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Gender-related efficacy of pulmonary surfactant in infants with respiratory distress syndrome
A STROBE compliant study

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Abstract

Whether gender influences the efficacy of exogenous pulmonary surfactant (PS) for replacement therapy in newborns with respiratory distress syndrome (RDS) has not been well studied yet.

Retrospective cohort study design. Data on PS therapy including blood gas, oxygenation function parameters, and therapy results were collected and analyzed from 370 infants diagnosed with RDS in 20 hospitals of the Northwest China Neonatal Collaboration from January 2011 to December 2011.

Female infants were more sensitive to PS treatment than males. In multivariate analysis, when adjusted for other variables, an increased initial dose of surfactant significantly reduced mortality risk (OR = 0.98, 95%CI [0.96, 0.99], P=.002). An interaction between gender and initial dose of PS was observed. In male infants, an increased initial dose of surfactant was correlated with reduced mortality risk (OR = 0.97, 95%CI [0.96, 0.99], P=0.005), while in female infants, we failed to found a relationship between the initial dose of surfactant and the risk of mortality (OR = 0.99, 95%CI [0.96, 1.02], P=.543). Moreover, the effect of surfactant replacement therapy was better for female infants than male infants at initial PS doses <130 mg/kg.

Gender influences the efficacy of PS treatment. An increased initial dose of PS should be used in RDS therapy for male infants.

Abbreviations: PS = pulmonary surfactant, RDS = respiratory distress syndrome.

Keywords: gender, infants, pulmonary surfactant, respiratory distress syndrome

1. Introduction

Respiratory distress syndrome (RDS) is the most common life-threatening form of respiratory failure in newborn infants worldwide.[1] RDS is primarily caused by a deficiency in the quality and quantity of pulmonary surfactant (PS), which then progressed into poor lung compliance and insufficient gas exchange, leading to the demand for high ventilatory pressure.[2] Exogenous PS replacement therapy is the main method used in clinics to prevent RDS.[3] This therapy has been shown to markedly reduce pneumothorax and mortality in many clinical reports.[4] However, for some infants, death is inevitable, despite intensive care and PS replacement therapy.

Many factors influence the outcomes of RDS in infants. Previous studies have reported that gestational age,[5] use of auxiliary ventilation,[6] selective cesarean section, severe birth asphyxia, maternal fetal infection, and male sex are closely correlated with full-term neonatal RDS outcomes.[7] Compared

with females of the same gestational age, male preterm infants are at greater risk of developing RDS, and need more initial respiratory and circulatory support.[8–11] Males also have been reported to be associated with a greater risk of neonatal mortality and respiratory illness.[12–14] Yet, whether gender influences the efficacy of exogenous PS replacement therapy in newborns with RDS has not been well studied.

Thus, the main purpose of this retrospective cohort study was to compare the therapeutic effects of exogenous PS between male and female infants with RDS. To the best of our knowledge, this study is the first to examine the combined effects of gender and PS replacement therapy in newborns with RDS.

2. Methods

2.1. Subjects

The protocol of this study was reviewed and approved by the National Legislation and Ethical Committee of Shannxi Provincial People's Hospital (affiliated with Xi'an Jiaotong University), China. Guardians of all infants in this study gave informed consent. A retrospective analysis was conducted at 20 hospitals in the Northwest China Neonatal Collaboration. Between January 2011 and December 2011, 370 neonates with RDS who received PS therapy were recruited. Infants who had a chromosomal abnormality or life-threatening major congenital malformation, such as cardiac anomaly or pulmonary hypoplasia, were excluded. We also excluded data from infants with incomplete records of PS application. The remaining 370 cases formed the analysis population. The decision to use PS therapy was based on doctor recommendations and the consent of the infant's guardians. The attending physician decided whether to replace the PS based on the patient's condition, as determined by chest radiography and blood gas analysis.

2.2. Study protocol

The retrospective analysis of clinical practices was conducted using medical records. Information included infant gender, gestational age, birth weight and length, birth asphyxia, general conditions in the first 1, 5, and 10 minutes of life (measured by Apgar score), RDS severity, respiratory support type and length, surfactant administration method and dosing regimen, child mortality rate at the patient's hospital during the time of the patient's stay, maternal age, education level, and history of antenatal corticosteroids and diabetes.

The diagnosis of RDS were based on clinical manifestations and chest X-ray findings.[15] The clinical signs and symptoms of RDS included respiratory distress, tachypnea, nasal flaring, groaning, and cyanosis after birth. A typical X-ray picture of RDS showed a grainy shadow, air bronchogram, and white lungs. Grade 1 involves a slight reticular (granular) decrease in lung transparency with no observable difference from normal findings. Grade 2 involves a slight decrease in transparency with an air bronchogram that overlaps the heart. Grade 3 involves a stronger decrease in transparency than in grade 2 and a blurry diaphragm and heart. Grade 4 involves practically homogenic lung opacity.[16] The X-ray images in our study were judged by 2 radiologists blinded to the patient's condition.

Surfactant was instilled into the trachea via an endotracheal tube using an orogastric tube. The primary treatment was performed by 50 to 240 mg/kg doses of porcine surfactant (Curosurf, Chiesi Farmaceutici SpA, Parma, Italy), followed by another 100 mg/kg dose in case that required repeated treatments. The outcome associated with RDS was mortality.

2.3. Respiratory management

Different primary modes of ventilation were provided for the subjects according to RDS severity. Nasal continuous positive airway pressure and nasal intermittent positive pressure ventilation were provided for RDS patients of grade 1 and grade 2, and high-frequency oscillatory ventilation and conventional mechanical ventilation were provided for RDS patients of grade 3 and grade 4. All infants with RDS were given surfactant as soon as practicably possible (within 24 hours after birth). The ventilator parameters were adjusted according to the clinical condition, blood gas values, and chest X-ray if mechanical ventilation was required after surfactant administration.

2.4. Statistical analysis

The test power of this study with 370 cases was 93.8% by using a log-rank test, with an odds ratio (OR) of 0.98 for every 1 mg/kg increase of PS dosage. The data distribution of baseline characteristics and in-hospital treatment of the population are presented as means (SD) for normal distribution, and median (Q1–Q3) for nonnormal distribution variables, and categorical variables are presented as number (percentage) (Table 1).

Table 1

Baseline characteristics and in-hospital treatment of the population.

Variables	Male (N = 245)	Female (N = 125)	Total (N = 370)
Maternal			
Maternal age, y	28.30 (5.19)	28.54 (4.89)	28.38 (5.09)
Glucocorticoids use	92 (37.55)	37 (29.60)	129 (34.86)
Cesarean	145 (59.18)	77 (61.60)	222 (60.00)
Prenatal fetal distress	28 (11.43)	19 (15.20)	47 (12.70)
Multiple pregnancy	47 (19.18)	24 (19.20)	71 (19.19)
Oligohydramnios	13 (5.31)	4 (3.20)	17 (4.59)
Diabetes mellitus	4 (1.63)	4 (3.20)	8 (2.16)
Abruption	19 (7.76)	7 (5.60)	26 (7.03)
Premature rupture	37 (15.10)	21 (16.80)	58 (15.68)
Gestational hypertension	39 (15.92)	27 (21.60)	66 (17.84)
Cholestasis	4 (1.63)	3 (2.40)	7 (1.89)
Neonatal			
Age at admission, h	1.00 (1.00–5.00)	1.00 (1.00–5.00)	1.00 (1.00–5.00)
Gestational age, wk	32.95 (2.90)	33.33 (2.76)	33.08 (2.86)
Birth weight, g	1986.29 (633.71)	1906.36 (587.13)	1959.29 (618.73)
Birth asphyxia	70 (28.57)	40 (32.00)	110 (29.73)
Apgar score 1 min	7.74 (2.14)	7.75 (2.12)	7.74 (2.13)
Apgar score 5 min	8.64 (1.61)	8.89 (1.42)	8.73 (1.55)
Apgar score 10 min	8.97 (1.35)	9.34 (0.92)	9.09 (1.23)
Chest radiography			
Grade 1	148 (60.41)	82 (65.60)	230 (62.16)
Grade 2	45 (18.37)	19 (15.20)	64 (17.30)
Grade 3	46 (18.78)	23 (18.40)	69 (18.65)
Grade 4	6 (2.45)	1 (0.80)	7 (1.89)
Use of INSURE	108 (62.43)	54 (64.29)	162 (63.04)
Use of PS	181 (73.88)	95 (76.00)	276 (74.59)
Initial dose of PS, mg/kg	94.26 (37.53)	93.85 (34.08)	94.12 (36.35)
Noninvasive ventilation	200 (81.63)	110 (88.00)	310 (83.78)
Invasive ventilation	31 (12.65)	11 (8.80)	42 (11.35)
Total time of AV, h	72.00 (39.00–120.00)	79.00 (42.00–127.00)	72.00 (39.25–120.00)
Blood gas analysis (at admission)			
pH	7.27 (0.13)	7.27 (0.12)	7.27 (0.12)
PaO_2, mmHg	62.00 (43.00–94.00)	57.00 (37.00–87.00)	61.50 (40.25–90.00)
$PaCO_2$ (mmHg)	51.14 (16.75)	51.14 (14.73)	51.14 (16.07)
BE, mmol/L	−5.80 (−11.20–2.10)	−8.60 (−12.20–3.90)	−6.85 (−11.85–2.82)
Mortality	26 (10.61)	9 (7.20)	35 (9.46)

Data are presented as means (SD), median (Q1–Q3), and categorical variables as number (percentage). AV = auxiliary ventilation, INSURE = tracheal intubation – use of pulmonary surfactant – tracheal extubation using CPAP, PS = pulmonary surfactants, SD = standard deviation.

Table 2

Effects of predictors on outcomes of infants with RDS by univariate analysis.

	Male		Female		Total	
	β/OR (95%CI)	*P*	β/OR (95%CI)	*P*	β/OR (95%CI)	*P*
Maternal age	0.99 (0.91, 1.07)	.815	1.06 (0.93, 1.22)	.355	1.01 (0.94, 1.08)	.800
Glucocorticoids use	2.51 (1.10, 5.74)	.029	2.01 (0.51, 7.96)	.319	2.37 (1.17, 4.80)	.017
Cesarean	0.66 (0.29, 1.49)	.316	2.30 (0.46, 11.56)	.312	0.89 (0.44, 1.79)	.735
Prenatal fetal distress	2.69 (0.98, 7.40)	.056	1.66 (0.32, 8.69)	.546	2.34 (0.99, 5.53)	.054
Multiple pregnancy	1.65 (0.65, 4.19)	.293	0.51 (0.06, 4.24)	.530	1.28 (0.55, 2.96)	.563
Abruption	2.47 (0.75, 8.11)	.135	2.29 (0.25, 21.43)	.467	2.43 (0.85, 6.93)	.097
Premature rupture	0.71 (0.20, 2.50)	.593	0.60 (0.07, 5.07)	.639	0.68 (0.23, 2.00)	.482
Gestational hypertension	0.96 (0.31, 2.94)	.937	0.43 (0.05, 3.62)	.440	0.77 (0.29, 2.08)	.612
Age at admission	0.98 (0.94, 1.02)	.299	1.00 (0.96, 1.06)	.861	0.99 (0.96, 1.02)	.404
Gestational age	0.78 (0.67, 0.92)	.003	0.91 (0.71, 1.17)	.455	0.82 (0.71, 0.93)	.003
Birth weight	1.00 (1.00, 1.00)	.091	1.00 (1.00, 1.00)	.075	1.00 (1.00, 1.00)	.089
Birth asphyxia	5.92 (2.49, 14.05)	<.001	8.80 (1.74, 44.59)	.009	6.50 (3.04, 13.87)	<.001
Apgar score 1 min	0.69 (0.58, 0.81)	<.001	0.80 (0.61, 1.06)	.120	0.72 (0.62, 0.82)	<.001
Apgar score 5 min	0.65 (0.52, 0.81)	<.001	0.83 (0.57, 1.21)	.339	0.69 (0.58, 0.83)	<.001
Apgar score 10 min	0.62 (0.47, 0.82)	.001	0.66 (0.37, 1.15)	.143	0.63 (0.49, 0.81)	<.001
Chest radiography						
Grade 1	1.0		1.0		1.0	
Grade 2	2.19 (0.68, 7.06)	.190	0.70 (0.08, 6.22)	.752	1.57 (0.58, 4.27)	.377
Grade 3	3.68 (1.30, 10.46)	.014	1.21 (0.23, 6.42)	0.826	2.60 (1.10, 6.16)	.030
Grade 4	87.50 (9.11, 840.36)	<.001	12.07 (1.03, 379.8)	.043	36.56 (6.46, 206.71)	<.001
Use of INSURE	0.25 (0.10, 0.66)	.005	0.54 (0.07, 4.03)	.547	0.29 (0.12, 0.69)	.005
Use of PS	2.96 (0.86, 10.22)	.086	1.11 (0.22, 5.67)	.897	2.20 (0.83, 5.85)	.115
Initial dose of PS	0.98 (0.97, 0.99)	.006	0.99 (0.96, 1.01)	.242	0.98 (0.97, 0.99)	.003
Noninvasive ventilation	0.14 (0.06, 0.33)	<.001	1.10 (0.13, 9.45)	.932	0.21 (0.10, 0.45)	<.001
Invasive ventilation	13.86 (5.55, 34.66)	<.001	1.32 (0.15, 11.69)	.800	8.38 (3.85, 18.26)	<.001
Total time of AV, h	1.00 (0.99, 1.00)	.423	1.00 (0.99, 1.01)	.634	1.00 (0.99, 1.00)	.352
pH	0.02 (0.00, 0.53)	.019	0.00 (0.00, 1.46)	.066	0.01 (0.00, 0.24)	.003
PaO_2, mm Hg	0.99 (0.98, 1.00)	.056	0.99 (0.98, 1.01)	.560	0.99 (0.98, 1.00)	.051
$PaCO_2$, mm Hg	0.99 (0.97, 1.02)	.537	1.01 (0.97, 1.06)	.527	1.00 (0.98, 1.02)	.802
BE, mmol/L	0.98 (0.93, 1.03)	.505	0.98 (0.90, 1.06)	.623	0.98 (0.94, 1.03)	.412

Data are presented as β/OR (95%CI) *P*-value. AV = auxiliary ventilation, CI = confidence interval, INSURE = tracheal intubation – use of pulmonary surfactant – tracheal extubation using CPAP, PS = pulmonary surfactants, OR = odd ratio, RDS = respiratory distress syndrome, SD = standard deviation.

Univariate logistic regression (Table 2) was used to estimate the ORs and 95% CIs to investigate the predictors associated with the outcomes of infants. The smoothing plot used to explore the relationship between initial dose of PS levels and the risk of mortality, after adjusting for potential confounders and stratified by gender (Fig. 1). We further applied multivariate logistic regression models to examine the independent effect of initial PS doses on the mortality risk, and interactions between initial PS doses and gender when adjusted for other variables (Table 3).
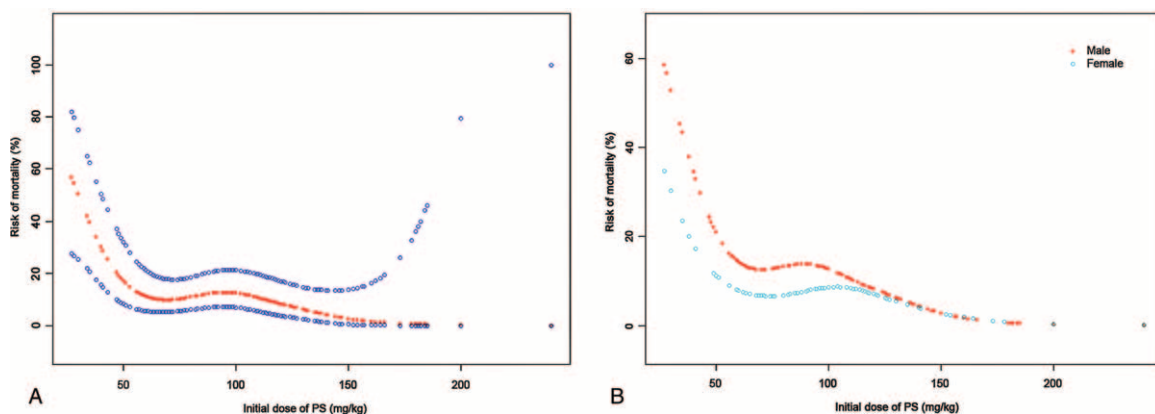
Figure 1. Relationship between initial dose of pulmonary surfactant and risk of mortality in infants with respiratory distress syndrome. (A) A linear relationship between the initial dose of pulmonary surfactant and risk of mortality was observed after adjusting for age at admission, gestational age, birth weight, birth asphyxia, Apgar score, and chest radiography grade. (B) A nonlinear relationship between the initial dose of pulmonary surfactant and risk of mortality was observed in male patients after adjusting for age at admission, gestational age, birth weight, birth asphyxia, Apgar score, and chest radiography grade (red); a linear relationship between the initial dose of pulmonary surfactant and risk of mortality was observed in female patients after adjusting for age at admission, gestational age, birth weight, birth asphyxia, Apgar score, and chest radiography grade (green). The intersection point of the 2 curves corresponds to the initial dose (130 mg/kg) of pulmonary surfactant.

Table 3

Effect of initial dose of PS use on outcomes of infants with RDS by multivariate logistic regression analysis (total and stratified by gender).

Model	Male β/OR (95%CI)	P	Female β/OR (95%CI)	P	Total β/OR (95%CI)	P
Nonadjusted						
Initial dose of PS	0.98 (0.97, 0.99)	.006	0.99 (0.96, 1.01)	.242	0.98 (0.97, 0.99)	.003
Initial dose of PS						
<130 mg/kg	Ref.		Ref.		Ref.	
≥130 mg/kg	0.35 (0.18, 0.73)	.005	0.63 (0.12, 4.25)	.554	0.37 (0.24, 0.80)	.006
Adjust I						
Initial dose of PS	0.98 (0.96, 0.99)	.003	0.98 (0.96, 1.01)	.184	0.98 (0.97, 0.99)	.001
Initial dose of PS						
<130 mg/kg	Ref.		Ref.		Ref.	
≥130 mg/kg	0.35 (0.19, 0.77)	.006	0.89 (0.17, 8.71)	.850	0.39 (0.22, 0.81)	.007
Adjust II						
Initial dose of PS	0.97 (0.96, 0.99)	.005	0.99 (0.96, 1.02)	.543	0.98 (0.96, 0.99)	.002
Initial dose of PS						
<130 mg/kg	Ref.		Ref.		Ref.	
≥130 mg/kg	0.34 (0.17, 0.88)	.018	0.99 (0.00, 82.5)	.998	0.36 (0.19, 0.84)	.011

Data are presented as β/OR (95%CI) P-value. Nonadjusted model adjust for: none; adjust I model adjust for: age at admission, gestational age, and birth weight; and adjust II model adjust for: age at admission, gestational age, birth weight, birth asphyxia, Apgar score, and chest radiography grade. CI = confidence interval, OR = odds ratio, PS = pulmonary surfactants, RDS = respiratory distress syndrome.

All data were double-entered and then exported to tab-delimited text files. All analyses were performed with R (www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc, Boston, MA).

3. Results

Among the 370 infants in the study, 245 (66.22%) were male and 125 (33.78%) were female infants. Of those, 276 (74.59%; 181 males and 95 females) received PS therapy, with a mean dose of (94.12 ± 36.35) mg/kg ([94.26 ± 37.53] mg/kg and [93.85 ± 34.08] mg/kg for male and female infants, respectively); 162 (63.04%; 108 males and 54 females) received INSURE treatment (tracheal intubation – use of PS – tracheal extubation using CPAP), the total mortality during hospitalization was 35 (9.46%; 26 males and 9 females). The demographic and clinical characteristics of maternal and infants were summarized in Table 1.

The univariate regression analysis showed that initial PS doses significantly correlated with mortality incidence (OR 0.98, 95% CI 0.97–0.99, $P = .003$), as a protective factor in the whole population. Interestingly, when the infants were separated by gender, the initial dose of PS only relevant to mortality incidence in male infants (OR 0.98, 95% CI 0.97–0.99, $P = .006$) rather than in female infants (OR 0.99, 95% CI 0.96–1.01, $P = .242$). The association between INSURE treatment and mortality incidence in male and female infants showed a similar trend ([OR 0.25, 95% CI 0.10–0.66, $P = .005$] and [OR 0.54, 95% CI 0.07–4.03, $P = .547$] for male and female infants, respectively). In addition, birth asphyxia ([OR 5.92, 95% CI 2.49–14.05, $P < 0.001$] in males [OR 8.80, 95% CI 1.74–44.59, $P = .009$] in females) and chest radiography grade ([OR 87.50, 95% CI 9.11–840.36, $P < .001$] in males [OR 12.07, 95% CI 1.03–379.8, $P = .043$] in females) were correlated with mortality incidence in both male and female infants; while gestational age ([OR 0.78, 95% CI 0.67–0.92, $P = .003$] in males [OR 0.91, 95% CI 0.71–1.17, $P = .455$] in females) and Apgar score ([OR 0.62, 95% CI 0.47–0.82, $P = .001$] in males [OR 0.66, 95% CI 0.37–1.15, $P = .143$] in females) correlated with mortality incidence only in male infants (Table 2).

In the multiple logistic regression of the whole study population, after adjusting for possible factors related to mortality incidence (eg, age at admission, gestational age, birth weight, birth asphyxia, Apgar score, and chest radiography grade), a linear relationship between the initial dose of PS and mortality risk was observed (Fig. 1A), when stratified by gender, a linear relationship between initial dose of PS and mortality incidence was observed in female patients; and a nonlinear relationship between initial dose of PS and mortality incidence was observed in male patients (Fig. 1B). We then performed a threshold effect analysis to determine the intersection point of the 2 curves, corresponding to the initial PS dose of 130 mg/kg.

The independent effect of initial dose of PS on mortality incidence was further analyzed. After adjusting for other variables, initial dose of PS remained negatively associated with mortality incidence (OR 0.98, 95% CI 0.96–0.99, $P = .002$); meanwhile, after dividing the initial dose of PS by 130 mg/kg, we found that higher PS dosages offered a protective factor in infants with RDS (OR 0.36, 95% CI 0.19–0.84, $P = .011$). Then we use gender as a stratification factor to further explore the effect of the initial PS dose on mortality incidence. As we expected, in male patients, after adjusting for potential confounding factors, the initial dose of PS remained negatively associated with mortality (OR 0.97, 95% CI 0.96–0.99, $P = .005$), when the initial dose of PS increased by 1 mg/kg, the risk of mortality decreased by 3%; the risk of mortality among infants who received PS doses ≥130 mg/kg fell by about 66%, compared to those who received lower doses <130 mg/kg (OR 0.34, 95% CI 0.17–0.88, $P = .018$); while in female patients, we failed to found a relationship between the initial dose of PS and mortality incidence either as a continuous variable (OR 0.99, 95% CI 0.96–1.02, $P = .543$), or as a categorical variable (OR 0.99, 95% CI 0.00–82.5, $P = .998$) (Table 3).

4. Discussion

RDS is a leading cause of high mortality rates in newborns. Previous studies have shown that RDS accounts for 10% to 20% of infant mortality around the world.[17–19] In the current study, 35 (9.46%) infants died due to RDS in the 6 months following

consultation, which is consistent with previous studies. Since 1990s, the introduction of multiple PS therapies has substantially improved outcomes among newborns with RDS.[20] The physiological functions of surfactants include the ability to lower surface tension and the ability to rapidly adsorb and spread, which is associated with the respiratory cycle. A series of studies have shown that a sufficient amount of PS given during the initial stages of treatment may shorten the duration of respiratory support and improve the outcomes.[21] One recent study has suggested that male preterm infants are more likely to experience RDS than females.[22] Another research using an ovine model of preterm birth showed that poorer respiratory adaptation in male preterm lambs (born at 0.9 of term) was likely due to lower lung compliance than in females, and that this difference may result from sex differences in surfactant phospholipid composition and function.[23] Whether the surfactant replacement therapy has similar gender-based efficacy in infants, and whether male and female infants have similar sensitivities to PS treatment have not yet been studied. The present study was thus designed to determine whether the efficacy of surfactant replacement therapy among infants could be influenced by gender. To the best of our knowledge, the present study is the first clinical study to demonstrate that male infants and female infants respond differently to PS treatment. We found that males exhibited a lower sensitivity than females to PS replacement therapy and that, for male infants, an increased initial dose of PS at least 130 mg/kg should be used to treat RDS.

A certain number of clinical and pharmacokinetic studies have shown that a higher dose of surfactant is more efficient in the clinical treatment of RDS.[24] The initial surfactant dose of 100 mg/kg is based on the fact that serum-derived protein inhibitors and inflammatory mediators that inactivate the surfactant system in RDS accumulate progressively; thus, treatment in the initial phase is effective with the 100 mg/kg dose.[25] In the current study, the initial dose of PS was 50 to 240 mg/kg. In the multiple logistic regression of the whole study population, we found that a linear relationship between the initial dose of PS and risk of mortality was observed after adjusting for age at admission, gestational age, birth weight, birth asphyxia, Apgar score, and chest radiography grade, and that the risk of mortality reduced 2% for every 1 mg/kg increase of the initial dose of PS application. This is consistent with the evidence that the use of exogenous PS may be associated with a decreased mortality risk.[3] Then we use gender as a stratification factor to further explore whether gender influenced the efficacy of PS on mortality incidence. In the smooth plot, a nonlinear relationship between the initial dose of PS and mortality risk was observed in male infants; whereas a linear relationship between the initial dose of PS and mortality risk was observed in female infants. The intersection point of the 2 curves corresponds to the initial 130 mg/kg dose of PS. In male patients, the risk of mortality reduced 3% for every 1 mg/kg increase of the initial dose of PS. Mortality rates among infants who received PS doses ≥130 mg/kg fell about 66% compared to those who received PS doses <130 mg/kg. However, in female patients, the smooth plot between the initial dose of PS and the risk of mortality showed that although the initial dose of PS <130 mg/kg, the treatment remained effective in improving the outcomes.

Birth asphyxia and chest X-ray findings are also important outcome predictors of RDS.[26] In the current study, infants with birth asphyxia had an about 6.50 folds increase in mortality, compared to those without birth asphyxia. Infants with higher chest radiography grades suffered from higher risk of mortality,

which is consistent with previous studies. Some studies also have shown that neonatal factors, such as low gestational age, low birth weight, and male sex, are predictors of poor outcomes of RDS.[27–30] In this study, we found that male infants with low gestational ages and low Apgar scores had higher mortality than females.

5. Limitations

The most important limitation of our study was that it was a retrospective cohort study based on the medical records from northwest China. Therefore, some indicators were missing and could not be analyzed. Many cases also ceased treatment for economic reasons. Although we excluded these latter cases to reduce the interference of subjective factors, it inevitably reduced our study population. Thus, nationwide well-designed prospective cohort trials are needed for future studies.

6. Conclusions

In conclusion, our study showed that among newborn infants who were diagnosed with RDS, female babies had a better response to surfactant treatment than male babies. For the male infants, the effect of surfactant replacement therapy was not as good as expected if the initial dose of PS <130 mg/kg.

Author contributions

Conceptualization: Li Liu.
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Formal analysis: Chen Chen.
Investigation: Chen Chen, Tian Tian, Juan Zhang, Huiling Fu.
Methodology: Li Liu.
Project administration: Li Liu.
Supervision: Li Liu.
Writing – original draft: Chen Chen, Juan Zhang, Huiling Fu.
Writing – review & editing: Chen Chen, Tian Tian.

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