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Surfactant Therapy for Patients with ARDS After Cardiac Surgery

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This multicenter study investigated the possibility of reducing mortality rate by administering natural lung surfactant additional to standard therapy to treat patients after cardiac surgery who developed an acute respiratory failure (ARDS/ALI).

A total of 78 patients (1998–2002) diagnosed with ALI or ARDS were enrolled in the study; patients were considered for study entry only if they developed ALI/ARDS within 72h after cardiac surgery. A total of 36 patients (2000–2002) received Surfactant-BL via bronchoscope at a dose of 3 mg/kg twice a day, and 42 patients (1998–2000) served as the historical control.

Within 24h after the first Surfactant-BL administration the PaO_2/FiO_2 ratio increased from (mean ± SEM) 129.7 ± 9.9 mm Hg to 187.6 ± 17.6 mm Hg ($p < 0.01$), FiO_2 decreased from (mean ± SEM) 0.71 ± 0.03 to 0.56 ± 0.03 ($p < 0.01$), and 69.4% of the patients treated with surfactant were weaned from the ventilator compared with 50% of the control group during a 28-day period. The mortality rate among patients treated with Surfactant-BL was 30.6% compared with 50% in the control group.

In conclusion, early administration of Surfactant-BL leads to the reduction of mortality in cardiac patients who develop postoperatively an ALI or ARDS.

Keywords ALI, ARDS, surfactant, post-bypass lung injury, open heart operation

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Introduction

The pathogenesis of acute lung injury of varying etiology is based on a systemic inflammatory reaction. This systemic inflammatory reaction leads to an increase in capillary endothelial and/or alveolar epithelial permeability, leak of leucocytes and plasma proteins into the interstitial and alveolar space, and an increase in pulmonary vascular resistance with reduced pulmonary perfusion. These processes cause ventilation/perfusion mismatch and extensive intrapulmonary shunting, manifesting as a severe disturbance of gas exchange. Leak of plasma proteins into the alveolar space represents an early event in the pathogenesis of lung injury and is related to the severity of the disease. Protein leak contributes substantially to inhibition of the pulmonary surfactant system, resulting in an increase in surface tension at the air-liquid interface and a corresponding decrease in lung compliance.

In 1967 Ashbaugh et al. (1967) described 12 patients who suffered from severe lung injury of non-cardiogenic nature and proposed the term "adult respiratory distress syndrome" (ARDS). In 1994 the American-European Consensus Conference (AECC) provided definitions and introduced strict diagnostic criteria for this condition (Bernard et al., 1994).

Evidence of a deficit of surfactant in ALI and ARDS (Gunther et al., 1996; Lachmann 1987), results from various models of ARDS (Lachmann 1987; Nieman et al., 1996) and the efficacy of exogenous surfactant therapy in the treatment of infant RDS, led to clinical trials of exogenous surfactant in ARDS and ALI. However, results on the feasibility and efficacy of the treatment of ALI and ARDS with different surfactant preparations were conflicting (Anzueto, 1996; Bautin et al., 2002; Gregory et al., 1997; Lachmann, 1987; Lewis et al., 1997; Osovskikh et al., 2002, 2003). For example, the synthetic Exosurf did not reduce mortality in sepsis-induced ARDS (Anzueto, 1996), whereas application of natural surfactants in the majority of cases led to improved gas exchange and an improved survival rate (Gregory et al., 2002; Lachmann, 1987; Lewis et al., 1997). Three randomized phase II clinical trials have demonstrated a tendency to a reduced mortality rate between patients treated with natural surfactant and their control group (Gregory et al., 1997; Seeger et al., 2002, Spragg, 2004).

Although the incidence of ALI and ARDS as a complication after open heart surgery is not high (ranging from 0.5 to 1.3% in different institutions), the mortality rate can be as high as 53-91%, respectively (Asimakopoulos et al., 1999; Christensen et al., 1996; Messent et al., 1992). Few data are available on the efficacy of surfactant therapy in patients developing ARDS after cardiac surgery (Satoh et al., 1998; Hermon et al., 2002). In 19 children with ARDS (6 of them after open heart surgery) who received surfactant administration at a dose of 50-100 mg/kg, Hermon et al. (2002) noted that there was no improvement in gas exchange, with the mortality rate of 50%. The results of another study (Satoh et al., 1998) investigating the effect of the administration of 30 mg/kg Surfactant TA in 11 patients (6 patients randomized to the therapeutic and 5 patients to the control group) with ARDS after resection of aneurism of thoracic aorta also showed significant improvement in oxygenation, but no data on the mortality rate were presented.

The present study aims to investigate the effect of exogenous surfactant on mortality in patients who developed ALI or ARDS after open heart surgery.

Methods and Materials

The Ethical Committee of the hospitals (Cardiovascular-surgery Clinic of the Military Medical Academy, Saint-Petersburg, Russia; Department of Anesthesiology and Resuscitation of the Institute of Transplantology and Artificial Organs, Ministry of Health, Moscow, Russia) approved the study protocol, and in all cases informed consent was

received from the patient's relative(s). A total of 78 patients were included into result analysis; all had undergone open heart surgery using cardiopulmonary bypass.

The treatment group (Group 1) comprised 36 patients (7 females, 29 males) aged 18 to 70 years who were hospitalized in 2000–2002. The inclusion criterion was the development of ARDS during the first 72h after open heart surgery, and the diagnosis of ARDS was based on the criteria defined by the AECC. In addition, the severity of lung injury had to exceed 2.5 points according to J. Murray's scale (Murray et al., 1988). Of the 36 patients in Group 1, 25 underwent coronary artery bypass grafting (CABG); heart valve replacement was performed in 7 cases of rheumatic heart disease and in 4 cases of septic endocarditis. ARDS in this group developed on average 43.9 ± 5.8 hours after operation. All patients were mechanically ventilated (Servo Ventilator 300 and Servo Ventilator 900) in a volume-controlled (28 patients) or a pressure-controlled (8 patients) mode; inversed ratio ventilation was not used. Basic therapy was aimed at achieving adequate oxygen delivery. The hemoglobin level was kept above 10 gm/dL. In cases of heart failure inotropic drugs were given. In all patients adequate fluid balance was kept under pressure monitoring in the pulmonary artery. If tracheobronchitis or pneumonia developed, antibiotics were prescribed according to the cultures of the bronchial lavage. Table 1 presents baseline data on blood gases and ventilatory parameters for patients in Group 1.

The control group (Group 2) comprised 42 patients (4 females, 38 males) hospitalized in the period 1996 to 1998 who developed ARDS after open heart surgery. These patients were retrospectively assessed using their medical records, X-ray images, and pathology studies. The inclusion and exclusion criteria for Group 2 were identical to those applied in Group 1. Because ARDS in Group 2 was treated with conventional therapy only (no surfactant was used), this group was considered to be a historical control group. Of the 42 patients in Group 2, 29 underwent CABG, heart valve replacement was performed in 10 cases of rheumatic heart disease and in 3 cases of septic endocarditis. ARDS was diagnosed on average 48.2 ± 12.7 hours after surgery. All patients in this group were mechanically ventilated (Servo Ventilator 900) in a volume-controlled mode. The basic therapy was the same as given to Group 1 patients. Table 1 presents baseline data on blood gases and ventilatory parameters for patients in Group 2. There were no significant differences in these parameters between the two groups.

The study was performed with Surfactant-BL (Bautin et al., 2002; Osovskikh et al., 2002, 2003; Rosenberg et al.,), a natural surfactant, obtained by the extraction of bovine minced lung

Table 1
Characteristics of the study population (n = 78) at baseline

Parameter	Patients treated with surfactant-BL (n = 36)	Historical controls (n = 42)
Age, years	57.8 ± 3.4	55.9 ± 2.5
PaO_2, mm Hg	80.3 ± 2.3	85.9 ± 5.6
PaO_2/FiO_2 ratio, mm Hg	129.7 ± 9.9	145.6 ± 9.7
Vt, ml/kg	9.7 ± 0.3	10.2 ± 0.9
PEEP, cm H_2O	7.0 ± 1.3	6.7 ± 0.9
PIP, cm H_2O	29.6 ± 3.7	33.1 ± 2.9
FiO_2	0.7 ± 0.03	0.62 ± 0.03

The data are presented as mean ± SEM. PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; Vt: tidal volume; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure.

with organic solvents, which contains phospholipids, neutral lipids, and the surfactant-associated proteins SP-B and SP-C (Biosurf, Ltd., St. Petersburg, Russia); Surfactant-BL was approved for clinical use in newborns with RDS in Russia in 2000, and for adults with ARDS in 2003). The results of preclinical trials have been published earlier (Rosenberg et al, 1998).

In the present study, the first administration of Surfactant-BL was within 24h of the start of ARDS (oxygenation index below 200 mm Hg). Surfactant-BL was bronchoscopically delivered in equal portions into the right and left main bronchi at a dose of 3 mg/kg in 40 mL of physiological solution. Further administrations were carried out every 12h so that the daily dose was 6 mg/kg. The criteria for ceasing Surfactant-BL administration were as follows: increase in oxygenation index to over 300 mm Hg (transfer to CMV with FiO_2 less than 45%), or an absence of further improvement in oxygenation after two administrations of Surfactant-BL. The average total dose was 615.7 ± 71.7 mg/body weight or 8.0 ± 0.2 mg/kg. The duration of therapy ranged from 24 to 72h (43.1 ± 5.0h). Surfactant-BL was administered twice in 20 patients, three times in 9 patients, and four times in 2 patients. Five patients experienced a significant and steady improvement in gas exchange after a single application of Surfactant-BL.

In all patients blood gases, oxygenation index (PaO_2/FiO_2 ratio) and alveolar/arterial oxygen difference ($D(A\text{-}a)O_2$) were assessed. Respiratory parameters were monitored with a Servo Ventilator 900 and a Servo Ventilator 300. Hemodynamic data were recorded by means of Swan-Ganz catheters. The length of mechanical ventilation, weaning success, and mortality were registered for all the patients.

It should be mentioned that all the patients who developed ARDS after cardiopulmonary bypass and met an inclusion criterion within the period of investigation were included into the study. ARDS rate was 5.7% of all the patients after cardiac surgery.

Statistical analysis was performed by first testing the normal distribution (Cholmogorov-Smirnov-test), followed by evaluation of differences using Student's t-tests.

Results

Gas exchange and ventilatory/respiratory data 12h after a decrease in the oxygenation index to below 200 mm Hg were considered as baseline data for the control patients in Group 2. The baseline oxygenation index was 145 ± 9.7 mm Hg, $D(A\text{-}a)O_2$ was 318.6 ± 25.4 mm Hg. In this group conventional therapy did not lead to a steady improvement in gas exchange parameters during the first two days (Table 2). A significant increase of the oxygenation index and a decrease in alveolar/ arterial oxygen difference were registered only after the (first) 98h.

In contrast, patients treated with Surfactant-BL showed a marked improvement in oxygenation 24h after the start of Surfactant-BL therapy. The oxygenation index increased from 129.7 ± 9.9 mm Hg to 187.6 ± 17.6 mm Hg ($p < 0.01$) (Table 3). The improvement in gas exchange allowed a concomitant decrease in respiratory support. The inspired oxygen concentration decreased from 0.71 ± 0.03 to 0.56 ± 0.03 ($p < 0.01$) 24h after the first Surfactant-BL administration. A steady decrease in the level of peak pressure (PIP) was registered 36h after the start of Surfactant-BL therapy.

In Group 1, 29 patients (80.6%) had improved gas exchange that allowed reducing FiO_2 to below 45% whereas, in spite of surfactant therapy, gas exchange deteriorated in 7 patients (19.4%). In Group 2, 23 of the control patients (54.8%) had improved gas exchange parameters after conventional treatment, whereas hypoxemia (one of the main causes of mortality) progressed in 19 patients. Of the patients who responded to Surfactant-BL therapy a safe level of FiO_2 (0.45) was achieved after 65.5 ± 10.2h, whereas patients of

Table 2
Data on gas exchange parameters and characteristics of respiratory support in the control group (n = 42)

Parameter	Initially	After 12h	After 24h	After 36h	After 48h
PaO_2, mm Hg	85.9 ± 5.6	88.2 ± 7.4	89.6 ± 5.1	94.6 ± 7.8	98.2 ± 5.6
PaO_2/FiO_2 ratio, mm Hg	145.6 ± 9.7	147.3 ± 12.4	149.4 ± 11.5	158.5 ± 12.4	157.8 ± 16.2
D (A-a)O_2, mm Hg	318.6 ± 25.4	318.4 ± 31.1	315.2 ± 25.6	310.5 ± 37.0	301.1 ± 36.2
FiO_2	0.62 ± 0.03	0.62 ± 0.05	0.61 ± 0.07	0.60 ± 0.05	0.60 ± 0.05
PIP, cm H_2O	33.1 ± 2.9	32.9 ± 2.5	32.5 ± 2.2	31.9 ± 2.4	31.8 ± 2.9

The data are presented as mean ± SEM. PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; D (A-a)O_2: alveolar-arterial difference for oxygen; PIP: peak inspiratory pressure.

Table 3
Data on gas exchange parameters and characteristics of respiratory support in the surfactant treated group (n = 36)

		Period of time after the first administration of surfactant-BL (h)			
Parameter	Initially	12	24	36	48
PaO_2, mm Hg	80.3 ± 2.3	85.7 ± 5.3	93.5 ± 3.2**	96.4 ± 5.4**	104.2 ± 4.9**
PaO_2/FiO_2. ratio, mm Hg	129.7 ± 9.9	135.5 ± 15.4	187.6 ± 17.6**	194.5 ± 19.3**	214.3 ± 20.1**
D(A-a)O_2, mm Hg	380.3 ± 28.5	351.8 ± 39.9	301.6 ± 24.2*	269.4 ± 25.7**	231.3 ± 21.3**
FiO_2	0.71 ± 0.03	0.65 ± 0.02	0.56 ± 0.03**	0.53 ± 0.07**	0.49 ± 0.06**
PIP, cm H_2O.	29.6 ± 3.7	25.5 ± 2.6	21.2 ± 2.1	20.3 ± 2.3*	20.1 ± 1.2*

The data are presented as mean ± SEM. PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; D (A-a)O_2: alveolar-arterial difference for oxygen; PIP: peak inspiratory pressure. *$p < 0.05$; **$p < 0.01$. Compared with baseline data.

the control group reached the same level after 98.4 ± 11.5h ($p < 0.05$). In the treatment group 25 patients (69.4%) were weaned from mechanical ventilation compared to only 21 patients (50%) in the control group. We found out a trend for a reduction in the respiratory support period in patients treated with Surfactant-BL; this time was 142.3 ± 21.9h in Group 1 and 227.5 ± 28.3h in Group 2 ($p < 0.05$).

In the treatment group 11 patients (30.6%) died; in 6 cases death was due to respiratory insufficiency, while 5 patients died from multiorgan failure. In the control group 21 patients (50%) died; in 19 patients death was due to deterioration of gas exchange, and 2 patients died from multiorgan failure.

Surfactant administration did not cause any allergic reactions and adverse events or side-effects except the following: 12 (33%) patients of the treated group had short (1–2h)

decrease in oxygenation of not more than 10% of baseline after endobroncheal surfactant administration. We think that it occurred because of the procedure of bronchoscopy.

Discussion

This study investigated the effect of exogenous surfactant on gas exchange and mortality in addition to standard therapy in patients who developed ARDS/ALI after cardiac surgery. Compared with the control group, patients receiving Surfactant-BL showed faster normalization of gas exchange parameters. In the treated group 69.4% of patients were switched to spontaneous breathing compared with 50% in the control group. Correspondingly, mortality rate was 30.6% in the patients treated with Surfactant-BL compared with 50% in the control group.

Our good results may be due to the following factors. First, the surfactant preparation itself is an important determinant (Bautin et al., 2002; Rosenberg et al., 2001; Rosenberg et al., 1998; Taeusch et al., 2002). Natural surfactant preparations with a composition close to that of the surfactant in situ are more efficient in animal models to improve gas exchange and in clinical practice (Bautin et al., 2002; Rosenberg et al., 2001). The biophysical and biochemical characteristics of Surfactant-BL are very similar to natural lung surfactant in situ (Rosenberg et al., 1998). Second, an early start of surfactant therapy may be important for the outcome of ARDS/ALI patients. We believe we are the first to show that one of the most important factors for efficient treatment is to start early with surfactant therapy (Bautin et al., 2002; Rosenberg et al., 2001); we demonstrated that early surfactant administration (i.e., within the first 24h of ARDS development) leads to a much better outcome compared with later administration, even during the second 24h (Bautin et al., 2002; Rosenberg et al., 2001). That is why in the present study the first surfactant administration was given within 24h of the decrease of the oxygenation index below 200 mm Hg.

It is well known that initiating events that lead to ARDS and ALI are widespread and diverse (Gattinoni et al., 1998), including aspiration, pneumonia, contusion, smoke inhalation, sepsis, trauma, massive transfusion, burns, etc. Often, patients with ARDS of different etiology are allocated to the same group, and the subsequent analyses and results of the trials pay no further attention to the nature of the ARDS. This means, for example, that patients with ARDS following sepsis (indirect ARDS) or aspiration of gastric content (direct ARDS) were grouped together, which can lead to incorrect interpretation of the results of clinical trials (Spragg, 2004). In spite of a similar severity of lung injury, surfactant therapy can have a different outcome depending on the etiology and development of ARDS. Earlier we showed that analysis of surfactant efficiency in homogenous groups of patients (aspiration of gastric content (Osovskikh et al., 2002), burns of respiratory tracts (Tarasenko et al., 2004) and postbypass lung injury (Bautin et al., 2002)) allowed us to demonstrate the high efficacy of surfactant to reduce mortality in patients with severe ARDS of these etiologies. The present study is another example of investigating surfactant efficacy in a homogenous group of patients. The results demonstrate that even in indirect lung injury, comparison of similar patients (in terms of the nature and severity of ARDS) allows to demonstrate the differences, not only in faster improvement of gas exchange, but also the difference in outcome between the surfactant-treated group and the control group.

We believe that the study of homogeneous groups of patients, in terms of the type of ARDS, and observing the above-mentioned conditions of treatment, can produce more promising results for further application of natural surfactants for the benefit of patients with ARDS and ALI.

Although we have not done a randomized controlled study and used the historical control group for comparison, we believe that our results are quite reliable because the treatment protocols for both groups were completely the same in terms of ARDS severity and basic therapy. The only difference between the treatment group and the historical control group was the use of surfactant for ALI/ARDS patients from the treatment group, which allows us to conclude that surfactant administration resulted in the improved outcome of surfactant treated patients.

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