Effect of low-dose exogenous surfactant on infants with acute respiratory distress syndrome after cardiac surgery: A retrospective analysis

Rongyuan Zhang
Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital
Xu Wang (fwpicu@163.com)
Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital
Shoujun Li
Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital
Jun Yan
Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Research article

Keywords: Infants, pulmonary surfactant, ARDS, cardiac surgery, congenital heart disease

Posted Date: June 17th, 2020

DOI: https://doi.org/10.21203/rs.2.20740/v2

Version of Record: A version of this preprint was published on August 6th, 2020. See the published version at https://doi.org/10.1186/s12890-020-01251-2.

Abstract

Background: To evaluate the effect of low-dose exogenous surfactant therapy on infants suffering acute respiratory distress syndrome (ARDS) after cardiac surgery.

Methods: We conducted a retrospective case-control study of infants diagnosed with **moderate-severe ARDS** after cardiac surgery. A case was defined as a patient that received surfactant and standard therapy, while a control was defined as a patient that underwent standard therapy. The primary endpoint was the improvement in oxygenation index (OI) after 24-hour of surfactant treatment; and secondary endpoints were the ventilator time and PICU time.

Results: 22 infants treated with surfactant were matched with 22 controls. Early low-dose (20mg/kg) surfactant treatment was associated with improved outcomes. After surfactant administration for 24-hour, the surfactant group was much better compared with the control group at the 24-hour in OI (difference in average change from baseline, -6.7 [95% CI, -9.3 to -4.1]) ($P < 0.01$) and VI (mean difference, -11.9 [95% CI, -18.1 to -5.7]) ($P < 0.01$). Ventilation time and PICU time were significantly shorter in the surfactant group compared with the control group (133.6h±27.2 vs 218.4h±28.7, $P < 0.01$; 10.7d±5.1 vs 17.5d±6.8, $P < 0.01$). Infants in the surfactant group under 3 months benefit more from OI and VI than the infants over 3 months in a preliminary exploratory analysis.

Conclusions: In infants with **moderate-severe ARDS after cardiac surgery**, early low-dose exogenous surfactant treatment could prominently improve oxygenation and reduce mechanical ventilation time and PICU time. **Infants younger than 3 months may get more benefit of oxygenation than the older ones.**

Background

ARDS is a life-threatening lung condition. It is a major cause of increased mechanical ventilation time and mortality. Despite lung protective low-tidal-volume ventilation, improved ICU management, availability of new antimicrobial therapies, nutritional support, and other factors, mortality from ARDS remains 25-35% [1], severe lung injury is associated with poor clinical outcomes [2], especially in infants with CHD undergoing cardiac surgery and CPB.

Exogenous surfactant therapy is widely used in treatment of neonates with respiratory distress syndrome. It is suggested that there may be expanded use of surfactant replacement for diseases such as meconium aspiration syndrome [3], pneumonia [4], bronchopulmonary dysplasia [5], and ARDS [6]. Surfactant replacement is an effective and safe therapy by rapidly improving oxygenation and mechanics, and it can improve lung physiology and clinical outcome [6].

The qualitative and quantitative changes in alveolar surfactant of patients with ARDS have been proven [7-9]. Similarly, due to endothelial cells damage, all post-cardiac surgery infants who had ARDS suffered surfactant dysfunction, destruction and inactivation [10-12]. Yet, limited study [13] showed preliminary therapeutic effect of surfactant therapy on these patients, especially, the association between age or drug dose and the efficacy of surfactant therapy. Therefore, this study will focus on: 1 evaluating whether low-dose surfactant therapy would improve oxygenation in infants who had ARDS after cardiac surgery with CPB; 2 identifying the most beneficial age of surfactant therapy.

Methods

Study design and patients

This is a retrospective, observational, case-control analysis, conducted from January 2015 to June 2019. Ethical Committee of Fuwai Cardiovascular Hospital approved the protocol (Approval NO. 2015-682), and informed consent was obtained from participant' parents before enrolment.

The study was conducted in a PICU (40 beds) at a 1521-bedded tertiary medical care center in China. Patients entry criteria included: (1) less than 1 year old; (2) complete repair of CHD with CPB; (3) PaO_2/FiO_2 lowered than 150 and had been mechanically ventilated for more than 48 hours. Exclusion criteria: (1) residual cardiac malformation that must be treated surgically; (2) ECMO; (3) cardiopulmonary resuscitation; (4) airway anomalies that will delay extubation; (5) ejection fracture < 45% (every patient received an ECHO when ARDS was diagnosed); (6) left atrial pressure>12 (Left atrial pressure of every infant was measured by placing a special catheter into the right atrium then punching through the interatrial septum).

The primary endpoint was the improvement in OI after 24-hour of surfactant treatment; and secondary endpoints were ventilator time and PICU time. A sample size calculation with power analysis was performed for this study. Based on the primary outcome-improvement in OI after 24-hour of surfactant treatment, 4 differences in OI between surfactant group and control group is considered significant, an SD of 4 was used. This SD is based on a previous study of infants suffering ARDS after cardiac surgery [13]. At 80% power and an alpha of 0.05, at least 16 subjects would be required in each group.

There were 2 different strategies to deal with these infants in our center. Some patients preferred to adopt surfactant, who met the criteria. Other patients preferred to use standard treatment, for worrying about the

potential complications such as airway obstruction, or for disliking extra economic burden. Everyone was offered surfactant at the beginning, but surfactant is not a part of our standard treatment protocol.

During the 42-month study, 7569 children that had cardiac surgery were admitted to PICU, and 3414 of them were infants. 343 infants used mechanical ventilation above 2 days. 78 infants were diagnosed with moderate to severe ARDS (PaO_2/FiO_2), and who matched inclusion and exclusion criteria. 22 infants who received surfactant in addition to standard care constituted surfactant group. In order to minimize potential bias caused by differences in baseline characteristics between groups, patients were matched in a 1:1 ratio using the following baseline features: age (±30d), weight (±3kg), RACHS-1, and initial PaO_2/FiO_2 (±10). These 22 controls were also offered surfactant but declined (high cost 5, guardians' preference to use standard treatment 5, and guardians' refusal for worrying about the potential complications 12). It was a comparative study evaluating the changes in clinical status and outcome between the two groups.

Study Drug

Surfactant (Calf Pulmonary Surfactant for injection, produced by Shuang he Inc, Beijing, CN) is a modified natural lung surfactant. It is produced by extracting the phospholipids, cholesterol, triglycerides, free fatty acids, surfactant protein B and surfactant protein C from bovine lung surfactant of newborn calf lungs. China Food and Drug Administration approved surfactant for neonatal respiratory distress syndrome.

Surfactant is a routine therapeutic choice for pre-term newborns suffering respiratory distress syndrome. The standard dose of surfactant is 50-100mg/kg [14,15], some patients may have side effects such as intense instant hemodynamic fluctuation and hypoxemia. Due to high cost and concern for dangerous acute side effects, we are cautious about surfactant dosage. Considering that the native surfactant system of these infants was nearly normal before operation, and self-repairing systems of epithelial cells could replenish surfactant after CPB, a low dose of 20 mg/kg nature surfactant as the treatment dosage was used.

Study intervention

All operations were performed by 2 senior surgeons. Patients in both groups had received standard care according to the hospital protocol. The basic care contained fluid resuscitation, enteral feeds and pain management, and other treatments including cardiac, diuretic, anti-inflammatory. Vital signs, oximetry and hemodynamic parameters would be continuously monitored. The cardiac functions and circulatory blood volume status were obtained by pumping multiple vasoactive agents mainly including catecholamine drugs and giving adequate fluid supplement. Rescue protocol for any severe hemodynamic fluctuation would be prepared. Sedation and mechanical ventilation treatment would be strictly controlled. Supportive management and antibiotics were given as per unit policy. ARDS was diagnosed based on the standard recommended by the North American-European Consensus Conference Committee [16]. The diagnosis of ARDS was confirmed by clinical, radiological and laboratory findings.

Lung protective ventilation strategy was applied to all infants before enrollment. All infants were intubated and supported by mechanical ventilation with synchronized intermittent mandatory ventilation mode of the ventilator (PB 840®). Ventilator settings were adjusted to arterial blood gas results. The peak inspiratory pressure was adjusted to reach a tidal volume goal of 6 ml/kg to 8 ml/kg. To keep the $PaCO_2$ below 45 mmHg, the inspiratory time would be set at approximately 0.5s, with respiratory rate 25-40/min, PEEP 4-8 cmH_2O. Also, to maintain arterial oxygen saturation above 85% and PaO_2 above 50 mmHg, peak inspiratory pressure and FiO_2 needed to be adjusted.

Natural surfactant (bovine) would be given 20mg/Kg (35mg/ml). After receiving the written parental permission, surfactant would be instilled into the trachea via an endotracheal tube using a small catheter in 4 equal aliquots, which would be instilled in four different positions (left, head up then down, right). Manual ventilation with 100% O_2 would be applied for 5 minutes after the treatment. With concomitant sedation and muscle relaxation, the next tracheal suctioning would be performed at least 4 hours later. The acute effects of surfactant therapy would be evaluated 24- hour after the treatment. Vital signs were monitored continuously and recorded for 60 minutes after the intervention. Chest radiographs were acquired before and after surfactant administration every day.

Data collection

Data was entered on a pre-designed case record form from the patients' archived files. The data extracted included patient demographics, blood gases, ventilator settings, complication, total time on ventilator, total time in PICU and clinical outcomes. Ventilator days were counted from the first day that a patient received mechanical ventilation. Ventilator parameters were recorded before the start of surfactant

administration. After surfactant treatment, OI and VI were derived from the measured data. OI was calculated via mean airway pressure * FiO_2 *100/PaO_2 and VI was calculated via $PaCO_2$ * peak inspiratory pressure * respiratory rate/1000.

The baseline demographic and clinical characteristics that were collected were age, weight, sex, RACHS-1, total on-pump time, aortic clamping time, OI, VI, PaO_2/FiO_2, PaO_2 and the status of the patient within the time of inclusion (Table 1). In addition, the severity of illness at the time of inclusion was recorded and assessed by using the SOFA score [17]. Moreover, the daily vital signs, urine output, laboratory data, ventilator settings, vasopressor dosage were extracted.

Statistical analysis

Qualitative data were presented as frequencies and percentages, whereas quantitative data were presented as mean, standard deviation. The unpaired t-test was used for comparison between patients in surfactant group and control group (or

the Fisher exact test when there were counts of <5). The cumulative percentages of extubated patients were analyzed using Kaplan-Meier survival analysis with the log-rank test. The data was analyzed using SPSS version 20.0. The p-value of <0.05 was considered as statistically significant.

Results

Detailed demographic information of patients in surfactant group and control group are listed in Table 1. There was no significant difference in baseline between the surfactant group and the control group. There was no significant difference in OI, VI, PaO_2/FiO_2 and **$PaCO_2$** between the two groups at the beginning (Table 1). The treatment was well tolerated as well. No side effects and complications were observed during surfactant treatment.

Early low-dose surfactant treatment was associated with improved outcomes. Infants in the surfactant group showed better result of oxygenation after surfactant treatment than the control group. With the administration of surfactant, OI of each patient gradually decreased. All variables before and after surfactant therapy are given in Table 2 and Figure 1-4. Infants receiving surfactant had significantly

shorter ventilation time and PICU time (Table 2). All patients were extubated within 15 days. Infants in surfactant group were extubated earlier than control group (P<0.01) (Figure 5).

The surfactant group was better compared with the control group at the 6-hour with respect to both OI (difference in average change from baseline, -6.4 [95% CI, -9.0 to -3.8]) (P < 0.01) and VI (mean difference, -14.8 [95% CI, -21.5 to -8.1]) (P < 0.01). At the 24-hour follow-up, the change from baseline in OI (difference, -6.7 [95% CI, -9.3 to -4.1]) (P < 0.01)and VI (mean difference,-11.9 [95% CI, -18.1 to -5.7]) (P < 0.01)were much better in the surfactant group than the control group (P < 0.01). (Figure 1 and Figure 2)

Similarly, surfactant treatment was associated with greater improvement (P < 0.01) compared with the control group at 6-hour in PaO_2 (mean difference, 34.1 [95%CI, 22.8 to 45.4]) (P < 0.01) and PaO_2/FiO_2 (mean difference, 41.6 [95% CI, 20.1 to 63.1]) (P < 0.01). At the 24-hour follow-up, the change from baseline in PaO_2 (mean difference, 48.8 [95% CI, 38.6 to 59]) (P < 0.01) and PaO_2/FiO_2 (mean difference, 90.6 [95% CI, 68.2 to 113.0]) (P < 0.01) were much higher in the surfactant group than the control group (Figure 3 and Figure 4).

None of the patients showed significant clinical deterioration and changes in hemodynamic status and other vital signs with the application of surfactant. 5 patients (22.7%) in control group and 2 patients (9.1%) in surfactant group had pneumothorax; and 1 (4.5%) patient in control group had digestive hemorrhage, none happened in surfactant group (P< 0.01). 3 patients (13.6%) in surfactant group and 8 (36.3%) in control group needed CPAP after extubation (P< 0.01). There were 2(9%) and 1(4.5%) patients in control group and surfactant group needing retracheal intubation and **peritoneal dialysis** respectively. 1(4.5%) patient in control group needed **HFOV**, none happened in surfactant group (P< 0.01).

The 22 patients in surfactant group were assigned to younger than 3 months subgroup (10 infants) and older than 3 months subgroup (12 infants). RACHS-1, total on-pump time and aortic clamping time of the two subgroups were similar (P<0.01) (Table 3). **For the subgroups based on age have very low numbers, preliminary exploratory analysis showed:** surfactant showed better efficacy in OI and VI in the less than 3 months subgroup (Table 4). There was no statistical difference in ventilator time and PICU time between the two subgroups (Table 3).

Discussion

In this study, with the treatment of low dose surfactant, rapid improvement in oxygenation, and significant decrease in duration of ventilator time and PICU time were observed. This is the first study

about low-dose surfactant therapy in infants after cardiac surgery with CPB. Preliminary exploratory analysis showed infants younger than 3 months benefited more from oxygenation improvement than the infants older than 3 months.

As prolonged mechanical ventilation was a common issue, post-cardiac surgery changes of the surfactant components could be detected in nearly one third of the infants [18]. Inflammatory response induced by CPB [18] could be exacerbated by accumulation of cytokines. Meanwhile mechanical ventilation itself could worsen ARDS by damaging the alveolocapillary barrier in the lungs [20]. The reduced compliance and a ventilation-perfusion mismatch hinted that the surfactant system was damaged [21, 22]. Exogenous surfactant may contribute in preventing the surfactant system from developing extreme disturbance.

Respiratory tract infections are the most common risk factors of ARDS in infants, and CPB is a risk factor reported in cardiac patients. Around 50% of patients in each group had clinical courses complicated by pneumonia, infants with unrepaired CHD often suffer from malnutrition and have weakened immune systems. They are more susceptible to lower respiratory tract infections before surgery, while postoperatively they are at risk for ARDS. The other 50% of infants' ARDS were cause for CPB. Children with cardiac disease may be particularly susceptible to deleterious CPB interactions induced by positive pressure ventilation. Surfactant dysfunction and inactivation are key contributors to the pathophysiology of ARDS by inducing areas of atelectasis and intrapulmonary shunting, which reduce lung volumes and compliance. Because failure to improve clinically over the first several days, particularly regarding oxygenation, predicts a complicated course and greater mortality risk, oxygenation improvement is particularly important for these infants [23].

The study population was strictly defined according to inclusion and exclusion criteria. Most infants with mild lung injury could be well managed with common treatment such as mechanical ventilation. **While those infants with moderate-severe ARDS should receive prophylactic or early rescue surfactant replacement to gain more advantage**. As a clinical predictive tool, a PaO_2/FiO_2 threshold of 150 was used in this study. Surfactant would be given as rescue treatment once mechanical ventilation failed in improving the oxygenation. Oxygenation improvement was reported in previous study [13, 24, 25]. Unlike previous studies, a decrease in the duration of ventilation and total time of PICU could also be observed.

Preliminary exploratory analysis showed: infants younger than 3 months of age achieved faster recovery of pulmonary function according to our result. Age is a risk factor of lung damage during CPB [26]. Lung

ischemia-reperfusion was more severe in the infants younger than 3 months, probably because of the combination of low antioxidant capacity and overproduction of reactive oxygen species in infants. Infants younger than 3 months may have worse ability to clear lung liquid and product insufficient surfactant after CPB. And the rescue surfactant treatment would help with the avoidance of further ventilator-induced lung injury and the maintenance of intact alveolar barrier.

Single-centered data and institution-specific variables may influence the results. Therefore, to determine and conclude the risks and benefits of surfactant therapy in infants with **moderate-severe** ARDS after cardiac surgery, a multi-center randomized controlled trial is necessary.

Conclusions

ARDS continues to be associated with prolonged mechanical ventilation in CHD infants that had surgery on CPB. There is an urgent need for therapies which could alter the treatment of the disease. This study has presented the experience with the management of ARDS using low-dose surfactant, and it could improve oxygenation and reduce respirator treatment time in infants with post cardiac surgery ARDS, more benefits could be obtained in the infants under 3 months. The present study suggest that low-dose surfactant may have a beneficial role in the management of ARDS.

Declarations

Ethics approval and consent to participate

Ethical Committee of Fuwai Cardiovascular Hospital approved the protocol (Approval NO. 2015-682), and informed consent was obtained from participant' parents before enrolment.

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors initials to refer to each author's competing interests in this section.

Funding

The work was supported by the Central Public Welfare Scientific Research Fund of China [2016-F01] and the National Key R&D Program of China [2017YFC1308100]. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

RZ analyzed and interpreted the data. XW was a major contributor in writing the manuscript. SL and JY were surgeons of all cases. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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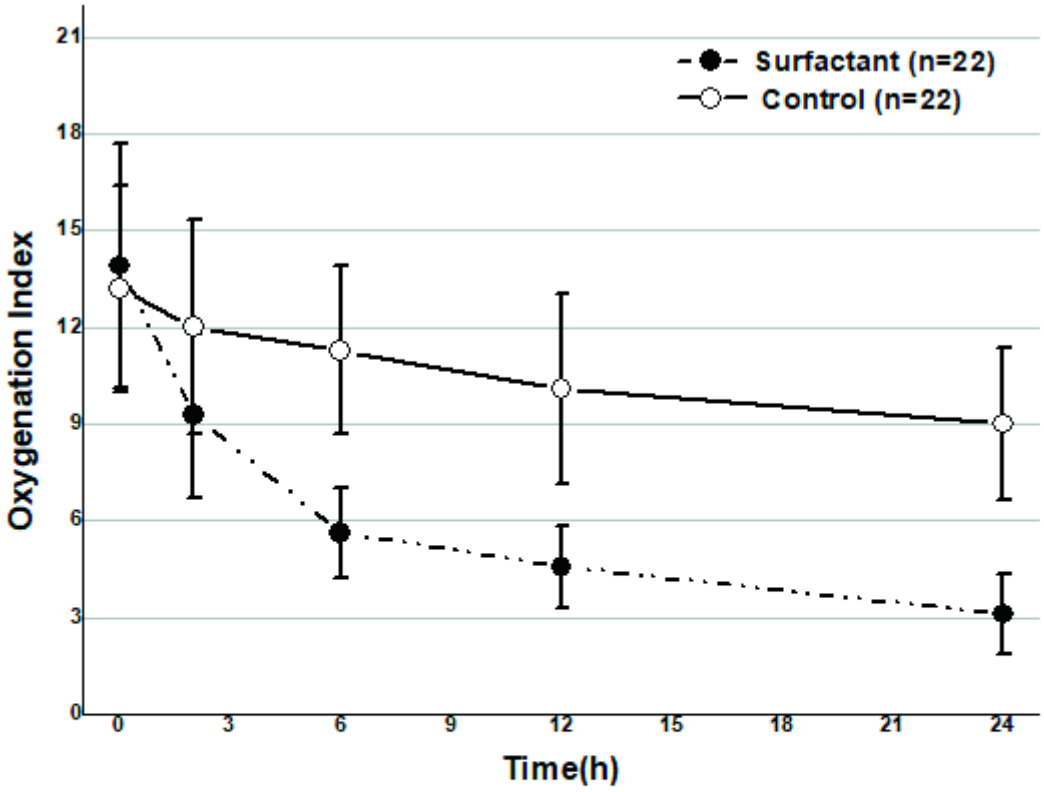
Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Abbreviations

ARDS: Acute respiratory distress syndrome; CHD: Congenital heart disease; CPB: cardiopulmonary bypass; PICU: Pediatric cardiac surgical intensive care unit; PaO_2/FiO_2: Arterial oxygen concentration to the fraction of inspired oxygen; ECMO: Extracorporeal membrane oxygenation; RACHS-1: Risk adjustment congenital heart surgery-1; OI: Oxygenation index; VI: Ventilation index ; CPAP: Continuous positive airway pressure; HFOV: High frequency oscillatory ventilation; CI: confidence interval

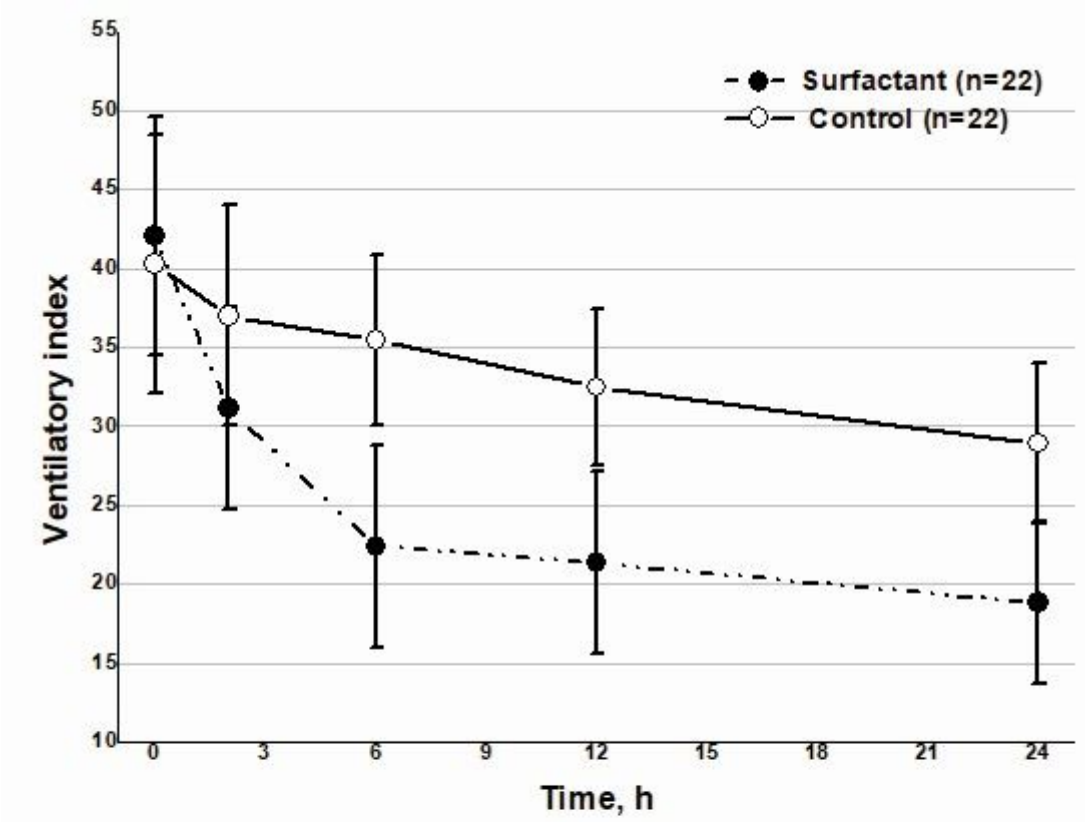
Figures



	Control	Surfactant	Difference in average change from baseline
Baseline	13.2 (10.0, 16.4)	13.9 (10.1, 17.7)	
6-hour	11.3 (8.7, 13.9)	5.6 (4.2, 7.0)	
Chang from baseline	-1.9 (-4.5, 0.7) *P* <0.01	-8.3 (-10.9, -5.7) *P* <0.01	-6.4 (3.8, 9.0) *P* <0.01
24-hour	9.1 (6.7, 11.5)	3.1 (1.8, 4.4)	
Change from baseline	-4.1 (-6.8, -1.4) *P* <0.01	-10.8(-13.3, -8.5) *P* <0.01	-6.7 (4.1, 9.3) *P* <0.01

Figure 1

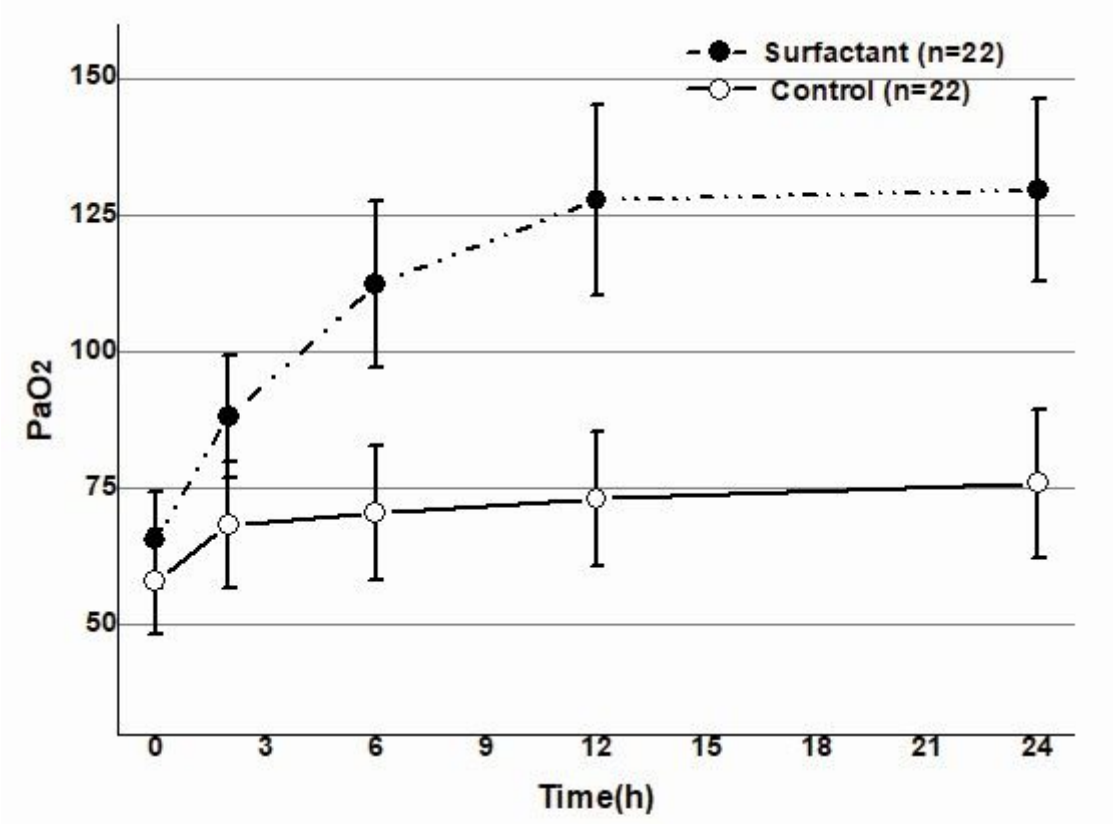
Change of Oxygenation Index (OI) before and after surfactant treatment compared with the control.



	Control	Surfactant	Difference in average change from baseline
Baseline	40.6 (32.1, 48.4)	42.4 (34.5, 49.5)	
6-hour	35.4 (30.0, 40.8)	22.4 (16.0, 38.8)	
Chang from baseline	-5.2 (-11.9, -1.6) *P* =0.02	-20.0 (-26.9, -13.1) *P* <0.01	-14.8 (-21.5, -8.1) *P* <0.01
24-hour	28.9 (23.8, 34.0)	18.8 (13.7, 23.9)	
Change from baseline	-11.7 (-18.3, -5.1) *P* <0.01	-23.6 (-29.3, -17.3) *P* <0.01	-11.9 (-18.1, -5.7) *P* <0.01

Figure 2

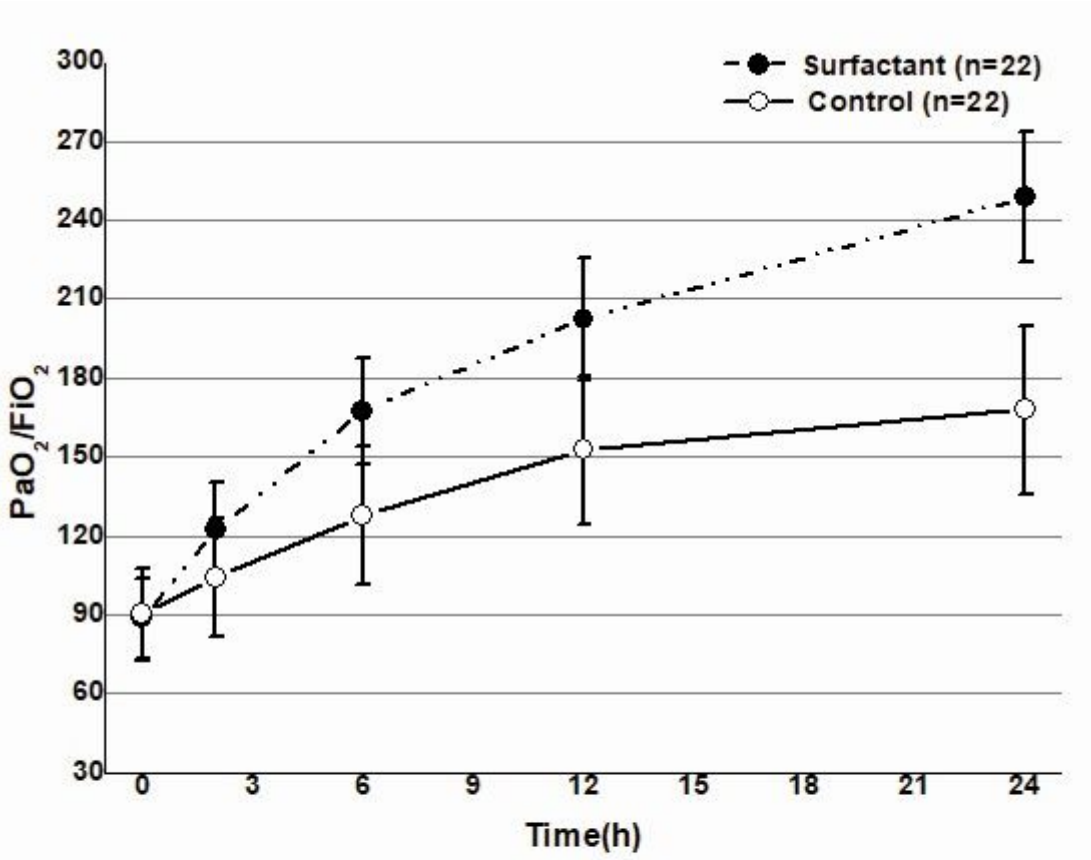
Change of Ventilatory Index (VI) before and after surfactant treatment compared with the control.



	Control	Surfactant	Difference in average change from baseline
Baseline	57.9 (48.3,67.5)	65.5 (57.7, 74.3)	
6-hour	70.6 (58.3, 82.9)	112.3(97.1, 127.5)	
Chang from baseline	12.7 (2.2, 23.6) *P* <0.01	46.8 (34.8, 58.8) *P* <0.01	34.1 (22.8, 45.4) *P* <0.01
24-hour	73.0 (54.9, 86.6)	129.4 (112.8, 146.0)	
Change from baseline	15.1 (3.5, 26.7) *P* <0.01	63.9 (55.1, 71.7) *P* <0.01	48.8 (38.6, 59) *P* <0.01

Figure 3

Change of PaO2 before and after surfactant treatment compared with the control.



	Control	Surfactant	Difference in average change from baseline
Baseline	90.3 (72.8, 107.8)	88.5 (73.1, 103.9)	
6-hour	127.8 (101.3, 154.3)	167.6 (147.3, 187.7)	
Chang from baseline	37.5 (12.3, 59.5) *P* <0.01	79.1 (61.3, 96.9) *P* <0.01	41.6 (20.1, 63.1) *P* <0.01
24-hour	159.9 (135.8, 200.1)	248.7 (242.2, 278.2)	
Change from baseline	69.6 (44.8, 94.4) *P* <0.01	160.2 (140.2, 180.1) *P* <0.01	90.6 (68.2, 113.0) *P* <0.01

Figure 4

Changes of PaO2/FiO2 before and after surfactant treatment compared with the control. FiO2 = fraction of inspired oxygen, PaO2 = arterial partial pressure of oxygen.

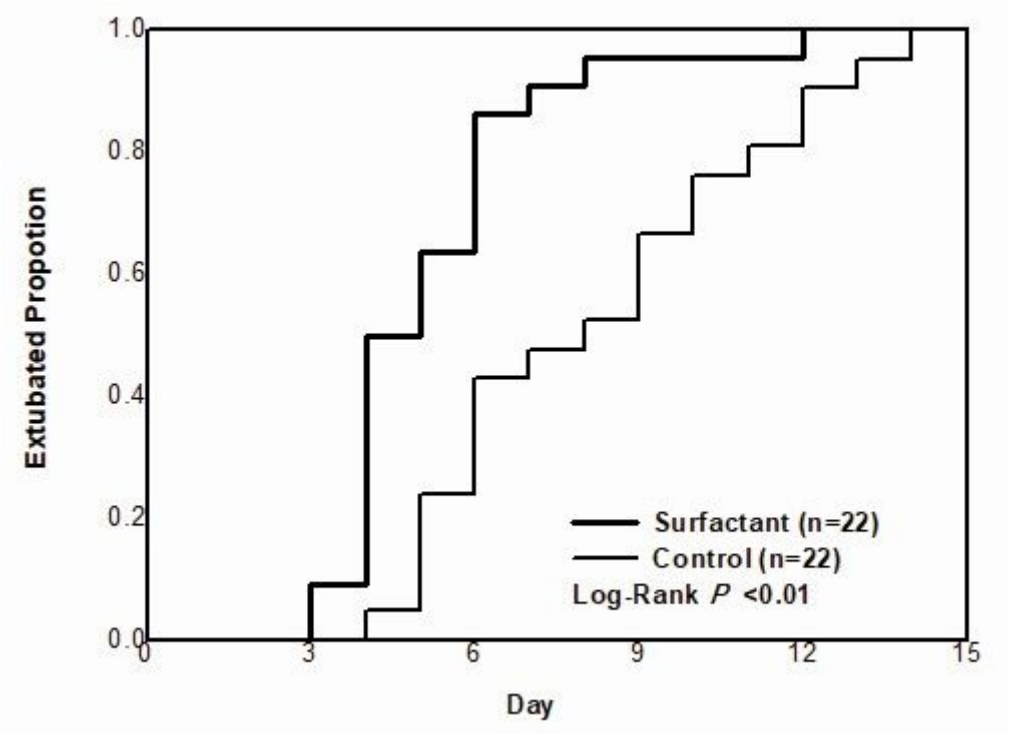


Figure 5

Extubated proportion of surfactant compared with control.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.docx
- table2.docx
- table3.docx
- table4.docx