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Treatment with bovine surfactant in severe acute respiratory distress syndrome in children: a randomized multicenter study

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Abstract *Objective:* To determine whether bovine surfactant given in cases of severe pediatric acute respiratory distress syndrome (ARDS) improves oxygenation. *Design:* Single-center study with 19 patients, followed by a multicenter randomized comparison of surfactant with a standardized treatment algorithm. Primary endpoint PaO_2/FIO_2 at 48 h, secondary endpoints: PaO_2/FIO_2 at 2, 4, 12, and 24 h, survival, survival without rescue, days on ventilator, subgroups analyzed by analysis of variance to identify patients who might benefit from surfactant. *Setting:* Multicenter study in 19 reference centers for ARDS. *Patients:* Children after the 44th postconceptional week and under 14 years old, admitted for at least 4 h, ventilated for 12–120 h, and without heart failure or chronic lung disease. In the multicenter study 35 patients were recruited; 20 were randomized to the surfactant group and 15 to the nonsurfactant group. Decreasing recruitment of patients led to a preliminary end of this study. *Interventions:* Administration of 100 mg/kg bovine surfactant intratracheally under continuous ventilation and PEEP, as soon as the PaO_2/FIO_2 ratio dropped to less than 100 for 2 h (in the pilot study increments of 50 mg/kg as long as the PaO_2/FIO_2 did not increase by 20%). A second equivalent dose within 48 h was permitted. *Results:* In the pilot study the PaO_2/FIO_2 increased by a mean of 100 at 48 h (n=19). A higher PaO_2/FIO_2 ratio was observed in the surfactant group 2 h after the first dose (58 from baseline vs. 9), at 48 h there was a trend towards a higher ratio (38 from baseline vs. 22). The rate of rescue therapy was significantly lower in the surfactant group. Outcome criteria were not affected by a second surfactant dose (n=11). A significant difference in PaO_2/FIO_2 in favor of surfactant at 48 h was found in the subgroup with an initial PaO_2/FIO_2 ratio higher than 65 and in patients without pneumonia. *Conclusions:* Surfactant therapy in severe ARDS improves oxygenation immediately after administration. This improvement is sustained only in the subgroup of patients without pneumonia and that with an initial PaO_2/FIO_2 ratio higher than 65

Keywords Acute respiratory distress syndrome · Surfactant · Children · Ventilation · Oxygenation · Pneumonia

Introduction

Acute respiratory distress syndrome (ARDS) is defined by radiographic diagnosis of diffuse bilateral alveolar infiltrates, the degree of hypoxemia, lung function, and histopathology. It is the final generalized inflammatory response of the lung to catastrophic events of various pulmonary and nonpulmonary origins and occurs in all age groups. The diagnostic criteria have been established by an American-European Consensus Conference [1, 2, 3]. ARDS in children is still associated with a high mortality. Mortality is correlated with the severity of the underlying disease [4, 5]; however, it is still generally accepted that the degree of hypoxemia predicts outcome [5, 6, 7, 8]. Mortality in children with a PaO_2/FIO_2 ratio lower than 100 in central Europe is still greater than 50% [5]. Another outcome criteria is the aggressiveness of ventilatory support, reflected in the peak inspiratory pressure (PIP), mean airway pressure, and ventilation index [9, 10]. The enforcement of standardized ventilation protocols and the lower incidence of both multiple trauma and sepsis in central Europe have caused a continuous decrease in severe ARDS incidence in children [11, 12, 13].

As the mortality is still high in children with profound hypoxemia and severe underlying conditions such as immunosuppression [4, 5, 8, 13], many other therapies in addition to baro- and volutrauma preventing ventilation strategies have been reported. Nevertheless, randomized controlled studies evaluating new therapeutic strategies for the treatment of severe hypoxemic ARDS as nitric oxide, high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), and surfactant treatment are lacking in the pediatric age group [14, 15, 16, 17, 18]. Exogenous surfactant improves oxygenation in neonates not only with respiratory distress syndrome but also in other conditions with secondary surfactant deficit such as meconium aspiration syndrome and congenital pneumonia, comparable with ARDS [19]. Oxygenation improved after surfactant administration in several case reports on adult ARDS patients [11, 20] and in a controlled study in moderate pediatric ARDS [10]. A retrospective and prospective survey of pediatric ARDS in all major German pediatric intensive care facilities demonstrated that the mortality and chronic illness after ARDS in patients with PaO_2/FIO_2 ratios above 150 is very rare, and that most patients with a PaO_2/FIO_2 ratio around 200 are not even ventilated [5]. For this reason the German-Austrian working group on ARDS performed a controlled, randomized study in severe, hypoxemic ARDS in children, associated with a very high mortality, and no evidence-based treatment options available.

Patients and methods

A single-center pilot study was carried out in 19 pediatric patients with ARDS and PaO_2/FIO_2 ratio lower than 100, aimed at dose finding and calculating the number of patients required. This pilot study treated patients with ARDS defined by consensus conference criteria and aged between the 44th postconceptional week and 14 years of age. They were included if their PaO_2/FIO_2 ratio was below 100 for at least 2 h. Ventilation in the pilot study was in accordance with the ventilation algorithm established by the German Working Group on Pediatric ARDS (Fig. 1). A bovine surfactant (Alveofact, Boehringer, Ingelheim, Germany) was administered in 50 mg/kg increments (intratracheal bolus under continuous ventilation and PEEP over maximally 5 min) as long as the PaO_2/FIO_2 ratio did not increase by 20% or decrease by 10%. The PaO_2/FIO_2 ratio was determined at 48 h The increase/decrease from baseline was evaluated using the Mann-Whitney *U* test. No other exclusion criteria were applicable [17, 19]. This pilot study as the following mulitcenter study were approved by the ethics review board of the principal investigators' institution (Medical University of Lübeck).

The subsequent multicenter study was an open, randomized, parallel group comparison performed at 19 German pediatric intensive care units between May 1997 and November 1999. These units were referral centers for children with severe respiratory failure. All children were randomized if they fulfilled the following criteria: ARDS Consensus Conference criteria, lung injury score [21] of at least 2, ventilation between 12 and 120 h, age between 44th postconceptional week and 14 years, admission for at least 4 h, no echocardiographically detectable left heart failure, and a PaO_2/FIO_2 ratio lower than 100. Written informed consent was obtained from the parents or legal guardians. Patients were excluded if they were under other investigational or experimental therapies: nitric oxide, high frequency ventilation with current disease, liquid ventilation, prostaglandins, steroids for therapy of ARDS, ECMO; chronic lung disease such as bronchopulmonary dysplasia or cystic fibrosis, participation in other clinical studies except treatment protocols and studies for oncological diseases. In addition, patients with severe hypoxemia, i.e., PaO_2 lower than 50 after 4 h of treatment in the referral center were excluded.

Thirty-eight patients were recruited over the 18-month period (mean age 3.9 years), but three randomized patients were not included in the study, as their PaO_2/FIO_2 ratio improved to 100 or higher before the start of treatment. All patients in the participating centers with ARDS in the specified age group who were not included as they did not fulfill all entry criteria were recorded and evaluated as "intended to treat patients" if their PaO_2/FIO_2 ratio was below 100. All patients in the participating centers were ventilated according to a ventilation algorithm (Fig. 1) [4], blood pressure was kept above the 50th percentile for age, fluid intake between 90% and 100% maintenance [22], and hemoglobin levels above 12 g/dl. As the PaO_2/FIO_2 ratio was less than 100, patients were randomized either to receive 100 mg/kg bovine surfactant (Alveofact, Boehringer-Ingelheim, Germany), administered under continuous PEEP and ventilation as a bolus over not longer than 5 min to the distal tip of the endotracheal tube (n=20), or be continuously treated based on the ventilation algorithm and concomitant therapy outlined above (n=15). In the surfactant group an additional dose of 100-mg/kg surfactant during the 48-h observation period was allowed if the PaO_2 decreased by 20% from the maximum level reached. Diagnoses, age, weight and other demographic characteristics are depicted in Table 2, including the ratio of immunosuppressed patients (after bone marrow transplant or under chemotherapy), PRISM III score, and pneumonia; there were no significant differences between the two groups in regard to these factors.

PaO_2, FIO_2, $paCO_2$, pH, peak inspiratory pressure, PEEP, ventilatory rate, tidal volume, blood pressure, heart rate, hemoglobin,

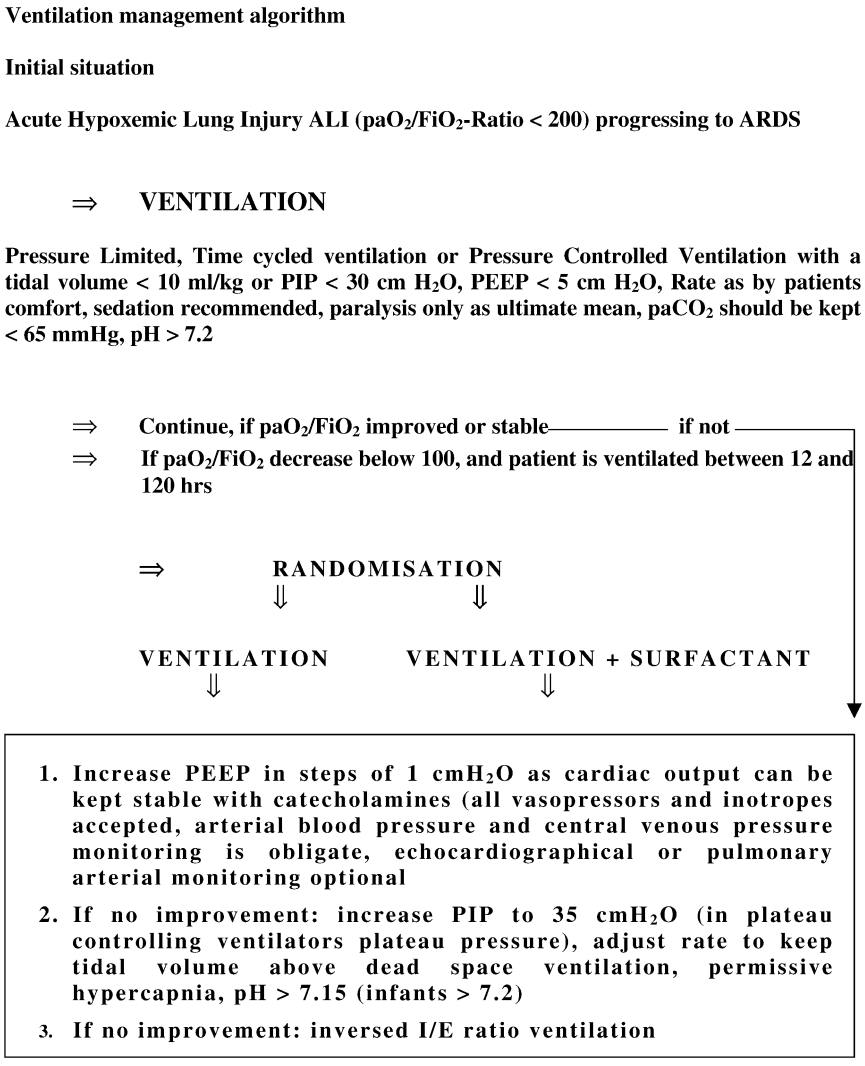

Fig. 1 Algorithm for ventilatory management in the study centers before and after randomization

Table 1 Reasons for not randomizing patients with ARDS and PaO_2/FIO_2 ratio less than 100 ("intended to treat"). The survival rates were not compared statistically because of the small number of patients in each section of the intended to treat patients; the overall survival rate was 36%

	n	Age range (months)	Nonsurvivors	
			n	%
Admission under resuscitation/death at arrival	6	8–152	6	100
On ventilator for longer than 120 h	6	3–152	5	80
Chronic lung or left heart disease	10	2.5–160	3	33
Under rescue therapy before study	11	3–156	8	72
No informed consent	6	3–145	3	50

all medications administered, fluid balance, and the derived variables (PaO_2/FIO_2, Hallman oxygenation index, ventilatory index, mean airway pressure) were recorded 2, 4, 12, 24, and 48 h after randomization. The patients were followed to day 30 or to discharge/transfer from the referral center to document outcome data: survival, rescue therapy, days on ventilator, days in the ICU, Pediatric Risk of Mortality (PRISM) III score [23], lung injury (Murray score) [21], and days in hospital.

Random allocation was performed centrally by telephone (24 h coverage). The randomization schedule was designed to achieve a 1:1 randomization at each participating center. If the PaO_2 decreased to below 50 mmHg for at least 1 h in any patient, all rescue therapies considered appropriate by the principal investigator of the center were allowed (e.g., NO, HFOV, additional surfactant, ECMO, vasodilators). Rotational therapy or prone positioning was obligatory.

Table 2 Patient characteristics in surfactant and nonsurfactant groups

	Surfactant	Controls	Overall	Comments
Randomized	22	16	38	–
Treated	20	15	35	–[a]
Age (range; years)	3.5 (0–13)	4.5 (0–12)	3.9 (0–13)	n.s.
Female	7 (35%)	7 (46.7%)	14 (40%)	–
Body weight (kg)	15.7±10.4	22.4±20.7	18.6±15.8	n.s.
Time since FIO_2 >0.5 (h)	35.2±25.5	49.8±44.5		n.s.
Time since PIP >30 cmH_2O (h)	24.9±21.8	34.1±32.9		n.s.
Causative diagnosis pneumonia	15 (68.2%)	11 (68.7%)		n.s.
Causative diagnosis sepsis	7 (31.8%)	5 (31.3%)		n.s.
Under immunosuppression	9	7		n.s.
Rescue ECMO	0	2		–[b]
Rescue NO	4	4		–[b]
Rescue HFOV	2	3		–[b]
Rescue surfactant	0	4		–[b]
Rescue vasodilators	1	1		–[b]
Nonsurvivors/mortality	8 (44%)	9 (60%)		p=0.29
Death and/or rescue	11 (56%)	12 (80%)		p=0.13
Ventilator-free (alive and without ventilator)				n.s.
0 days	12 (63.2%)	9 (64.3%)		
10–20 days	3 (15.8%)	3 (21.4%)		
>20 days	4 (21.1%)	2 (14.3%)		
PRISM III at randomization, median	11.5	11		n.s.
Lung injury score (Murray) at randomization	3.0	3.3		n.s.
PaO_2/FIO_2 at baseline	71.3±13.7	64.3±16.2		n.s.
2nd surfactant dose	11	–		

[a] Three patients improved within the 2 h between reaching a PaO_2/FIO_2 <100 and final randomization
[b] Rescue therapy after the study surfactant medication was given

The study was conducted as a multicenter, open, randomized parallel comparison. The primary variable was the change from baseline in the PaO_2/FIO_2 ratio at 48 h after the first administration of surfactant or randomization to the control group. Secondary endpoints were: peak inspiratory pressure, positive end-expiratory pressure, mean airway pressure, in- and expiration time, respiratory rate, FIO_2, PaO_2, $paCO_2$, SaO_2, pH, heart rate, and blood pressure 2, 4, 12, 24, 48, and 120 h after randomization. In addition Murray Score, PRISM III score at baseline, 48 and 120 h, clinical status at 30 days after randomization, days on ventilator, days in intensive care, days on supplemental oxygen, mortality at day 30, ventilator-free days at day 30, and the necessity of rescue therapy as ECMO, HFOV, NO, or rescue surfactant. The primary hypothesis defined was tested by the Mann-Whitney U test at an error level of $\alpha \leq 0.05$. A secondary analysis was performed to detect changes from baseline for all other time points up to 48 h by the same test procedure.

For all other variables the same procedures were performed. The number of deaths was compared between groups by means of Fisher's exact test, as were patients who received rescue therapy (each rescue therapy was summarized by frequencies). In a third analysis the combined event death and/or rescue therapy was investigated. We performed multiple regression analyses for changes in the oxygenation index at 2, 4, 12, 24, and 48 h to analyze differences between special subgroups. We used a linear model for repeated measurements. For this post hoc analysis the following subgroups were evaluated: baseline PaO_2/FIO_2 less than vs. 65 or higher, baseline PRISM III score less than vs. 12 or higher, age under 1 year vs. 2 years or older, girls vs. boys, body weight less than vs. 12 kg or higher, time since FIO_2 being higher than 0.5 at randomization shorter than 24 vs. 24 h or longer, time since PIP being higher than 30 cmH_2O shorter than 30 h or longer, pneumonia vs. no pneumonia, sepsis vs. no sepsis, and immunosuppression vs. no immunosuppression.

Results

In the pilot study the average increase in PaO_2/FIO_2 was 54 at 4 h and 103 after 48 h (p<0.01). Seven patients died despite improved oxygenation. The average dose of surfactant given was 94 mg/kg (Table 3). This led to the multicenter study dose of 100 mg/kg.

Regarding the primary variable, change in PaO_2/FIO_2 over the 48-h observation period, PaO_2/FIO_2 was significantly higher in the surfactant group 2 h after the first surfactant dose (p<0.003). Even after 48 h the surfactant group patients still showed a greater, albeit not significantly greater, increase in PaO_2/FIO_2 ratio (Fig. 2). Using the Hallman oxygenation index as oxygenation parameter produced similar results; oxygenation was significantly improved after 2 and 4 h (p<0.00222 and p<0.05). Considering secondary endpoints, mortality and mortality and/or rescue therapy was lower in the surfactant group, however not significantly so at all times during the study period. Mortality in both groups was considerably lower than that in the "intended to treat" patients (64%). Patients in the surfactant group received significantly less rescue therapy than those in the nonsurfactant group (p<0.05).

There was a reduction in mean airway pressures used in the surfactant group after 2 and 24 h (p<0.05, p<0.007; (Fig. 3, Tables 4, 5) – there was no difference

Table 3 Data of the pilot study in 19 patients, their diagnoses, age, body weight and PaO_2/FIO_2 ratio at baseline, 4 and 48 h (*RSV* respiratory syncytial virus)

Patient no.	Diagnosis	Age (months)	Weight (kg)	PaO_2/FIO_2			Outcome
				0 h	4 h	48 h[a]	
1	Meningococcemia	24	15	84	111	444	Survived
2	Pneumonia	26	10.3	31	109	160	Survived
3	Pneumonia	18	8	48	148	242	Survived
4	RSV bronchiolitis	13	8	38	115	151	Survived
5	Pertussis pneumonia	14	7.2	116	99	145	Died
6	Near drowning	38	12	43	174	240	Survived
7	Liver failure	9	4	65	96	108	Died
8	Sepsis	2	3	61	242	50	Died
9	Sepsis	7	8	32	57	–	Died
10	Pneumonia	38	9	64	53	–	Died
11	Burns	54	17	61	84	65	Died
12	RSV bronchiolitis	2	2.5	59	94	137	Died
13	Pneumonia	54	15	64	100	113	Died
14	Pneumonia	3	2.5	64	96	92	Survived
15	Near drowning	69	23	63	176	290	Survived
16	Aspiration	10	8	47	66	109	Survived
17	Aspiration	12	10	46	87	105	Survived
18	Pneumonia	3	3.2	60	128	122	Survived
19	Aspiration	6	6	63	88	160	Survived
	Mean±SD	21±20	9±5	58±19	112±46	161±97	$p<0.01$

[a] n=17

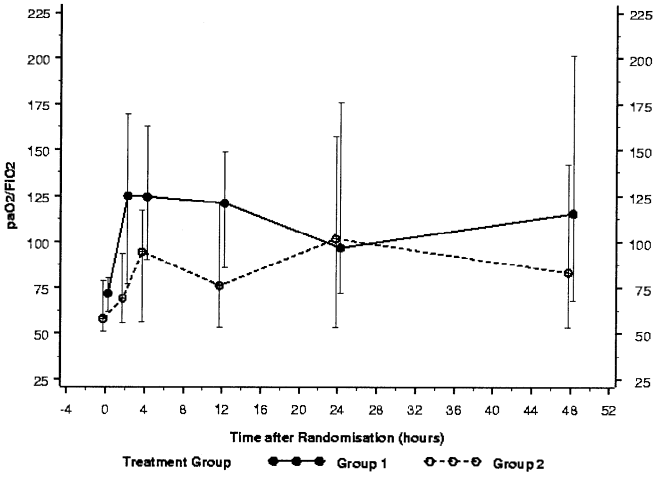

Fig. 2 Medians and interquartile ranges (25–75 percentiles) of the oxygenation index (PaO_2/FIO_2) in the 48-h observation period of the surfactant group (*group 1*) and controls (*group 2*)

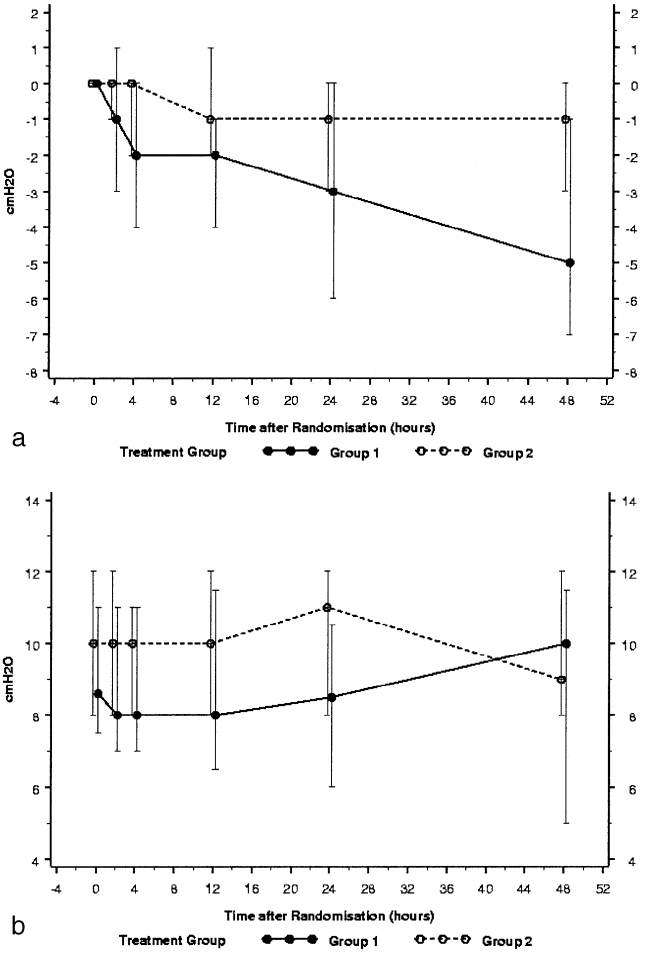

Fig. 3 Medians and interquartile ranges (25–75 percentiles) of changes of peak inspiratory pressure in cmH_2O (**a**) and positive end-expiratory pressure (**b**) over the 48-h observation period in the surfactant group (*group 1*) and controls (*group 2*)

Table 4 Physiological and ventilation variables at baseline and after 2, 4, 12, 24, and 48 h (changes from baseline): median (25th/75th percentiles) or mean ±SD (*RR* ventilatory/respiratory rate, *OI* oxygenation index, *CVP* central venous pressure)

	Surfactant						Controls					
	Baseline	2 h	4 h	12 h	24 h	48 h	Baseline	2 h	4 h	12 h	24 h	48 h
Oxygen. index PaO_2/FIO_2	71.3	+54 (16/90)	+57 (19/92)	+39 (19/72)	+24 (3/106)	+38 0/122)	64.3	+9 (0/25)*	+20 (1/50)	+20 (0/47)	+42 (0/98)	+22 (0/78)
Hallman OI		−10 (−17/−7)	−11 (−16/−7)	−12 (−15/−4)	−7 (−19/−2)	−9 (−18/−3)		−2 (−7/1)	−4 (−9/0)	−4 (−12/0)	−6 (−12/−2)	−5 (12/−2)
(cmH_2O/mmHg)												
PaO_2 (mmHg)		+14 (7/38)	+10 (0/37)	+9 (−5/22)	+5 (−1/9)	+5 (−4/25)		+4 (−2/11)*	+3 (−2/25)	+6 (−4/19)	+6 (−2/33)	+6 (−2/19)
$paCO_2$ (mmHg)		−4 (−9/5)	−4 (−7/9)	+2 (−7/14)	+7 (−1/14)	+2 (−8/13)		−3 (−12/4)	−4 (−12/8)	−5 (−12/6)	−4 (−12/2)	−1 (−10/5)
RR (1/min)		0.0 (−5/0)	−1.5 (−4.5/0)	−3 (−4/0)	−3 (−12/0)	−2.8 (−9/0.5		0 (0/0)	0 (0/0)	0 (0/3)	0 (−2/3)	0 (−1/4)
PIP (cmH_2O)		−1 (−3/1)	−2 (−4/0)	−2 (−4/−1)	−3 (−6/0)	−5 (−7/−1)		0 (−1/0)	0 (−2/0)	−1 (−2/1)	−1 (−3/0)	−1 (−3/0)
PEEP (cmH_2O)		0.0 (−0.9/0)	0.0 (−0.9/0)	0.0 (−1/0)	0.0 (−1.6/0)	−0.5 (−2/0)		0.0 (0/0)	0.0 (0/0)	0.0 (−2/1)	0.0 (−1/1)	0.0 (−1/1)
Mean airway pressure (cmH_2O)		−1 (−1.7/0)	−1 (−2.7/0.1)	−1 (−3.2/0.5)	−1.5 (−5/−0.9	−1 (−6/1.3)		0.4 (0/1.5)*	0.4 (−2/2)	0.4 (−2/2)	0.0 (−2/2)*	0.0 (−2/1.5)
Ventilatory index (RR×PIP×pCO_2/1000)		−7 (−12/−1)	−5 (−11/1)	−3 (−12/5)	−5 (−15/5)	−5 (−16/5)		−9 (−18/−1)	−10 (−22/1)	−10 (−25/5)	−10 (−24/3)	−6 (−19/6)
BP systolic (mmHg)	109±19	109±13	108±31	109±19	104±24	105±16	97±13	100±21	102±24	112±14	112±26	110±18
BP diastolic (mmHg)	56±18	61±13	55±12	60±13	58±16	57±12	51±9	52±11	51±12	60±11	58±12	56±11
CVP (mmHg)	11±5	11±5	11±5	10±5	10±4	9±5	13±6	11±5	12±5	11±6	11±5	12±7
Heart rate (1/min)	143±29	134±32	136±31	133±27	134±22	117±34	138±28	139±26	133±24	139±24	130±22	130±22
Hemoglobin (g/dl)	11.9±2.3	12.4±2.4	12.0±2.0	12.2±1.6	13.1±2.1	13.5±1.8	11.1±1.8	11.0±1.7	11.3±1.6	12.5±1.9	12.2±2.1	11.7±1.8

Fig. 4 *Z* statistic of the primary endpoint, change in PaO_2/FIO_2 ratio at 48 h between the surfactant group (*group 1*) and controls (*group 2*)

between $paCO_2$ or pH in the two groups at any time of the 48-h observation period. Tidal volumes were kept below 10 ml/kg in all cases as specified in Fig. 1. Lung injury and PRISM III scores decreased from 0 to 48 h; however, only the decrease in PRISM III reached the level of significance (p 0.05). No other significant differences in secondary outcome criteria were detected. Eleven patients in the surfactant group received the possible second dose of 100–mg/kg surfactant; no significant increase in PaO_2/FIO_2 after this second dose was observed at any time. No treatment associated adverse events were observed in the surfactant group; however, the expected risk of intermittent obstruction of the endotracheal tube with a short time deterioration in oxygenation was observed in three patients.

In a post hoc analysis of the PaO_2/FIO_2 changes from baseline between 2 and 48 h considering various patient characteristics as additional information no significant differences were found regarding Murray Score PRISM III score, age, sex, time with FIO_2 longer than 0.5, PIP higher than 30 cmH_2O, sepsis vs. no sepsis, or immunosuppression vs. no immunosuppression (Table 6). However, a significant difference in PaO_2/FIO_2 increase was found between those whose initial ratio was higher than 65 and those whose initial ratio was less and 65 and group 2 patients (p<0.028, Fig. 4); patients with the lower ratio had a 100% mortality in both groups even when rescue therapy was applied. In addition, surfactant patients without pneumonia had significantly better oxygenation after 48 h than nonsurfactant patients with pneumonia (p<0.0017, Fig. 5). In addition, a trend to efficacy of surfactant was seen in patients weighing at least 12 kg (p=0.055).

The study had to be stopped earlier than originally planned due to increasing recruitment difficulty. To demonstrate that the trial was not being stopped at a

Table 5 PRISM III and Murray score at baseline, 48, and 120 h (no significant differences)

	Surfactant			Controls		
	Baseline	48 h	120 h	Baseline	48 h	120 h
PRISM III	11.5±6.5	11.55±6.5	11.0±6.7	11.0±4.5	11.0±7.0	11.0±4.0
Murray score	3.0±0.7	2.8±0.4	2.6±1.0	3.3±0.4	3.1±0.7	3.1±0.5

Table 6 *p* values in linear models for the change from baseline in the PaO_2/FIO_2 ratio between 2 and 48 h including various additional factors of clinical concern. The significant interactions between treatment and morbidity characteristics (e.g., pneumonia, PaO_2/FIO_2<65) indicate that the difference between treatment groups depends on the baseline value of the oxygenation index and on the presence of pneumonia as a causative diagnosis for ARDS. These differences are clearly demonstrated by the median profiles which are displayed separated for the respective subgroups

Factor of interest	Surfactant treatment	Factor of interest (morbidity characteristics)	Treatment by factor
No	0.079	–	–
Baseline PaO_2/FIO_2 (<65 vs. >65)	0.220	0.019	0.028
Baseline lung injury score (<3.1 vs. >3.1)	0.103	0.958.	0.426
Baseline PRISM III (<12 vs. >12)	0.069	0.232	0.786
Age (<1 vs. ≥2 years)	0.076	0.291	0.783
Sex	0.139	0.727	0.285
Body weight (≤12 vs. >12 kg)	0.059	0.570	0.055
Time since FIO_2 >0.5 before randomization (<24 vs. >24 h)	0.122	0.617	01.77
Time since PIP >30 cmH_2O before randomization (<30 vs. >30 h)	0.096	0.269	0.893
Pneumonia (primary pulmonary ARDS)	0.001	0.047	0.002
Sepsis	0.123	0.085	0.965
Under immunosuppression	0.135	0.135	0.743

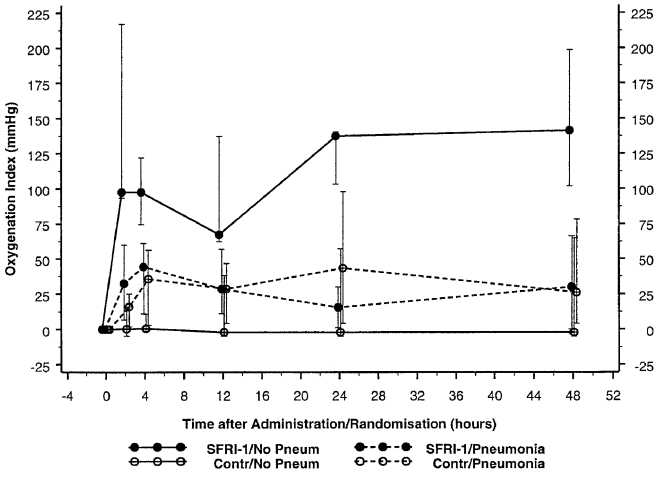

Fig. 5 PaO_2/FIO_2 changes from baseline in the group of patients with an initial PaO_2/FIO_2 ratio less than and greater than 65 (*dotted lines*) in the surfactant group (*group 1*) and controls group (*group 2*)

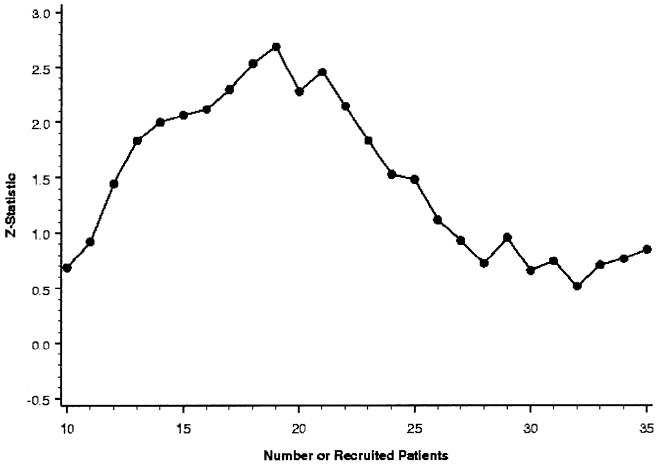

Fig. 6 PaO_2/FIO_2 changes from baseline in the group of patients with (*dotted lines*) and without pneumonia in the surfactant group (*group 1*) and controls (*group 2*)

prejudicial time point the primary comparison between treatments was performed sequentially, post hoc beginning with the first ten evaluable patients. The resulting *Z* statistics, which are approximately normally distributed, are depicted graphically vs. the number of patients (Fig. 4).

Discussion

In patients with ARDS less endogenous surfactant is produced, and this is inactivated, modified, and not reused, thus causing an absolute and relative surfactant deficiency [20, 24, 25, 26, 23]. As surfactant is a major biological factor for alveolar recruitment, surfactant deficit is a key problem in ARDS, and substitution of surfactant in

ARDS could be an important therapeutic tool [19, 23, 26]. As early as 1989 it was hypothesized that surfactant could be of therapeutic value not only in premature infant's respiratory distress syndrome but also in ARDS [24]. In that year the first case report of a successfully surfactant-treated child with severe hypoxemic ARDS was published [27]. Surfactant therapy in preterm infants is now based on sound data (e.g., [28, 29, 30]). In respiratory failure of term infants, in some ways resembling ARDS, a randomized study demonstrated a significant reduction in the need for ECMO [31]. Several uncontrolled studies have been published on adult ARDS [32, 33]; a large controlled study using small doses of aerosolized synthetic surfactant found no advantage of surfactant [33], and a smaller administering a bolus reported improved oxygenation and slightly increased survival in the treatment group [34]. In the pediatric population surfactant has been used in several case reports and in small uncontrolled studies of near fatal ARDS [17, 19, 24, 35]. In mild to moderate ARDS (Hallman oxygenation index less than 10) a randomized study demonstrated improved oxygenation immediately after surfactant administration and most ventilation-associated parameters [36]. In patients with severe hypoxemia we observed a short period of improved oxygenation, as in the study by Willson et al. [36] in patients with less severe hypoxemia.

The originally planned number of patients, however, could not be recruited in the time period scheduled. This might be due to the fact that the overall incidence of ARDS in children decreased dramatically in central Europe during the study period [13, 37]. The study was stopped as the recruitment dropped in this obviously high mortality group. As a sequential analysis of the primary endpoint (normalized *Z* statistics) demonstrated, the study was not stopped at a point at which there was a significant difference in respect of the primary outcome criteria; this would have been true at an earlier time point.

The overall mortality rate in this study is comparable to that of other studies carried out in severe hypoxemic pediatric ARDS [4, 5, 13]. The trend towards a decreased mortality and need for rescue medication in such a high mortality population might nevertheless be important as no other evidence-based treatment option exists. Surfactant may be only one factor in improving oxygenation in severe ARDS; it enhances the benefits of the "open lung concept," prone positioning, and NO-induced pulmonary vasodilatation [25, 38, 39]. The improvement in oxygenation in the control group, which was managed only on a strictly enforced ventilation algorithm and blood pressure and fluid intake protocol, suggests that standardized treatment alone using conventional methods leads to an overall improvement in patient outcome. This is in line with similar findings by Steinhard et al. [12] who reported improved patient outcome simply by introducing enforced ventilatory management protocols. Surfactant might also be directly involved in improving the balance of pro- and anti-inflammatory mediators in ARDS and therefore be a causative approach [39, 40, 41]. The design of modified surfactant solutions being more prone against inactivation by different proteins in the course of ARDS could enhance and prolong the effect of surfactant on oxygenation [42].

As patients without pneumonia showed a significant improvement and patients weighing more than 12 kg had a benefit from surfactant, it can be speculated that these small infants, in whom pneumonia is the principal cause of ARDS, would require much higher surfactant doses. This would be in accordance with experimental results in which in pneumonia surfactant inactivation was increased, compared with other causes of ARDS [38]. Higher doses of the surfactant preparation used cannot be applied as they would obstruct the major airways. A second dose showed no benefit in our study, either in the data analysis of primary and secondary endpoint criteria or in the post hoc analysis of subgroups. If at all, higher initial doses in selected patients could be considered if a preparation were available with lower volume, lower viscosity, and perhaps more prone to inactivation. Surfactant treatment with a listed price of € 200–400/100 mg is still very expensive.

Conclusions

This study reveals the difficulty in obtaining conclusive results from randomized studies in an intensive care setting and patients with a high mortality. Many "intended to treat" patients could not be randomized as they had underlying lung or heart disease, were dying at arrival in the ICU, or had been ventilated for more than 5 days in regional hospitals. An additional difficulty for such a study is the decreasing incidence of ARDS in children. Our study confirmed results of a previous randomized study by Willson et al. [38] reporting improved oxygenation in pediatric patients with mild to moderate ARDS. The improvement in oxygenation was sustained for patients without pneumonia as underlying disease and with a PaO_2/FIO_2 ratio greater than 65. The latter subgroup does not seem to benefit from any other available rescue tool at this moment. Ventilation variables could be reduced in the surfactant group. The devastating consequences of aggressive ventilation in these children with severe ARDS can probably be ameliorated with surfactant treatment. We conclude that surfactant treatment in severe pediatric ARDS might offer benefits to the patients.

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