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

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Abstract

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

Materials and methods: We conducted a retrospective case-control study of the archive data of infants diagnosed with ARDS after cardiac surgery and admitted to pediatric cardiac surgical intensive care unit (PICU). A case was defined as a patient that received surfactant and standard therapy; a control was defined as a patient that underwent standard therapy. Controls were identified by matching patients based on age(±30d), weight(±3kg), risk adjustment congenital heart surgery-1 (RACHS-1), and initial ratio of partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) (±10). Outcome variables namely oxygenation indices (OI), ventilation index (VI), mechanical ventilation time and PICU time were compared.

Results: Forty-four patients, 22 who received surfactant (surfactant group) and 22 who did not (control group) were analyzed. Surfactant group obtained a significant improvement on OI (13.9 vs 5.62; p=0.000) and VI (42.0 vs 22.4; p=0.000) in 6 hours, while control group got no improvement on OI (13.2 vs 11.5; p=0.065) and VI (40.2 vs 36.4; p=0.100). Compared with control group, surfactant group had shorter ventilation time (133.6h vs 218.4h; p=0.000) and PICU time (10.7d vs 17.5d; p=0.001). Infants in surfactant group under 3 months benefit more from OI and VI than infants over 3 months.

Conclusions: In congenital heart disease infants with post-surgery ARDS, low-dose exogenous surfactant treatment could prominently improve oxygenation and reduced mechanical ventilation time and PICU time. And the improvement of oxygenation is more effective for infants under 3 months.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a serious complication, especially in infants undergoing congenital heart disease (CHD) surgery on cardiopulmonary bypass (CPB), and it is a major cause of prolonged mechanical ventilation and postoperative mortality. Although the therapeutic effects of lung-protective ventilation in these patients have been confirmed [1], severe lung injury is associated with poor clinical outcomes [2].

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 neonatal diseases such as meconium aspiration syndrome (MAS) [3], pneumonia [4] and bronchopulmonary dysplasia (BPD) [5]. Surfactant replacement may be life saver by rapidly improving oxygenation.

The qualitative and quantitative changes in alveolar surfactant of patients with ARDS have been proven [6–8]. Similarly, due to endothelial cells damage, all post-cardiac surgery infants who had ARDS suffered surfactant dysfunction, destruction and inactivation [9–11]. Yet, limited study [12] 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.

2. Material And Methods

2.1 Study design and patients

This is a retrospective, case-control analysis, conducted from January 2015 to June 2019. This study was carried out in a pediatric cardiac surgical intensive care unit (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 congenital heart disease with cardiopulmonary bypass (CPB), (3) the ratio of arterial oxygen concentration to the fraction of inspired oxygen (PaO_2/FiO_2) lower than 150 after 48 hours of mechanical ventilation. Exclusion criteria: (1) residual cardiac malformation that must be treated surgically, (2) extracorporeal membrane oxygenation (ECMO), (3) cardiopulmonary resuscitation, (4) airway anomalies that will delay extubation, (5) ejection fracture < 45% (every patient received an ECHO once 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.)

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 (Fig. 1). 22 infants who received surfactant in addition to standard care constituted to surfactant group. Controls were identified by matching infants based on age(±30d), weight(±3kg), risk adjustment congenital heart surgery-1 (RACHS-1), and initial ratio of partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) (±10). Therefore, one control individually matched for age, weight, RACHS-1, and initial ratio of PaO_2/FiO_2 was selected per case. The controls were received all other standard care but did not receive surfactant. It was a comparative study evaluating the changes in clinical status and outcome between the two groups. Ethical Committee of Fuwai Cardiovascular Hospital approved the protocol (Approval NO. 2015-682), and informed consent was obtained from participant' parents before enrolment.

2.2 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 relatively expensive, and some infants were not covered under medical or health insurance. Thus, participant' parents are offered the choice to receive surfactant in addition to the standard supportive care. Surfactant is not a part of our standard treatment protocol.

2.3 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 had fluid resuscitation, enteral feeds and pain management, and other treatments include 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 [13]. 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 (SIMV) 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 (PIP) 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 was 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. Chest radiographs were acquired before and after surfactant administration every day. The control one took the same day after operation when the case used surfactant as the time of inclusion.

2.4 Data collection

Data was entered on a pre-designed case record form (CRF) 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, oxygen index (OI) and ventilation index (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, PaO_2/FiO_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 [14]. Moreover, the daily vital signs, urine output, laboratory data, ventilator settings, vasopressor dosage were extracted.

2.5 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. 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.

3. Results

Detailed demographic information and diagnosis of patients in surfactant group and control group are listed in table 1. Also, table 1 summarizes the demographic characteristics of the 44 neonates. There was no significant difference in demographics between the surfactant group and the control group. There was no significant difference in OI and PaO_2/FiO_2 between the two groups (table 1).

Results of the two groups are shown in table 2. The primary end point was the duration of mechanical ventilation. Infants receiving surfactant had significantly shorter ventilation time and PICU time (table 2). The acute effects of surfactant therapy would be evaluated 24 hours after the treatment. Vital signs were monitored continuously and recorded for 60 minutes after the intervention. With the administration of surfactant, OI gradually decreased in every patient. All variables 24 hours before and after surfactant therapy are given in table 2 and figure 2-5. The mean value of OI (figure 2) and VI (figure 3) decreased from 13.9 to 5.6 and 42.0 to 22.4 at the 6 hours respectively ($p<0.05$) and sustained until 24 hours ($p<0.05$). Within 2 hours, the mean arterial PaO_2 (figure 4) was raised to 88.1 mmHg from 65.5 mmHg ($p<0.01$), which could be maintained till 24 hours, while the FiO_2 was reduced from 0.74 to 0.52 within 24 hours ($p<0.01$) (figure 5).

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

Exogenous surfactant treatment could significantly reduce the incidence of complications. All patients were extubated within 15 days; the average total time on ventilator in surfactant group was 133.6 hours, control group 218.4 hours. The cumulative percentages of extubated patients in each group were shown in figure 6.

The 22 patients in surfactant group were assigned to less than 3 months subgroup (10 infants) and above 3 months subgroup (12 infants). The total on-pump time and aortic clamping time of the two subgroups were similar (table 3). The surfactant showed better efficacy in OI, VI and P/F ratio of the less than 3 months subgroup (table 3). There was no statistical difference in ventilator time and PICU time between the two subgroups.

4. Discussion

In this study, with the treatment of low dose surfactant, rapid improvement in oxygenation, and significant decrease in duration of ventilator time, PICU time and complications incidence were observed. This is the first study about low-dose surfactant therapy in infants after cardiac surgery with CPB. Infants younger than three months benefit more from oxygenation improvement than the infants above 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 [15]. Inflammatory response induced by CPB [16] could be exacerbated by accumulation of cytokines. Meanwhile mechanical ventilation itself could worsen ARDS by damaging the alveolocapillary barrier in the lungs [17]. The reduced compliance and a ventilation-perfusion mismatch hinted that the surfactant system was damaged [18, 19]. Exogenous surfactant may contribute in preventing the surfactant system from developing extreme disturbance.

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. As a result, both the cost and the risk of airway obstruction caused by excessive volume of drugs were greatly reduced. The treatment was well tolerated as well. No side effects and complications were observed during surfactant treatment.

Oxygenation improvement was reported in previous study [12, 20]. Unlike previous studies, a decrease in the duration of ventilation and total time of PICU could also be observed. Moreover, patients had fewer complications, such as pneumothorax, rate of re tracheal intubation, hemorrhage, and the use of more advanced life support devices (HFOV, peritoneal dialysis, CPAP) were reduced as well.

More importantly, 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 [21]. 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 ARDS after cardiac surgery, a multi-center randomized controlled trial is necessary.

ARDS continues to be associated with prolonged mechanical ventilation in CHD infants who 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.

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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.

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Not applicable

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Tables

Table 1. Study population and base line characteristics.

Characteristic	Surfactant n=22	Control n=22	*P* Value
Age (months)	5.5(±1.6)	5.3(±1.8)	0.698
Weight (kg)	6.2(±1.2)	6.3(±1.5)	0.808
Sex (male/female)	13/9	12/10	0.585
RACHS-1 II	7(31.8)	7(31.8)	-
RACHS-1 III	8(36.3)	8(36.3)	-
RACHS-1 IV	7(31.8)	7(31.8)	-
Total on-pump time (min)	146.8(±44.5)	138.4(±35.8)	0.382
Aortic clamping time (min)	57.3(±18.1)	52.3(±15.2)	0.326
Time of inclusion (days after operation)	3.0(±1.6)	2.9(±1.4)	0.826
OI	13.9(±3.8)	13.2(±3.2)	0.512
PaO_2/FiO_2	88.5(±15.4)	90.3(±17.5)	0.719
SOFA score	11.5(±3.1)	11.2(±2.8)	0.738
Use of neuromuscular blockers	12(54.5)	14(63.6)	0.106
renal replacement therapy	3(13.6)	3(13.6)	-
Vasopressor use	22(100)	22(100)	-
Body temperature (℃)	37.2(±0.4)	36.9(±0.5)	0.053
Mean arterial pressure	44.6(±18.4)	47.2(±15.6)	0.616
White cell count (10^9/L)	13.4(±4.2)	12.1(±3.8)	0.288
Procalcitonin (ng/L)	13.5(±7.2)	9.2(±6.7)	0.047
C-reactive protein(mg/L)	148.6(±53.4)	125.2(±40.7)	0.110
Lactate (mmol/L)	1.1(±0.4)	0.8(±0.3)	0.013
Creatinine (umol/L)	84.8(±52.2)	115.1(±60.5)	0.083
Clinical pneumonia	10(45.5)	12(54.5)	0.823
Proved pneumonia	7(31.8)	9(40.9)	0.234
Viral, non-RSV	2(9)	3(13.6)	0.001
RSV	1(4.5)	2(9)	0.000
Bacterial	3(13.6)	4(18)	0.002

Surfactant: patients who had ARDS after cardiac surgery received standard treatment plus exogenous surfactant.

Abbreviations: RACHS-1, risk adjustment congenital heart surgery-1. The data are presented as number (%), mean ± standard deviation.

Table 2 Clinical Outcomes (in 30 days)

Characteristic	Surfactant n=22	Control n=22	*P* Value
Alive/death (n/n)	22/0	22/0	-
Total time on ventilator (h)	133.6±27.2	218.4±28.7	0.000
Total time in PICU (day)	10.7±5.1	17.5±6.8	0.001
Complication			
Reasons of complication: CPAP	3(13.6)	8(36.3)	0.015
Reasons of complication: pneumothorax	2(9)	5(22.7)	0.001
Reasons of complication: PD	1(4.5)	2(9)	0.000
Reasons of complication: HFOV	0(0)	1(4.5)	0.000
Reasons of complication: re tracheal intubation	1(4.5)	2(9)	0.000
Reasons of complication: hemorrhage, digestive tract	0(0)	1(4.5)	0.000

Values are presented as number (%), mean ± standard deviation. Surfactant: patients who had ARDS after cardiac surgery received standard treatment plus exogenous surfactant. Abbreviations: CPAP, treatment with continuous positive airway pressure; PD, treatment with peritoneal dialysis; HFOV, treatment with high frequency oscillatory ventilator.

Table 3. Comparison of surfactant group infants in different age groups

Characteristic	≤3 months subgroup n=10	>3 months subgroup n=12	*P* Value
Age (months)	2.2±0.7	7.0±2.1	0.000
Weight (kg)	5.3±1.2	7.3±2.2	0.018
Sex (male/female)	6/4	7/5	0.671
RACHS-1 II	3	4	0.228
RACHS-1 III	4	4	0.387
RACHS-1 IV	3	4	0.228
Total on-pump time (min)	155.2±43.6	146.9±46.7	0.673
Aortic clamping time (min)	52.0±19.4	49.6±20.6	0.782
ratio of PaO_2/FiO_2, before	76.8±16.6	98.2±18.9	0.011
ratio of PaO_2/FiO_2, 24h after	233.8±50.3	261.2±47.8	0.205
oxygenation index, before	16.3±3.1	11.9±4.0	0.010
oxygenation index, 24h after	3.7±0.7	2.9±1.3	0.096
Ventilatory index, before	49.2±7.9	39.6±6.3	0.004
Ventilatory index, 24h after	21.2±4.2	19.4±3.2	0.267
Time of inclusion, (days after operation)	2.4±0.6	3.3±1.1	0.031
complication	3	3	0.148
Total time on ventilator (h)	140.2±32.8	123.6±47.5	0.361
Total time in PICU (day)	12.8±4.2	10.7±4.0	0.244

Values are presented as number (%), mean ± standard deviation.

Figures

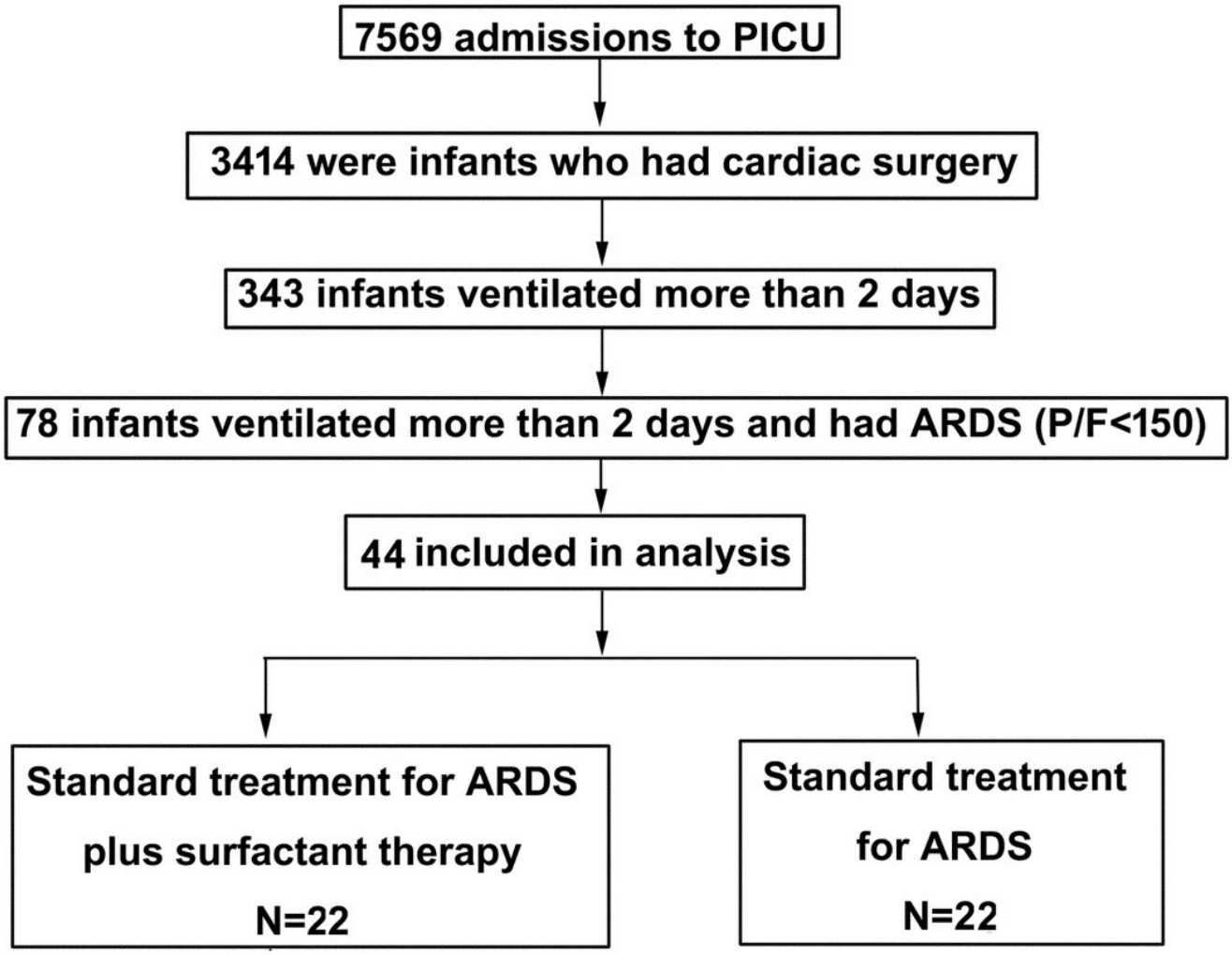

Figure 1

Study diagram. PICU= pediatric cardiac surgical intensive care unit. ARDS=acute respiratory distress syndrome. P/F=PaO2/FiO2= the ratio of arterial oxygen concentration to the fraction of inspired oxygen.

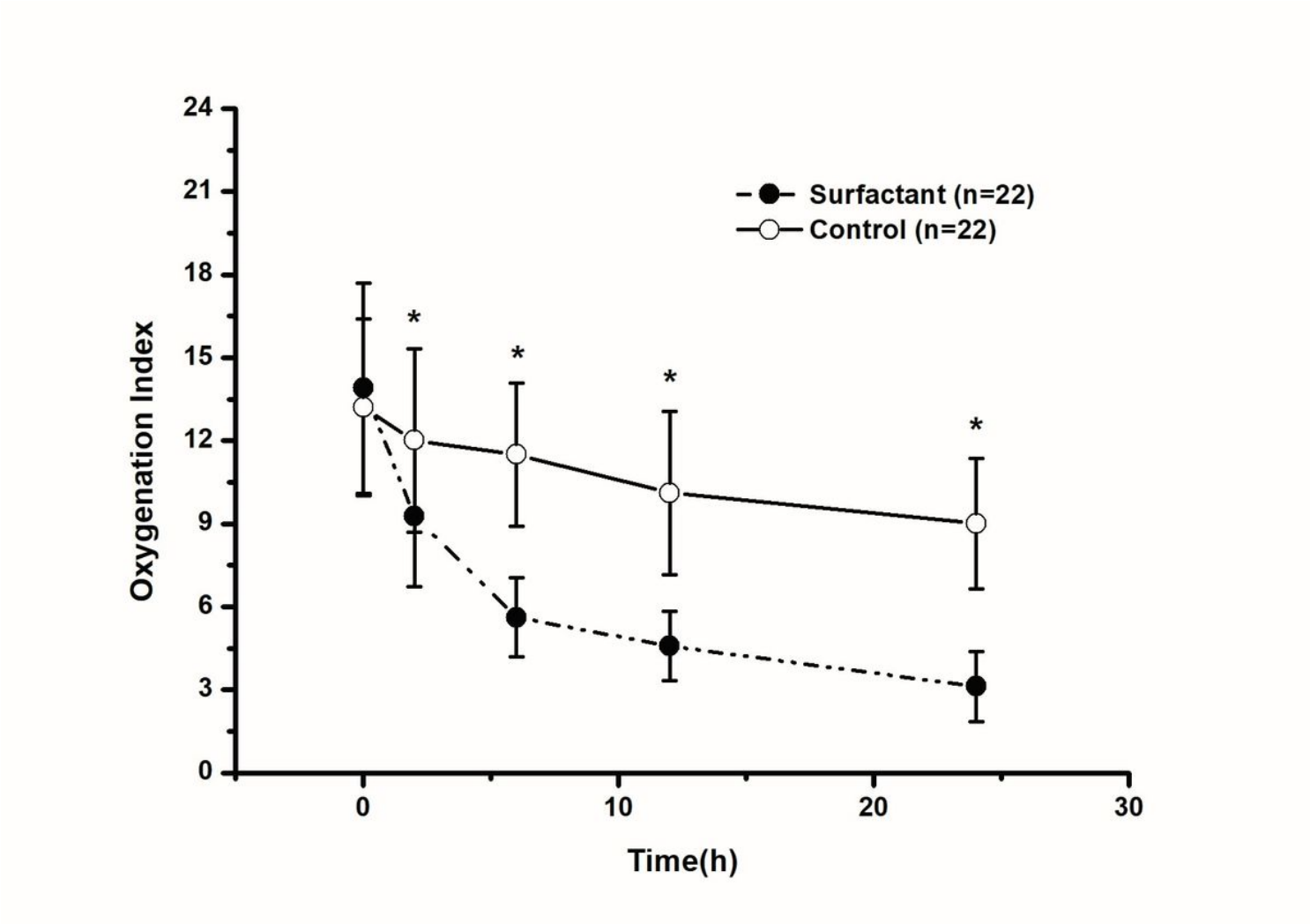

Figure 2

Change of Oxygenation Index (OI) before and after surfactant treatment compared with control. * P< 0.01 vs OI the same time point.

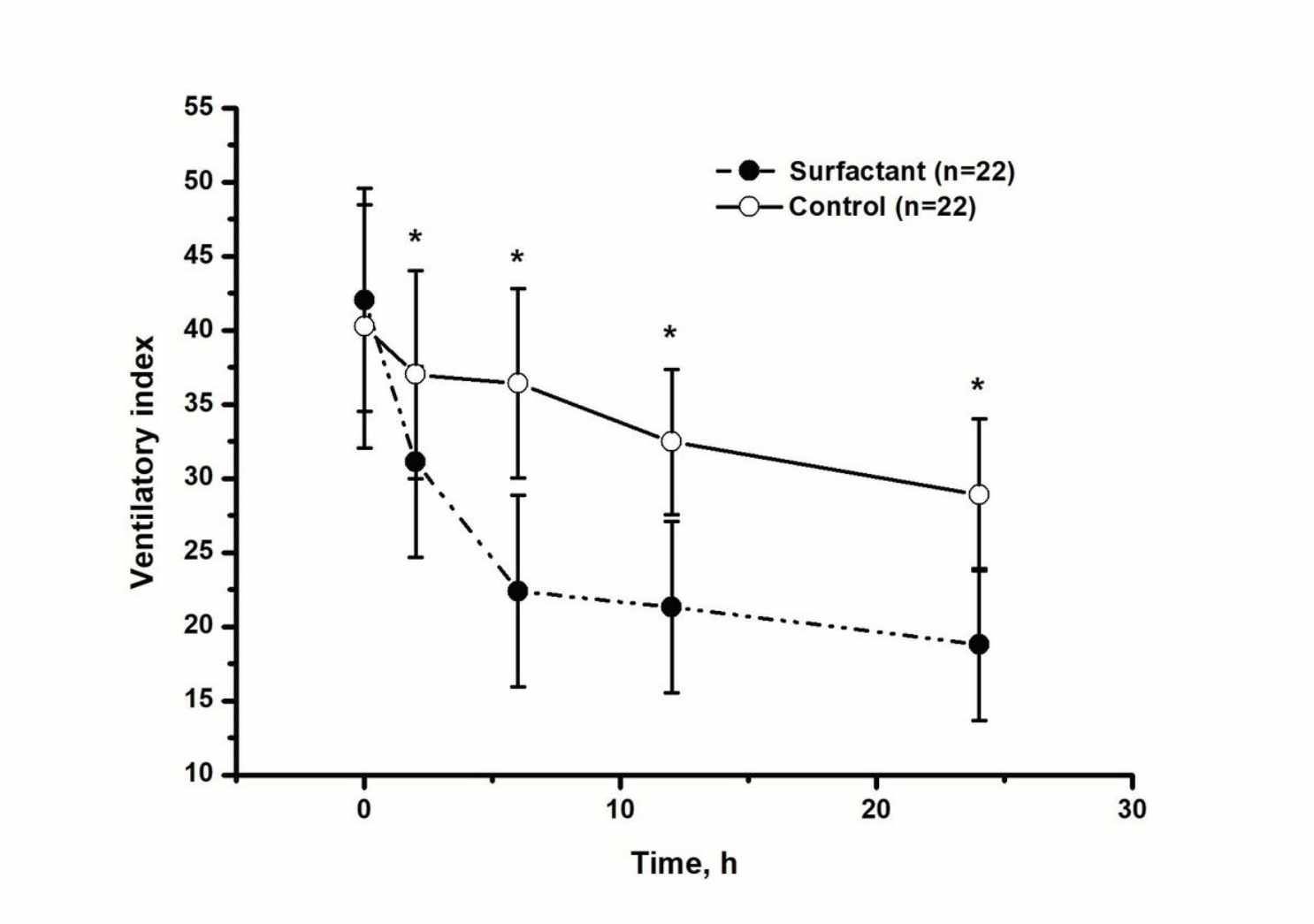

Figure 3

Change of Ventilatory Index (VI) before and after surfactant treatment compared with control. * P< 0.01 vs VI the same time point.

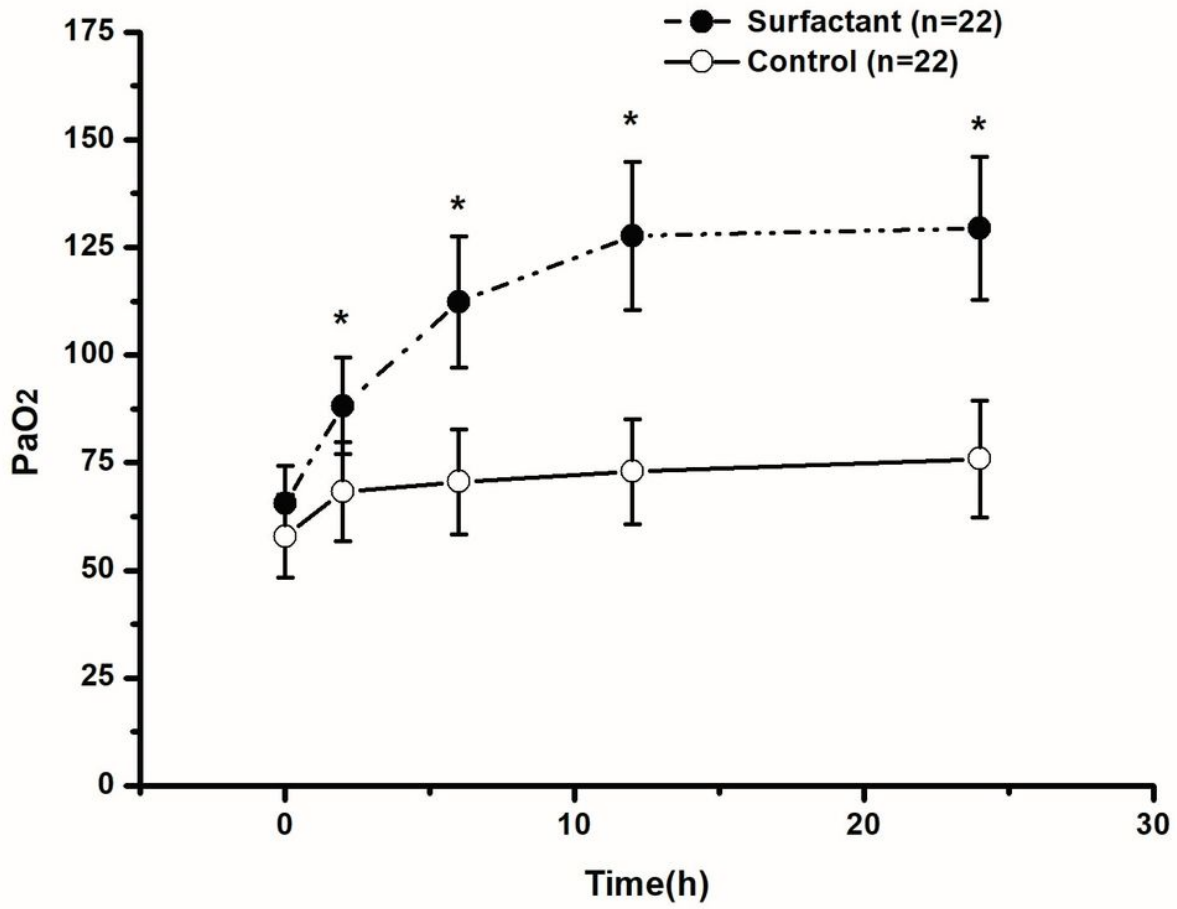

Figure 4

Change of PaO2 before and after surfactant treatment compared with placebo. PaO2 = arterial partial pressure of oxygen. * P< 0.01 vs PaO2 the same time point.

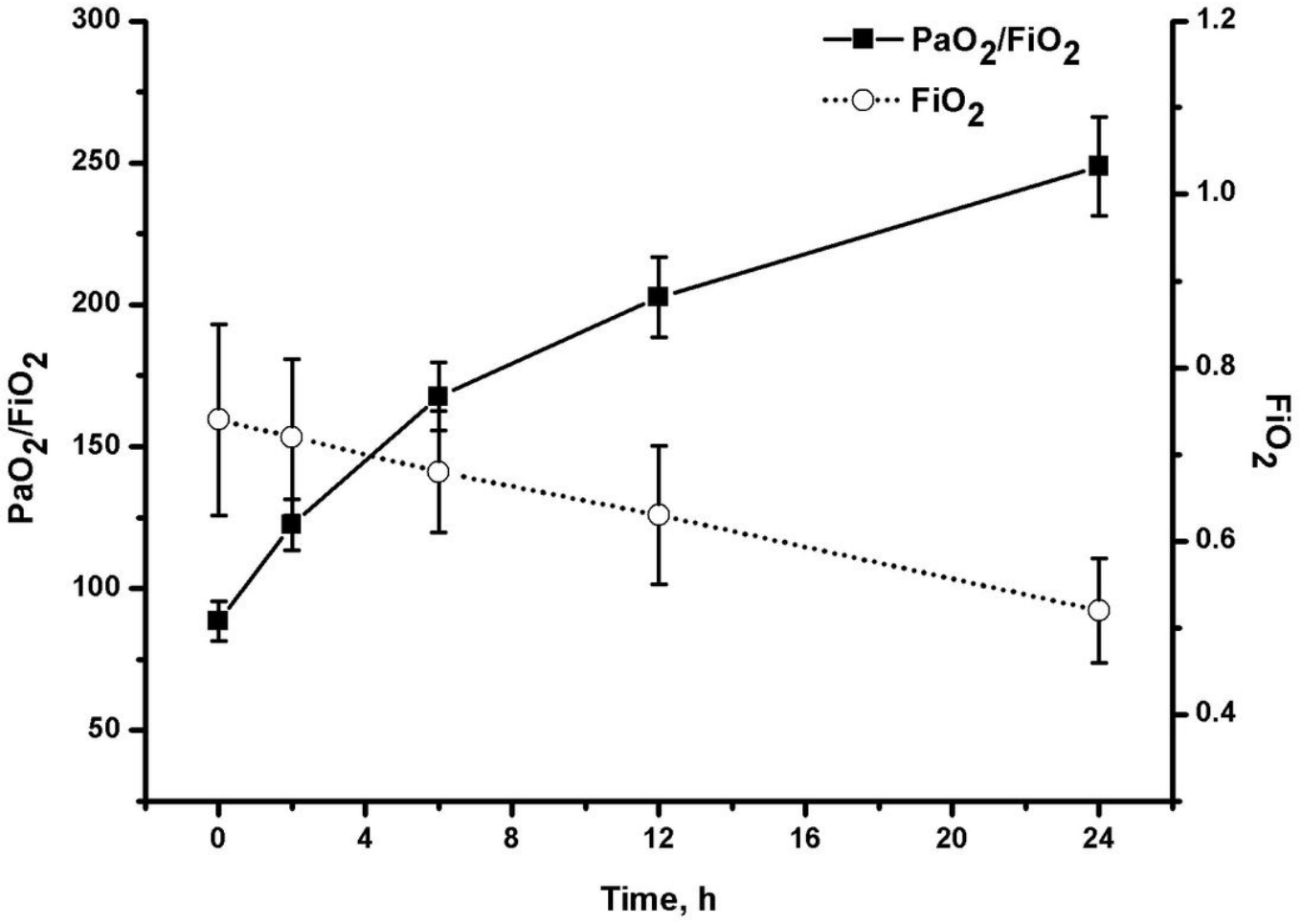

Figure 5

Changes of FiO2 and PaO2/FiO2 after surfactant treatment from 0 to 24 hours in surfactant group. FiO2 = fraction of inspired oxygen, PaO2 = arterial partial pressure of oxygen.

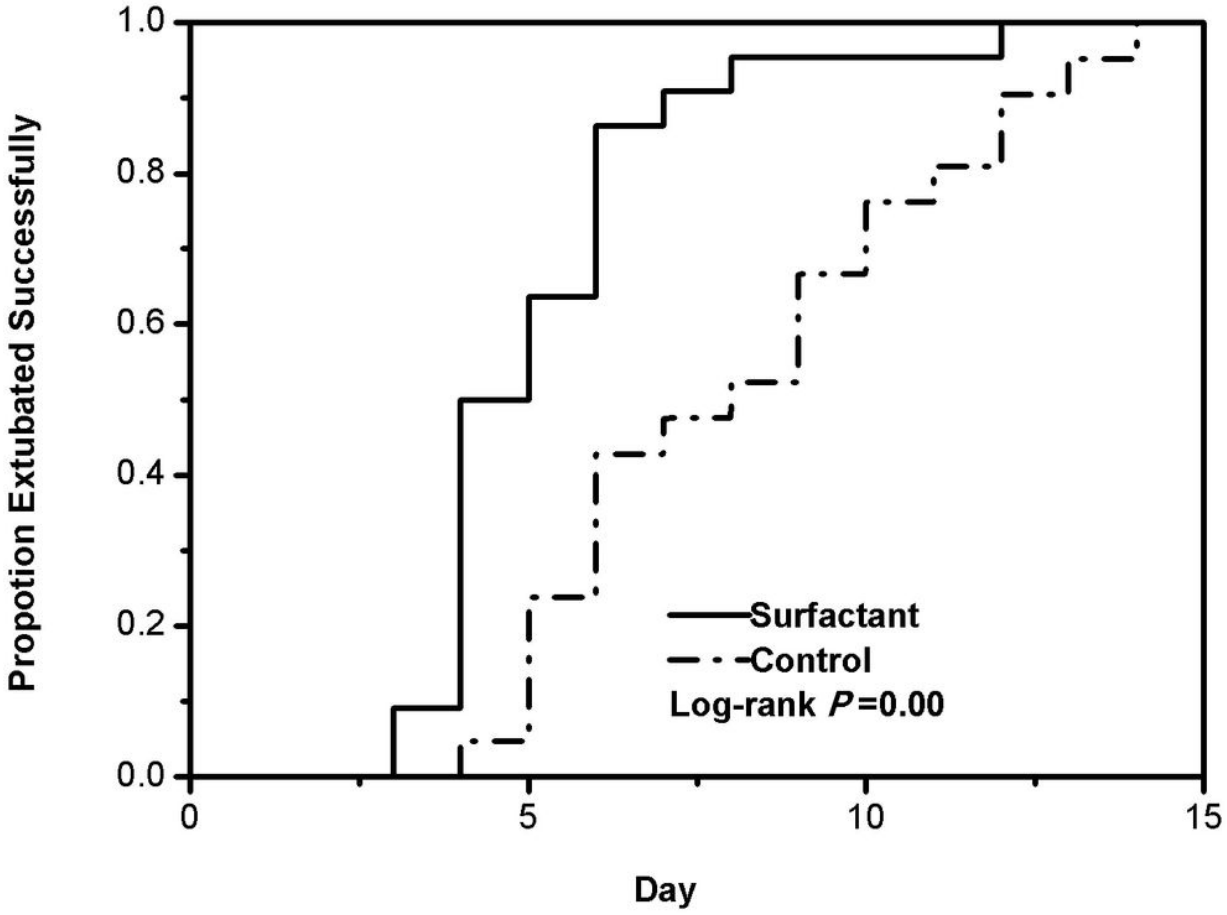

Figure 6

Proportion of surfactant compared with control patients successfully extubated after study entry (22 patients in surfactant group and 22 in control group).