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Pharmacoeconomic evaluation of different doses of Curosurf for treating neonatal acute respiratory distress syndrome

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Abstract: Neonatal acute respiratory distress syndrome (ARDS) is a serious stage of acute lung injury (ALI) which can be treated by exogenous surfactant. The aim of this study was to explore the clinical efficacy of two different doses of Poractant alfa (Curosurf®) for treating neonatal ARDS and to perform an economic evaluation. Fifty-four patients were divided into Group A (high dose) and Group B (low dose). Pharmacoeconomic evaluation was performed on the two groups regarding the treatment expenses, and the output was the cure rate and complication rate. There were significant differences between Group A and Group B for the duration of receiving oxygen therapy in moderate cases (6.4±3.5d:8.9±2.6d) ($P<0.05$) and severe cases (10.0±2.6d:14.8±1.3d) ($P<0.05$). There were significant differences between them for the duration of undergoing mechanical ventilation in severe cases (1.7±2.3d:5.5±2.4d) ($P=0.01$). There was a significant difference between Group A and Group B for hospitalization expenses in severe cases ($P<0.05$). There were no significant differences between them in all types of cases for the cure rate ($P>0.05$). A high dose of Curosurf had an advantage in treating neonatal ARDS, especially in severe cases, with lower final costs and better effects.

Keywords: Neonates, respiratory distress syndrome, economic evaluation, surfactant.

INTRODUCTION

Neonatal acute respiratory distress syndrome (ARDS) is a disease that is different from neonatal respiratory distress syndrome (NRDS). It is caused by severe infection and asphyxia, which is a serious stage of neonatal acute lung injury (ALI). It is characterised by extensive lung inflammation and surfactant catabolism leading to lung dysfunction. The main clinical manifestations are tachypnea, distress, and progressive hypoxemia, and a chest X-ray and CT imaging are characterized by diffuse, bilateral, and irregular opacities or infiltrates, or complete opacification of the lungs, which are not fully explained by local effusions, atelectasis, NRDS, Transient Tachypnea of Newborn(TTN), or congenital anomalies (De Luca *et al.,* 2017). The main treatment strategy consists of oxygen therapy, including hoods, nasal cannula, nasal continuous positive airway pressure (nCPAP), and mechanical ventilation, combined with antibiotics, parenteral nutrition and enteral nutrition. In recent years, with the development of pulmonary surfactants (PSs) (including the porcine extract Poractant alfa Curosurf® produced in Italy, the bovine extract Bovactant Alveofact® produced in Germany, and the bovine extract Calf Pulmonary Surfactant produced in China), neonatologists have begun to apply a PS in some other diseases in addition to NRDS, including neonatal ARDS, meconium aspiration syndrome, and bronchopulmonary dysplasia (Ricci *et al.,* 2017). Clinical trials reported that exogenous surfactant therapy can be beneficial in infants with ARDS/ALI without significant adverse long-term effects (Amigoni *et al.,* 2017).

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The price of exogenous PS is quite expensive, whether it is Curosurf from Italy or Calf Pulmonary Surfactant from China. However, PS is not included in the scope of Medicare drugs and is not covered by insurance in many areas of China. Therefore, PS is an economic burden for patients. Many neonatal clinicians tend to choose a low dose (e.g. 100 mg/kg of Curosurf) to save costs for patients. However, it is questionable that a low-dose treatment guarantees the desired effect and saves final medical costs for patients without affecting the prognosis. This needs further study. Based on this consideration, we carried out the following retrospective study.

MATERIALS AND METHODS

Study design

Data for this retrospective analysis were obtained from Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. The patients who had neonatal ARDS with complete data were assessed from January 1, 2011 to August 30, 2013. In total, 54 cases who met the diagnosis were involved, and all of them received a single dose of endotracheal Curosurf instillation. The diagnostic criterion was from the Berlin Definition by ARDS Definition Task Force (Ranieri Vm Fau - Rubenfeld *et al.,*, 2012). The severity was classified based on the degree of hypoxemia: mild (200 mm Hg $< PaO_2/FiO_2 \leq$ 300 mm Hg), moderate (100 mm Hg $< PaO_2/FiO_2 \leq$ 200 mm Hg), and severe ($PaO_2/FiO_2 \leq$ 100 mm Hg). The licensed dosage of Curosurf is between 100mg/kg and 200mg/kg. Two groups according to the dosage were defined as below: the dose of Group A was ≥150 mg/kg (high dose of

Curosurf) and the dose of Group B was < 150 mg/kg (low dose of Curosurf). All data were analyzed, including mild, moderate, and severe cases in Group A and Group B. Six groups were defined according to the PaO_2/FiO_2 severity: ungrouped cases (not classified by severity), mild cases, moderate cases, severe cases and moderate-severe cases. Because the sample size for any group was not big enough, moderate and severe cases were combined to form a new group called "the moderate-severe group" to improve the accuracy of the statistics.

The mechanical ventilation rates, cure rates, complication rates, duration when receiving oxygen therapy, duration when undergoing mechanical ventilation and hospitalization expenses were compared between the two groups of patients. Pharmacoeconomic evaluation was carried out on the two groups, including the cost of treatment, and the output was cure rate and complication rate. The mechanical ventilation rate was defined as the proportion of patients with invasive breathing support for all patients. The cure rate was defined as the percentage of patients who had been discharged from hospitalization. Complications included Patent Ductus Arteriosus (PDA), Persistent Pulmonary Hypertension (PPHN), Intracranial Hemorrhage (ICH), pulmonary hemorrhage, Ventilator Associated Pneumonia (VAP), pneumothorax, and Multiple Organ Dysfunction. The complication rate was defined as the proportion of patients with any of the above complications in all patients.

The ventilators were the neonatal ventilator "CHRISTINA HF 300 SIMV" produced by F. Stephen GmbH Medizintechnik Company in USA and the Newport ventilator "Newport e360" in USA. CPAP machines were "Stephen CPAP machine" in USA. Air and oxygen mixtures were "Air and oxygen mixture AD3000-SPB" produced by Guangdong pigeon medical equipment company in China. Blood gas meter was for "ABL77 SCi blood gas analyzer" produced by Radiometer in Denmark.

Chinese Currency is Renminbi (RMB) or Chinese yuan (CNY). The Renminbi is the official currency of China. Yuan is the basic unit of Renminbi, and is also used to refer to the Chinese currency generally. The patient's expenses were valued in Renminbi in this study.

Participants

A total of 54 participants who met the criteria were involved from January 1, 2011 to August 30, 2013. All the admission times were within 30 minutes to 10 hours after birth, and the onset time of tachypnea was within 30 minutes to 6 hours after birth.

STATISTICAL ANALYSIS

Statistical analyses were conducted with SPSS 18.0 software; group comparisons were performed using t-tests for continuous variables, and a χ^2 analysis was performed for categorical variables. $P<0.05$ was considered statistically significant.

RESULTS

Study participants

Fifty-four patients participated in the study (table 1). All of them were diagnosed shortly after birth, and approximately 83.3% were male. The mean birth weight was 2750 g. The gestational age varied from 34 w^+ to 39 w^+. The patients with a 1 minute Apgar score ≥8 accounted for 68.5%, while the others whose Apgar score≤7 accounted for 31.5%. Based on PaO2/FiO2, all patients were classified into mild (22.2%), moderate (51.9%), and severe (25.9%). Thirty (55.6%) cases belonged to Group A (high dose) with a mean dose of 175.3 mg/kg, and 24 (44.4%) cases were included in Group B (low dose) with a mean dosage of 123.8 mg/kg. The dosages of Group A and Group B were significantly different with $P<0.05$ (mean value175.3±12.5mg/kg: 123.8±14.5mg/kg).

Table 1: Demographic characteristics of the participants with Neonatal ARDS (mean ± standard deviation)

Variables	No. (%) of participants (n=54)
Postnatal age, h	1.5±1.66
Sex	
Male	45 (83.3)
Female	9(16.7)
Birth weight mean, g	2750±365
Admission year	
2011	22(40.7)
2012	25(46.3)
2013	7(13.0)
Gestational age	
$34w^+$	11(20.4)
$35w^+$	13(24.1)
$36w^+$	8(14.8)
$37w^+$	9(16.7)
$38w^+$	10(18.5)
$39w^+$	3(5.5)
Apgar score	
Apgar score≥8	37(68.5)
Apgar score≤7	17(31.5)
Cases of different severity	
Mild	12(22.2)
Moderate	28(51.9)
Severe	14(25.9)
Cases of different doses	
Group A	30(55.6)
Group B	24(44.4)
Doses mean of Curosurf, mg/kg	
Group A	175.3 ± 12.5
Group B	123.8 ± 14.5

ARDS = acute respiratory distress syndrome

Initial data comparison

The initial data after admission were compared between Group A and Group B (table 2). Table 2 summarizes the characteristic comparisons including gestational age, birth weight, sex, cesarean section or eutocia, blood gas, and PaO2/FiO2 severity. From table 2, there were no significant differences between Group A and Group B on their initial data after admission.

Table 2: Characteristic comparisons of the participants (mean ± standard deviation)

Characteristic	No. (%) of participants		
	Group A	Group B	P value
Gestational age, w	35.9±1.6	36.3±1.6	>0.05
Birth weight mean, g	2684.7±399.4	2832.5±304.5	>0.05
Male	26(86.7)	19(79.2)	>0.05
Cesarean section	29(96.7)	23(95.8)	>0.05
Blood gas			
PH	7.24±0.1	7.23±0.1	>0.05
PO_2(SD), mmHg	54.4±11.6	53.5±10.3	>0.05
PCO_2(SD), mmHg	56.0±12.8	52.3±11.6	>0.05
Severity			
Mild	7(23.3)	5(20.8)	>0.05
Moderate	16(53.3)	12(50.0)	
Severe	7(23.3)	7(29.2)	

Table 3: Outcome comparisons of the participants (mean ± standard deviation)

Outcome	Group A	Group B	P value
Duration when receiving oxygen*, d	6.3±3.9	8.3±4.5	>0.05
Mild	2.2±0.4	2.8±0.8	>0.05
Moderate	6.4±3.5	8.9±2.6	<0.05
Severe	10.0±2.6	14.8±1.3	0.01
Moderate-severe	7.4±3.6	10.4±3.5	<0.05
Duration when undergoing mechanical ventilation*, d	0.4±1.2	1.5±2.5	>0.05
Mild	0	0	>0.05
Moderate	0.1±0.3	0.8±1.6	>0.05
Severe	1.7±2.3	5.5±2.4	<0.05
Moderate-severe	0.5±1.3	2.0±2.7	<0.05
Mechanical ventilation rate	0.172	0.4	>0.05
Mild	0	0	>0.05
Moderate	0.063	0.25	>0.05
Severe	0.571	1	>0.05
Moderate-severe	0.217	0.526	<0.05
Cure rate	0.966	0.88	>0.05
Mild	1	1	>0.05
Moderate	1	1	>0.05
Severe	0.857	0.571	>0.05
Moderate-severe	0.957	0.842	>0.05
Complication rate	0.207	0.52	<0.05
Mild	0.167	0	>0.05
Moderate	0.063	0.583	<0.005
Severe	0.571	0.857	>0.05
Moderate-severe	0.217	0.684	<0.005
Hospitalization expense*, RMB	29196.6±9320.4	31650.7±12141.6	>0.05
Mild	17894.0±943.5	16873.3±1625.7	>0.05
Moderate	29268.2±6378.6	33166.1±6574.4	>0.05
Severe	40308.0±6683.8	49270.6±3027.6	<0.05
Moderate-severe	32279.1±8063.7	37192.3±9241.3	>0.05

* Data exclude cases of death

Treatment and outcome

Endotracheal intubation and intratracheal injection of Curosurf were given for all patients. Then, nCPAP or mechanical ventilation was administered depending on the situation. The nCPAP indications were PaO_2<50 mmHg or $TcSO_2$<90% (FiO_2>0.4). The mechanical ventilation indications were (1) PaO_2 <50 mmHg or $TcSO_2$<90% (FiO_2>0.6, except for cyanotic congenital heart disease); (2) $PaCO_2$ >60-70 mmHg and pH <7.25; and (3) severe apnea. Mechanical ventilation could be changed to nCPAP when tachypnea was relieved and PaO_2 >50 mmHg (FiO_2 <0.6). nCPAP could be changed to oxygen hood when blood gas was PaO_2 >50 mmHg (FiO_2<0.4). In addition to the above treatment, antibiotics were given to avoid infection, ambroxol to promote the synthesis of an alveolar surfactant, and enteral and parenteral nutrition as support. Chest X ray and blood gas analyses were dynamically monitored. Patients were discharged when oxygen was removed and the patient was stable.

Of all cases, 15 (27.8%) patients received mechanical ventilation, 4 (7.4%) patients were dead, and the duration when receiving oxygen was 2-16 days with the average duration 7.2±4.3 days. Complications included: PDA in 7 cases, PPHN in 4 cases, ICH in 1 case, pulmonary hemorrhage in 2 cases, VAP in 3 cases, pneumothorax in 4 cases and MOD in 2 cases. Except for the cases of death, the hospital costs of patients varied from RMB15503.29 to RMB53462.22 with the average cost RMB 30276.39±10609.45.

Data comparison after treatment

The cases of death did not receive the complete treatment; therefore, they had relatively short hospital stays. Their duration when receiving oxygen and the duration when undergoing mechanical ventilation were shorter than the cured cases, and their hospitalization expenses were less. Therefore, the cases of death were excluded when these three items were analyzed; otherwise, the final results would be unreasonable. The cases of death were included in the analyses of the mechanical ventilation rate, cure rate, and complication rate comparisons between Group A and Group B, 6 outcome items were compared (table 3).

From table 3, there were significant differences between Group A and Group B in moderate cases (P<0.05), severe cases (P=0.01) and moderate-severe cases (P<0.05) for the duration when receiving oxygen, in severe cases (P<0.05) and moderate-severe cases (P<0.05) for the duration when undergoing mechanical ventilation, in moderate-severe cases (P<0.05) for the mechanical ventilation rate, in ungrouped cases (P<0.05), moderate cases (P<0.005) and moderate-severe cases (P<0.005) for the complication rate, and in severe cases (P<0.05) for hospitalization expenses. There were no significant differences between Group A and Group B in all types of cases for the cure rate (P>0.05).

We used "A=B" to indicate there were no significant differences between Group A and Group B, and "A<B" to indicate there were significant differences when the value of Group A was less than that of Group B (table 4). Table 4 is a summary of the results of all comparisons. There were no significant differences between Group A and Group B for mild cases on all 6 items. "A<B" occurred in moderate-severe cases for most items.

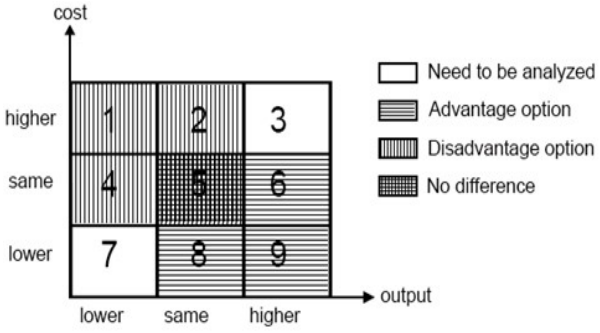

Fig. 1: Nine situations for whether to do cost-output analysis

Pharmacoeconomic evaluation

Method

The cost index for the economic evaluation was the treatment expense and the output indices were cure rate and complication rate. The price of Curosurf in Hubei Province of China was RMB6495/bottle (240 mg, 3 ml) and RMB3787.5/bottle (120 mg, 1.5 ml) in 2011-2012, and it was RMB5994/bottle (240 mg, 3 ml) and RMB3526/bottle (120 mg, 1.5 ml) in 2013. The average expense for Curosurf in Group A was RMB13262.4 ± 2230.8, and it was RMB10097.2±1225.2 in Group B. There were significant differences between them (P<0.001). It seems that the cost for Curosurf in Group A was more than that of Group B; however, table 4 shows that the final total cost of hospitalization of Group A was not statistically different from that of Group B in most cases and, even in severe cases, the hospitalization cost of Group A was lower. Therefore, it is necessary to do a further comparative statistical analysis. The analysis should include the cases of death and direct non-medical costs and indirect costs need to be considered.

Taking into account no significant difference in the cure rates between the two groups and that there were significant differences in the complication rates, we believe there were still differences between the two groups regarding output. Therefore, Cost Minimization Analysis (CMA) is not suitable for this analysis, and whether Cost Effectiveness Analysis (CEA) should be applied depends on the final statistical results.

Research perspective

Patients of neonatal ARDS were selected to be the perspective for this study and the measurement range of the costs included the direct medical costs, direct non-medical costs and indirect costs.

Table 4: Summary of outcome comparisons of the participants

Outcome	Ungrouped	Mild	Moderate	Severe	Moderate-severe
Duration when receiving oxygen*, d	A=B	A=B	A<B	A<B	A<B
Duration when undergoing mechanical ventilation*, d	A=B	A=B	A=B	A<B	A<B
Mechanical ventilation rate	A=B	A=B	A=B	A=B	A<B
Cure rate	A=B	A=B	A=B	A=B	A=B
Complication rate	A<B	A=B	A<B	A=B	A<B
Hospitalization expense*, RMB	A=B	A=B	A=B	A<B	A=B

*Data exclude cases of death

Table 5: Comparisons of costs before and after the discount (mean ±standard deviation)

Cost	Before discount		After discount	
	Group A	Group B	Group A	Group B
Direct medical costs, RMB				
Expense X	1429.0±567.3	1705.5±752.7	1382.6±545.1	1690.7±753.1
Expense Y	8637.3±4496.5	10586.4±5982.2	8350.0±4329.3	10486.2±5955.0
Expense Z	19434.1±4877.3	18261.4±5699.9	18807.0±4668.5	18073.1±5636.0
Direct non-medical costs, RMB	727.4±385.2	871.7±468.1	702.6±368.7	863.7±466.4
Indirect costs, RMB	934.9±498.8	1079.5±575.5	903.9±480.7	1069.3±572.4
Total costs, RMB	31162.6±10156.0	32504.5±13125.6	30146.1±9737.5	32182.9±13042.3
P value	<0.001		<0.001	

Cost establishment

The direct medical costs included bed fees, diagnosis fees (daily ward round), nursing fees, examination fees (CT, MRI, and ultrasound), laboratory fees, material fees and medicine (drug) expenses. During the three years 2011-2013 in Wuhan China, the bed fees, diagnosis fees, nursing fees, and examination fees did not change; the laboratory fees and materials fees rose partially; medicine expenses declined partially; i.e., the price of Curosurf in 2013 was lower than in 2011 and 2012. Therefore, fees were divided into 3 parts: Expense X: bed fee, diagnosis fee, nursing fee, examination fee (unchanged fee in 2011-2013); Expense Y: laboratory fee, materials fee (rising partially in 2011-2013); Expense Z: medicine expense (declining partially in 2011-2013).

The direct non-medical costs that were generated were transportation, accommodations, etc. Because some parents were locals and some outsiders either stayed in their own houses or in a hotel (RMB50-500/day), direct non-medical costs varied. We assumed these expenses to be RMB100/day.

The indirect costs are the lost income due to the shutdown, decreased working ability, reduced contribution to society and loss due to early death. It was calculated by the human capital approach and the method of willingness to pay. In this study, the main indirect costs were the lost income of parents (mainly baby's father). The average wage level in Wuhan City was RMB3633/month in 2011, RMB4078/month in 2012, and RMB3245/month in the first and second quarter of 2013 (from Wuhan Bureau). Therefore, the lost income on average was: RMB3633/30days = 121/day in 2011, RMB4078/30days = 136/day in 2012 and RMB3245/30days = 108/day in 2013.

Output indicators

In this study, the cure rates and complication rates were output indicators.

Discounted research

The participants in the study were born in 2011-2013, a range of three years. Taking into account the effects of inflation during the three years, discounted research is necessary, and 3% was adopted as the discount rate, which is the usual rate (Sruamsiri *et al.,* 2014).

Considering the discount rate: RMB100 next year is equivalent to 100/ (1+3%) = RMB97.1 this year. Therefore, RMB100 (in 2012) = RMB97.1 (in 2011), RMB100 (in 2013) = RMB 94.3(in 2011). Finally, all fees

were discounted to the monetary value in 2011 (table 5). Before the discount, the final costs of Group A were RMB31162.6±10156.0, which were lower than that of Group B (RMB32504.5±13125.6) (P<0.001). The results were the same after the discount: the costs of Group A were RMB30146.1± 9737.5 lower than that of Group B (RMB32182.9±13042.3) (P<0.001).

Even though the total costs of group A were lower than that of group B, there was no significant difference for the cure rates between them and the complication rates of Group A were lower than that of group B in most situations (table 4). They belonged to the eighth situation and the ninth situation respectively in the nine situations for whether to do cost-output analysis (fig. 1). Therefore, the treatment of Group A was the advantage option; it was not necessary to do the further CEA analysis, and only a sensitivity analysis was performed (Li *et al.,* 2008).

Sensitivity analysis

Data in the pharmacoeconomic study have uncertainty and potential offsets, and the cost and effectiveness of the same treatment in different populations and different medical institutions may be different. Many uncontrollable factors had an impact on the final results of the analysis. Therefore, a sensitivity analysis is very important for ultimate credibility of the final results. A sensitivity analysis does not require all of the uncertainties to be taken into account, but the unstable factors and the factors more likely to affect the results should be identified.

During the three years, bed fee, diagnosis fee, nursing fee, and examination fee remained unchanged. Medicine expense and materials fee fluctuated. With the progress of health care reform in China, the medicine expense and examination fee would be reduced. With the progress of health care reform, reducing the expense of inpatient medical fees and laboratory examination fees is the trend for the future. With the inflating and the growing importance on medical and nursing expertise, treatment fees and nursing fees may increase in future. Direct non-medical costs and indirect costs were much lower than direct medical costs and in the three years per capita income levels and consumption levels were not quite different. Therefore, the direct non-medical costs and the indirect costs were not taken into account in the sensitivity analysis. Assuming that in future Expense X would rise by 10%, Expense Y would decrease by 5%, Expense Z would decrease by 5%, what would be the result? The final costs of Group A after changes were RMB28926.5±9367.4, and the costs of Group B were RMB30924.0± 12549.8. These costs would be significantly different (P<0.001). The costs of Group A would still be lower than that of group B. Therefore, the results of the sensitivity analysis would not change the original results. This indicates the original results are reliable and will not affect the results of this study when the direct medical costs fluctuate within a certain range.

DISCUSSION

There are five kinds of pharmacoeconomic evaluation methods: Cost of Illness analysis (COI), Cost Minimization Analysis (CMA), Cost Effectiveness Analysis (CEA), Cost Utility Analysis (CUA) and Cost Benefit Analysis (CBA). CEA and CMA are commonly used in medical institutions, but each has its indications. If different treatments have the same output and different costs, CMA should be chosen. If one treatment has a higher cost and a higher output, CEA can be selected. In this study, although Group A (high dose of Curosurf) had relatively higher costs of Curosurf, the final total costs of treatment were lower than that of Group B (low dose of Curosurf), and Group A had the same cure rates and lower complication rates.

From fig. 1, they belonged to the eighth situation and the ninth situation respectively, so A is the advantage option, and it does not require CEA analysis.

Discounted research is required when the pharmacoeconomic study duration lasts over a year. The costs and output data need to be discounted for different year. The national assessment guidelines vary in regard to choosing the discount rate, and there is no standard. The "China Pharmacoeconomics evaluation guide" does not recommend a fixed discount rate and most researchers choose a 3% or 5% discount rate. The guide lists the costs and output data before and after the discount and then uses a 0-10% discount rate on the sensitivity analysis research. In this study, currency was the cost unit, and the output indicators were the cure rates and complication rates, which cannot be discounted; therefore, the discounting research was only done on the costs, and a discount rate of 3% was used.

Sensitivity analysis is a common method of studying uncertainty in economic evaluation. On the basis of deterministic analysis, it further analyzes the impact of uncertainty factors on the final economic indicators of the project. It is unnecessary to take all of the uncertainties into account in sensitivity analysis, but the unstable factors and the factors more likely to affect the results should be identified. In this study the direct medical costs were the most unstable factors. They were divided into 3 parts: Expense X, Expense Y and Expense Z. The sensitivity analysis was conducted by increasing Expense X by 10%, decreasing Expense Y by 5%, and decreasing Expense Z by 5%. Compared to the direct medical costs, the direct non-medical costs and indirect costs were lower, and in the three years the income and consumption levels changed little, so they were not considered in the sensitivity analysis.

Natural pulmonary surfactant plays an essential role in lung physiology. It can lower surface tension within the alveoli and maintain the functional integrity of the distal airways. It is a phospholipoprotein formed and stored by type II alveolar cells. It reduces surface tension by covering the air-water interface of alveoli due to its hydrophilic head groups that stay in the water and its hydrophobic tails, which face towards the air. Lack of surfactant results in respiratory failure, secondary to atelectasis, alveolar flooding and severe hypoxaemia (Amigoni *et al.,* 2017, Echaide *et al.,* 2017). Exogenous PS replacement therapy reduced the mortality of respiratory distress syndrome in neonates by 50% (Sweet *et al.,* 2017).

Acute respiratory distress syndrome (ARDS) is a devastating process that involves pulmonary inflammation, alveolar damage and hypoxemic respiratory failure. The mechanisms of ARDS include biophysical inactivation or chemical alterations of surfactant by injury-related inhibitors. Inflammatory cytokines can also influence the metabolism of surfactant by altering type II pneumocyte function and responses, resulting in depletion or inactivation of the surfactant. The presence of surfactant deficiency or dysfunction forms the rationale for the use of exogenous PS in ARDS (Mok *et al.,* 2014). Many studies have demonstrated the efficacy of surfactant therapy in the neonatal respiratory failure including meconium aspiration syndrome and bronchopulmonary dysplasia (BPD) (Echaide *et al.,* 2017, Ricci *et al.,* 2017). The PaO2, PaCO2, PaO2/FiO2 Oxygenation Index (OI) and survival were improved after PS therapy in ARDS in term neonates and children (Liu *et al.,* 2017, Rodriguez-Moya *et al.,* 2017) .

According to the evidence-based practice advices for different therapy of neonatal ARDS, the effect of surfactant bolus could reduce mortality, shorten mechanical ventilation, shorten the intensive care unit length of stay in RSV-related ARDS, improve oxygenation, and reduce the need for ECMO in MAS (De Luca *et al.,* 2012). Curosurf in this study is an exogenous PS extracted from pigs. Higher doses can better compensate for the inactivation of endogenous PS to improve oxygenation, reduce oxygen demand, improve the arterial/alveolar oxygenation ratio, and lower the peak inspiratory pressure and mean airway pressure, thereby reducing the duration with oxygen and mechanical ventilation and reducing the mechanical ventilation rate, while reducing the chance of complications.

In this study, all patients received a single dose of Curosurf instillation without repeated use. This study suggests that high dose therapy did not increase the economic burden of patients' family, but can guarantee the treatment effect, especially in the moderate-severe cases of neonatal ARDS, the complication rates and mechanical ventilation rates were lower, and the duration when receiving oxygen therapy and duration when undergoing mechanical ventilation were shorter. The limitation of this study is that the sample size was small; it needs to expand the sample size, and add multiple doses of surfactant treatment in the research to confirm the conclusion.

CONCLUSION

Although in the early course of neonatal ARDS the costs of the high dose group were higher, bringing great economic pressures to the family of patients, and bringing great psychological stress to neonatal clinicians, the final costs were not higher than in the low dose group, and the outcome of treatment was superior to the low dose group, especially in the moderate to severe cases. Thus, in the future, when facing a similar situation, a higher dose solution could be recommended to the family of patients to achieve the best therapeutic effect.

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