospholipid injection, poractant alfa injection, continuous positive airway pressure, hyaline membrane disease, newborn

Introduction

Neonatal hyaline membrane disease (HMD), also known as neonatal respiratory distress syndrome (NRDS), is a disease that causes continuous shrinkage of the lungs of newborns. The lack of pulmonary surfactant (PS) produced by type II alveolar cells leads to a lack of air

exchange in newborns, leading to dyspnea [1, 2]. Patients with HMD always suffer cyanosis and tachypnea. Newborns with progressive dyspnea will suffer respiratory failure [3]. HMD is very prevalent in premature newborns. It is less and less prevalent in them with an increase of gestational age [4]. Some surveys have shown that newborns born at 26-28 weeks gestation

have an incidence of about 50%, while newborns born at 30-31 weeks gestation show an incidence reduced to about 25% [5]. With the maturity of neonatal life support technology, premature newborns have become the main group in neonatal intensive care units. Improving survival rates and life quality of premature newborns, while lowering incidence of HMD complications, remains a major challenge.

With the growing maturity of medical technology and medical instruments, outstanding progress has been made in the treatment of HMD with nasal continuous positive airway pressure ventilation (NCPAP). Respiratory failure can be effectively prevented by expanding the alveoli, increasing lung volume, and timely recovering the respiratory function of newborns [6, 7]. However, long-term treatment with NCPAP will cause many complications and affect the recovery and prognosis of newborns. Thus, it is necessary to reasonably combine drugs to shorten ventilation times and reduce complications [8]. PS, as a metabolic protein in the lungs to maintain normal function of the body, is a mixture of phospholipid proteins synthesized by type II alveolar epithelial cells. Its main components are phospholipids, proteins, and neutral phospholipids [9, 10]. PS has played an important role in protecting lung function of newborns. It has been clearly affirmed in the clinical treatment of HMD. Clinical doctors have gradually improved the regimen of PS in the treatment of newborns with HMD, based on many clinical trials. However, there remains some controversy regarding the use of bovine lung phospholipids and poractant alfas [11, 12]. Bovine lung phospholipids are PS isolated from the lungs of healthy newborn calves and poractant alfas are natural PS prepared from the alveolar surface of porcine pulmonary. Bovine lung phospholipids are cheaper than poractant alfas, showing no significant differences with poractant alfas in terms of efficacy.

Therefore, this study compared bovine lung phospholipids and poractant alfas in the treatment of HMD with NCPAP, providing a selection basis for clinical doctors.

Materials and methods

Materials about the newborns

In this study, a total of 136 newborns with neonatal HMD, treated in the First Affiliated

Hospital of Nanchang University, from June 2014 to April 2017, were selected as research objects and analyzed, retrospectively. The newborns were divided into the group treated with bovine lung phospholipid injections combined with NCPAP (group A) and the group treated with poractant alfa injections combined with NCPAP (group B). This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. Family members of all newborns read and signed the informed consent.

Inclusion criteria: Newborns without congenital heart disease or genetic disorders that were diagnosed with HMD through a chest X-ray and by an attending physician or doctor with at least 10 years of experience.

Exclusion criteria: Newborns with congenital disabilities; Newborns born based on consanguineous marriages; Newborns with other respiratory diseases or failure of important organs; Twins; Newborns allergic to drugs adopted in this study; Newborns without complete materials; Newborns whose family members were reluctant to accept treatment or were uncooperative.

Therapeutic scheme

Newborns in group A were injected with bovine lung phospholipid (Calsurf) at a dose of 70 mg/kg. They were then treated with rewarming. When the temperature reached 37°C, water (2 mL) was mixed in and pipetted by a sterile syringe. The newborns were placed in a supine position. Airway secretions were cleaned before injection to ensure a smooth airway. Mixed Calsurf injection was injected slowly through a syringe along with and the tracheal intubation. The newborns were treated with NCPAP after participating in the test. The method was to collect arterial blood from newborns for blood gas analysis by controlling the ventilation flow rate to 6 L/min, positive end-expiratory pressure (PEEP) to 5 cm H₂O, and the inhalation oxygen concentration to 40%. According to test results, the ventilator parameters of the newborns were adjusted in time to ensure that the oxygen saturation was maintained at 90%. The newborns were observed in real time. If they still showed symptoms of respiratory distress after medication, the medication was given again 9 hours later.

Table 1. Clinical information of children and pregnant women

Group	Group A (n=66)	Group B (n=70)	t/ χ^2	P
Gender			0.232	0.630
Male	35 (53.03)	40 (57.14)		
Female	31 (46.97)	30 (42.86)		
Age in hours (h)	3.53±0.71	3.43±0.52	0.941	0.349
Weight (kg)	1.68±0.29	1.73±0.35	0.904	0.368
Gestational age (week)	32.15±1.41	31.88±1.58	1.049	0.296
Pregnant age (year)	28.64±4.58	29.33±5.24	0.816	0.416
Parity			0.471	0.492
First birth	35 (53.03)	33 (47.14)		
More than two births	31 (46.97)	37 (52.86)		

Table 2. Vital signs between the two groups before and after treatment

Variable	Before treatment	12 h treatment	24 h treatment
Breathing (rpm)			
Group A	44.84±8.54	45.24±6.33	51.35±11.31
Group B	43.58±6.24	49.54±9.35**	52.12±12.69
Heart rate (rpm)			
Group A	132.58±12.51	149.35±15.35	147.22±23.57
Group B	130.39±11.28	152.62±20.55	149.33±14.25
Mean blood pressure (kPa)			
Group A	4.01±0.19	4.05±0.22	4.08±0.24
Group B	4.02±0.28	4.02±0.30	4.06±0.29
SpO ₂ (%)			
Group A	91.54±1.37	91.69±1.22	92.85±2.63
Group B	90.83±1.25	94.35±1.91**	93.17±2.31

Note: Compared with Group A, **P<0.01. SpO₂, pulse oxygen saturation.

The newborns in group B were injected with poractant alfa injection (Curosurf) at a dose of 70 mg/kg. Other steps were performed as described above. NCPAP treatment was also performed as described above.

Observation indexes

Main observation indexes included vital signs, blood gas analysis indexes, and ventilator parameter indexes. They were observed before treatment and at 12 and 24 hours after treatment. Main indexes included respiration, heart rate, and blood pressure. Arterial blood was collected and detected through a blood gas analyzer (PL2200 Ruifeng blood gas analyzer), detecting percutaneous blood oxygen saturation, PH value, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂), and arterial carbon dioxide partial pressure (PaCO₂).

Secondary observation indexes included complications and infections. They were recorded. A survival curve was drawn through 6 months of follow-up, namely telephone follow-ups at 1, 3, and 6 months after treatment.

Statistical analysis

Collected data were analyzed using SPSS20.0 statistical software. Figures were drawn using GraphPad Prism 7 software. Measurement data are represented by mean ± standard deviation ($\bar{x} \pm sd$) and were processed with Student's t-test. Enumeration data are represented by rates (%) and were analyzed with Chi-squared test. Kaplan-Meier method was used for survival analysis. P<0.05 is considered statistically significant.

Results

Comparison of basic data between the two groups

Group A included 66 newborns (35 males and 31 females) at the age of 1~10 hours, with an average age of 3.53±0.71 hours. Group B included 70 newborns (40 males and 30 females) at the age of 1~9 hours, with an average age of 3.43±0.52 hours. There were no statistical differences between the two groups in gender, age, and body weight (all P>0.05). There were also no differences between the mothers of newborns in the two groups regarding age, gestational age, and parity (all P>0.05). See **Table 1**.

Comparison of vital signs between the two groups before and after treatment

Vital signs of the newborns in the two groups, before and after treatment, were compared. It

Table 3. Blood gas analysis and ventilator parameter changes of newborns in the two groups before and after treatment

Variable	Before treatment	12 h treatment	24 h treatment
PH value			
Group A	7.05±0.33	7.33±0.15	7.36±0.15
Group B	7.07±0.28	7.27±0.17*	7.35±0.20
PaO ₂ /FiO ₂ (%)			
Group A	18.29±2.15	16.30±3.17	17.77±2.90
Group B	17.81±1.47	12.95±1.44**	16.99±1.93
PaCO ₂ (kPa)			
Group A	6.32±0.68	5.51±0.43	5.57±0.33
Group B	6.24±0.73	5.76±0.52**	5.49±0.51
PEEP (mbar)			
Group A	5.42±2.31	3.34±1.25	3.49±0.88
Group B	5.44±2.36	3.86±1.70*	3.22±0.92

Note: Compared with Group A, *P<0.05 or **P<0.01. PaO₂/FiO₂, arterial partial pressure of oxygen/fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

was found that before treatment, they showed no differences in respiratory, heart rate, mean blood pressure, and pulse oxygen saturation (SpO₂; all P>0.05). At 12 hours of treatment, newborns in the two groups showed no differences in heart rates and mean blood pressure (both P>0.05), but group B showed significantly higher respiratory frequency and SpO₂% than group A, with statistical differences (P=0.002, P=0.001). At 24 hours after treatment, newborns in the two groups showed no differences in respiratory, heart rate, mean blood pressure, and SpO₂ (all P>0.05). See **Table 2**.

Blood gas analysis and ventilator parameter changes in the two groups before and after treatment

Blood gas analysis and ventilator parameter changes of newborns in the two groups, before and after treatment, were observed through different methods. Results indicated that before treatment, there were no statistical differences between group A and group B in PH value, PaO₂/FiO₂, PaCO₂, and PEEP (all P>0.05). The PH value of group A was significantly lower than the normal value. At 12 hours after treatment, compared with group B, group A showed a significant increase in PH value and PaO₂/FiO₂ and significantly lower PaCO₂ and PEEP. These differences were statistically significant (P_{PH value}=0.031, P_{PaO2/FiO2}=0.001, P_{PaCO2}=0.003, P_{PEEP}=0.045). At 24 hours of tr-

eatment, the two groups showed no statistical differences in PH value, PaO₂/FiO₂, PaCO₂, and PEEP (all P>0.05). See **Table 3**.

Complications and infections in the two groups

Complications and infections of the newborns in the two groups were observed. Compared with newborns in group B, newborns in group A showed a significant increase in incidence of complications. This increase was statistically significant (P<0.05). See **Table 4**.

Comparison of hospitalization time, treatment costs, and survival between the two groups

Comparison of hospitalization times between the two groups showed that, compared with group A, the hospitalization time in group B was significantly shortened. This difference was statistically significant (P=0.037). Comparison of treatment costs between the two groups showed that treatment costs in group B were significantly lower than in group A (P=0.041). See **Table 5**. Finally, a K-M survival curve was drawn based on 6 months of follow-up. It indicated no statistical differences between group A and group B in deaths (P=0.261). See **Figure 1**.

Discussion

NRDS, one of the most common respiratory diseases among premature infants, can result in early death in severe cases. The main cause of the disease in newborns is a lack of PS. In terms of pathological features of the disease, end-expiratory diffuse alveolar atrophy and decreased lung compliance occur. A transparent membrane on the alveolar wall can be observed by an optical microscopy, thus NRDS is also called HMD [13, 14]. If NRDS is not treated timely, it can lead to pulmonary hemorrhaging, local infections, and pulmonary hypertension. NRDS is mainly diagnosed through chest X-rays.

PS is a phospholipid protein complex secreted by type II alveoli, mainly distributed on the alveolar surface. Type II alveoli begins to secrete PS in a fetus when it grows to about 22 weeks, peaking at 35 weeks. The main role of PS is to reduce alveolar surface tension, prevent

Table 4. Incidence of complications in the two groups of patients

Group	Infect	Aerothorax	Bronchopulmonary dysplasia	Reti-nopathy	Cerebral injury	Total incidence of complications
Group A	5 (7.58)	4 (6.06)	3 (4.54)	3 (4.54)	4 (6.06)	19 (28.79)
Group B	1 (1.43)	1 (1.43)	1 (1.43)	1 (1.43)	1 (1.43)	5 (7.15)
χ^2						3.309
P						0.001

Table 5. Comparison of hospitalization times and treatment costs

Group	Group A	Group B	t	P
Length of stay (day)	35.44±14.35	31.84±12.69	2.110	0.037
Cost of treatment (ten thousand)	5.46±1.83	4.84±1.66	2.065	0.041

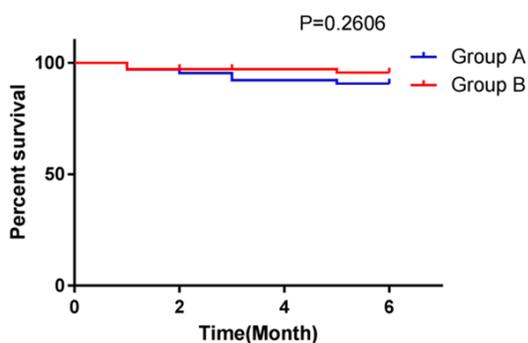


Figure 1. Deaths of newborns of the two groups within 6 months The K-M survival curve showed no statistical differences between group A and group B in deaths (P=0.261).

alveolar atrophy, and maintain lung compliance. It also maintains the balance between alveoli and capillary fluid, prevents pulmonary edema, and regulates respiratory immune defense mechanisms, protecting non-epithelial cells [15-17]. There are two main types of exogenous PS currently in use. One is natural PS (Curosurf) extracted from the alveolar surface of porcine pulmonary, with main components of phospholipids (relatively high content) and specific proteins [18]. The other is PS (Calsurf) isolated from the lungs of healthy newborn calves, with main components of phospholipids, cholesterol, triglycerides, free fatty acids, and a small number of specific proteins [19]. Although many studies have shown that Curosurf is the drug of choice for treatment of HMD [20, 21], the present study adopted and compared Curosurf and Calsurf to treat HMD with NCP-AP, respectively, providing a treatment selection basis for clinical doctors.

Results showed that, at 12 hours of treatment with Curosurf, newborns in group B showed stable indexes, along with improved vital signs and alleviated dyspnea. Compared with newborns in group A treated with Calsurf, group B showed significantly improved blood gas indexes. However, after the two drugs

were used for 24 hours, the indexes of both groups were recovered. There were no differences between them, indicating that both PS have certain curative effects for HMD. A study done by Sinha et al. [22] showed that the efficacy and safety of the two PS in the treatment of NRDS were basically consistent, consistent with present results. However, a comparison of complications and infections between the two groups showed that the number of newborns in group B suffering complications after being treated with Curosurf was significantly lower than in group A after being treated with Calsurf. A study done by Gharehbaghi et al. showed no differences in complications between the two groups, in contrast with present results. This may be due to the difference in the number of samples [23]. In addition, a comparison of hospitalization times and treatment costs between the two groups showed that hospitalization times and treatment costs in group B were significantly lower than those in group A, with significant differences. In terms of treatment times and treatment costs, Curosurf for HMD can obviously shorten these factors. At the end of the study, a survival curve was drawn. This curve showed no differences between the two groups in survival rates. Therefore, the present study concludes that, in the treatment of HMD, the short-term effects of Curosurf are better than Calsurf. Additionally, Curosurf can reduce complications.

However, there were certain limitations to the present study. First, the sample size was small, which may have led to bias. Second, this study was a clinical trial and mechanisms were not further explored.

In summary, although efficacy differences between the two groups were not large, poractant alfa injections are more advantageous in terms of safety, hospitalization times, treatment costs, and so forth. Therefore, poractant alfa injections have greater application value and are worthy of clinical promotion.

Declaration of conflict of interest

None.

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