Surfactant treatment for acute respiratory distress syndrome

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Abstract

***Objective*—To determine prospectively the efficacy of surfactant in acute respiratory distress syndrome.**

***Study design*—Twenty patients, 1 month to 16 years of age, diagnosed with an acute pulmonary disease with severe hypoxaemia (PaO_2/FiO_2 < 100) (13 with systemic or pulmonary disease and seven with cardiac disease) were treated with one to six doses of 50–200 mg/kg of porcine surfactant administered directly into the trachea. The surfactant was considered to be effective when the PaO_2/FiO_2 improved by > 20%.**

***Results*—After initial surfactant administration the PaO_2/FiO_2 increased significantly in patients with systemic or pulmonary disease from 68 to 111, and the oxygenation index (OI) diminished significantly from 36.9 to 27.1. The PaO_2/FiO_2 and OI did not improve in children with cardiac disease. The improvement of the patients who survived was greater than that of those who died.**

***Conclusions*—Surfactant moderately improves oxygenation in some children with severe acute respiratory distress syndrome secondary to pulmonary or systemic disease.**

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Keywords: surfactant; acute respiratory distress syndrome; lung disease

Acute respiratory distress syndrome (ARDS) in children can be secondary to multiple causes acting by different mechanisms, such as: direct endothelial damage, decrease and alteration of surfactant, cellular damage by mediators of inflammation (cytokines, complement, products of coagulation, metabolites of arachidonic acid, proteases, and free radicals), and the activation of platelets and leucocytes. These causes produce an alteration in the alveolar capillary membrane, which results in increased permeability and secondary pulmonary oedema.[1]

Despite the use of new treatments such as controlled pressure ventilation and the inversion of the inspiratory/expiratory ratio,[2] permissive hypercapnia,[3] postural changes,[4] high frequency ventilation,[5] administration of inhaled nitric oxide,[6 7] and extracorporeal membrane oxygenation (ECMO),[8] the mortality from ARDS is still very high.[9 10]

Several studies have shown, by means of bronchoalveolar lavages, that patients with ARDS show a quantitative and qualitative alteration of surfactant, and this alteration begins in the first phases of the disease.[11 12] The decrease of surfactant in ARDS might be the result of many factors: inactivation of the surfactant by plasma proteins that pass into the alveolus; inhibition or damage to the protein component or phospholipid component of the surfactant by mediators of inflammation, such as lipases, proteases, or oxidants; incorporation of the surfactant into hyaline membranes; alterations of the synthesis, storage, or release of the surfactant as a result of damage to type II pneumocytes; and the loss of the surfactant caused by high volume mechanical ventilation.[11 12] The decrease of

Table 1 Clinical characteristics of the patients with pulmonary or systemic disease

Patient	*Age*	*Sex*	*Diagnosis*	*Murray index*	*Surfactant doses (n)*	*Outcome*
1	1 year	M	Bronchopneumonia Tracheo-oesophageal fistula	3	2	Died
2	1 month	M	Bronchiolitis	3	4	Lived
3	8 years	F	*Pneumocystis carinii* pneumonia AIDS	3	3	Died
4	16 years	M	Duchenne muscular dystrophy Postoperative pneumonia	3	3	Died
5	1 year	F	Meningococcal septicaemia	3.3	4	Lived
6	8 years	F	Multiple trauma Pulmonary contusion	3.6	1	Lived
7	10 years	F	Crohn's disease Abdominal surgery Sepsis	3.7	3	Lived
8	4 months	F	Pseudomona sepsis	3.3	3	Died
9	4 months	M	*P carinii* pneumonia AIDS	3.3	2	Lived
10	1 months	M	Bronchiolitis	3	1	Lived
11	6 months	M	Bronchopulmonary dysplasia Bronchiolitis	3	2	Lived
12	7 years	F	Hip surgery Pneumonia	4	1	Lived
13	5 months	F	*P carinii* pneumonia Neuroblastoma	3.6	2	Lived

Patient 2 has been published previously.[22]

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Table 2 Clinical characteristics of the patients with cardiac disease

Patient	*Age*	*Sex*	*Diagnosis*	*Murray index*	*Surfactant doses (n)*	*Outcome*
1	1 year	M	Tetralogy of Fallot	3.6	2	Died
2	7 months	M	VSD, PHT	3.3	3	Died
3	1 year	M	Down's, VSD, PHT	3	2	Died
4	4 months	M	Complex cardiopathy	3	2	Lived
5	1 year	M	Down's, VSD, PHT	3	2	Died
6	11 months	M	Down's, AVSD	2.6	1	Died
7	5 months	M	VSD, PHT, bronchiolitis	2.6	1	Died

AVSD, atrioventricular septal defect; PHT, pulmonary hypertension; VSD, ventricular septal defect; Down's, Down's syndrome.

surfactant causes respiratory failure by decreasing compliance and residual pulmonary capacity, the formation of atelectasias, and pulmonary oedema.[11 12]

Multiple studies have shown that the intratracheal administration of surfactant in the newborn with respiratory distress syndrome leads to a great improvement in oxygenation and ventilation, allowing a decrease in respiratory assistance and significantly decreasing mortality.[13] Despite this, there are few studies that have analysed the efficacy of surfactant in ARDS, either in adults[14–17] or in newborns and children.[18–22]

Patients and methods

Between October 1993 and July 1997, surfactant was administered to 20 patients (13 boys and seven girls) aged from 1 month to 16 years, who had been diagnosed with severe ARDS with a Murray index modified for infancy[3] greater than 2.5 (range, 2.6–4). ARDS was defined as an acute pulmonary disease, non-cardiogenic in origin, with diffuse bilateral infiltrates on the chest *x* ray, and hypoxaemia with a PaO_2/FiO_2 (arterial oxygen tension/fraction inspired oxygen ratio) lower than 200 mm Hg.[1] We divided the patients in two groups: (1) 13 patients with ARDS secondary to pulmonary or systemic disease (table 1 gives their diagnoses and clinical characteristics); and (2) seven patients with hypoxaemic pulmonary pathology in the postoperative period of cardiovascular surgery, in whom the clinical evolution, chest *x* ray, and echocardiography suggested that the pulmonary alteration could not be attributed to cardiac pathology alone, despite not having monitored the pulmonary capillary pressure. Table 2 gives the diagnoses and clinical characteristics of these patients.

Once informed consent was obtained from the parents of the patients, the surfactant was administered according to a previously established protocol, as compassionate treatment approved by the Institutional Review Board, when faced with the failure of conventional treatment. Our standard treatment for ARDS is controlled pressure ventilation with an I:E ratio of 1:2 to 3:1, positive end expiratory pressure (PEEP) that allows the optimum degree of oxygenation, and an FiO_2 necessary to maintain a saturation between 85% and 90%, with a PaO_2 greater than 50–60 mm Hg, and permissive hypercapnia up to a $PaCO_2$ of 85–90 mm Hg, maintaining a pH higher than 7.15–7.20. In patients with pulmonary hypertension in the postoperative period of cardiac surgery, we try to maintain the pH between 7.45 and 7.50 with hyperventilation and administration of bicarbonate, additional treatment with prostaglandin E1 or prostacyclin, and the administration of inhaled nitric oxide. (We gave inhaled nitric oxide to 15 of our patients, at a concentration of between 3 and 25 ppm.) We did not use high frequency ventilation or ECMO, as this is not available in our hospital. Tables 3 and 4 show the ventilation parameters of the patients before the administration of the surfactant.

In 14 of the patients, one to six doses of porcine surfactant (Curosurf) were given at 50 mg/kg at intervals of between six and 24 hours, with a total of 37 administrations of surfactant. In the remaining six patients, we used surfactant doses of 200 mg/kg, in nine doses. The surfactant was given in two equal aliquots through a tube introduced as distally as possible through the tracheal tube, one towards the right lung and the other towards the left. All patients had continuous electrocardiogram monitoring, as well as central venous pressure (CVP) and intra-arterial blood pressure monitoring. In addition, four patients had pulmonary artery pressure monitoring by means of a catheter passed through the right ventricle during cardiac surgery, and one patient had a Swan-Ganz catheter. A chest *x* ray and arterial blood gas extraction were performed before the surfactant was administered. Whenever possible, after administration we tried to keep the same parameters on the respirator until new blood gas measurements were carried out. New blood gas controls were performed at 30, 60, 120, 240, and 360 minutes after administering the surfactant. The response was considered to be positive if the PaO_2/FiO_2 ratio improved > 20% in the first four hours after the surfactant was given, without any modification

Table 3 Respiratory assistance before the surfactant treatment in patients with pulmonary or systemic disease

Patient	*Peak pressure (cm H_2O)*	*PEEP (cm H_2O)*	*Frequency (rpm)*	*I:E ratio*	*FiO_2*	*Paw (cm H_2O)*
1	52	8	35	1:1.5	1	25
2	40	7	42	1:1	1	25
3	40	7	20	1:1	0.75	24
4	44	10	20	1:1.5	0.9	21
5	32	8	40	1:2	1	16
6	41	14	25	1:1	1	26
7	38	10	31	1:1	1	23
8	43	12	35	3:1	1	35
9	38	4	60	1:1.5	1	17
10	33	8	60	1:2	1	16
11	28	6	40	1:1.5	0.6	13
12	44	16	30	1;1	1	30
12	44	16	30	1:1	1	30
13	37	12	27	1:1.5	0.85	22

PEEP, positive end expiratory pressure; Paw, mean airway pressure.

Table 4 Respiratory assistance before the surfactant treatment in patients with cardiac disease

Patient	*Peak pressure (cm H_2O)*	*PEEP (cm H_2O)*	*Frequency (rpm)*	*I:E ratio*	*FiO_2*	*Paw (cm H_2O)*
1	42	13	32	1:2	1	23
2	37	10	26	1:2	1	18
3	31	12	35	1:2	1	21
4	35	12	30	1:1	0.85	21
5	31	8	20	1.5:1	0.6	20
6	31	8	35	1:1	0.7	18
7	40	4	23	1:1	1	18

PEEP, positive end expiratory pressure; Paw, mean airway pressure.

Table 5 PaO_2/FiO_2, $PaCO_2$, and oxygenation index (OI) before and after the first dose of surfactant treatment in patients with pulmonary or systemic disease

	PaO_2/FiO_2		OI		$PaCO_2$	
Patient	Before	After	Before	After	Before	After
1	59	72	43	33	38	38
2	57	164	43	9	56	35
3	99	136	24	19	41	25
4	72	93	29	27	46	43
5	58	83	27	27	50	66
6	44	52	60	50	66	65
7	65	84	48	37	79	100
8	54	61	65	55	80	83
9	94	252	18	7	78	65
10	57	69	25	23	45	25
11	99	76	13	18	60	59
12	53	77	56	39	66	65
13	74	227	29	9	44	33
Mean	68	111.2	36.9	37.1	57.6	54
SD	18	64.7	16.6	15.2	15	23

$PaCO_2$ measured in mm Hg.
Increase in PaO_2/FiO_2, $p < 0.01$. Reduction in OI, $p < 0.05$.

of respiratory assistance. We also calculated the oxygenation index (OI; mean pressure in the airway $\times FiO_2 \times 100/PaO_2$). When the surfactant improved oxygenation during more than one blood gas control we reduced respiratory assistance (peak of pressure or FiO_2, depending of the previous assistance). The administration of a repeated dose depended on the blood gas response to the first dose and the clinical evolution of the patient. Statistical software (BMDP; University of California, Berkeley, California, USA) was used for statistical analysis of the results. Statistical analysis was performed by using analysis of variance, the Student's *t* test, two tailed Mann-Whitney test, and Wilcoxon test. Values of $p < 0.05$ were considered significant.

Results

In the 13 patients with pulmonary or systemic pathology the mean (SD) PaO_2/FiO_2 increased after the first dose of surfactant from 68 (18.4) to 111.2 (64.7) ($p < 0.01$) and the mean (SD) OI was reduced from 36.9 (16.6) to 27.1 (15.2). The PaO_2/FiO_2 improved > 20% in 10 patients. There was no significant change in the $PaCO_2$ (table 5). When each of the 33 administrations of surfactant was analysed separately, the mean (SD) PaO_2/FiO_2 increased from 73.2 (19.7) to 100.8 (49.7) ($p < 0.01$). In 17 of the 33 administrations there was a > 20% increase in the PaO_2/FiO_2. The mean (SD) OI diminished from 34.4 (14) to 28.6 (13.7) ($p < 0.05$), and the mean (SD) $PaCO_2$ from 59.9 (16.7) mm Hg to 56.8 (23.5; NS).

Table 6 PaO_2/FiO_2, $PaCO_2$, and oxygenation index (OI) before and after the first dose of surfactant treatment in patients with cardiac disease

	PaO_2/FiO_2,		OI		$PaCO_2$	
Patient	Before	After	Before	After	Before	After
1	37	53	61	41	33	42
2	51	53	35	57	42	42
3	62	52	30	33	31	33
4	60	93	29	27	39	46
5	90	96	22	21	27	31
6	100	100	18	20	38	33
7	46	40	30	52	77	75
Mean	63.7	69.5	32.1	35.8	41	43.1
SD	23.1	25.5	13.9	14.6	16.6	15.1

$PaCO_2$ was measured in mm Hg.

Table 7 Comparison of the response to surfactant between the patients who died and those who lived

	Lived (n = 10)	Died (n = 10)
PaO_2/FiO_2 before	66.7 (18.7)	67 (22.4)
PaO_2/FiO_2 after	117.7 (70.8)	75.6 (30)
OI before	34.8 (16)	35.7 (15.9)
OI after	24.6 (14.3)	35.9 (14.7)

Increase of PaO_2/FiO_2 and reduction of oxygenation index (OI) in patients who lived, $p < 0.05$.

In the seven patients with cardiac pathology there were no significant changes in PaO_2/FiO_2, OI, or $PaCO_2$ after the first dose of surfactant. The PaO_2/FiO_2 improved > 20% in only two patients (table 6). When each of the surfactant administrations was analysed separately, the mean (SD) PaO_2/FiO_2 increased from 65.3 (24.7) to 70.6 (22); the PaO_2/FiO_2 increased > 20% in only three of the 13 surfactant administrations. The mean (SD) OI diminished from 36.9 (17.4) to 35 (13.6) and the mean (SD) $PaCO_2$ increased from 34.2 (8.1) to 36.2 (9.1; NS).

The mean (SD) PaO_2/FiO_2 increased from 73.4 (20.8) to 115.2 (77.8) after administration of 200 mg/kg of surfactant, and after 50 mg/kg it increased from 70.4 (21.6) to 86.7 (32.9). The difference between the two doses was not significant. In six of the nine surfactant administrations of 200 mg/kg there was an increase in the PaO_2/FiO_2 of > 20%, whereas this occurred only in 14 of the 37 administrations of 50 mg/kg. There was no correlation between the increase in PaO_2/FiO_2 and the patients' ages.

Improvement after the administration of surfactant began between 30 minutes and four hours, with three quarters of the patients showing an improvement in the first hour. The administration of surfactant produced initial hypoxaemia, bradycardia, and hypotension in three patients, in one of them ventilation decreased because of a partial obstruction of the trachea by the surfactant, and in another, a patient with a pneumothorax, an increase of the pneumothorax was found one hour after the administration.

Ten patients died: five as a result of a cardiogenic shock with multiple organ system failure, three because of refractory respiratory failure, one as a result of pulmonary haemorrhage, and one because assistance was withdrawn as a result of the irreversible underlying disease (AIDS). The mortality of cardiac patients with ARDS was greater (six of seven) than that of patients with pulmonary or systemic disease (four of 13). The improvement in the oxygenation of the patients who survived was greater (PaO_2/FiO_2 increase of 51 points and OI decrease of 10 points) than that of the patients who died (PaO_2/FiO_2 increase of 8 and no decrease in OI) (table 7). The differences between the two groups were significant ($p < 0.05$).

Discussion

There are only two prospective, comparative studies that analyse the efficacy of surfactant in patients with ARDS, both of which are in adult patients, and one of which suggests that

surfactant produces an improvement in oxygenation and a decrease in mortality.[16 17] The remaining studies refer to small series of patients. With the exception of the newborn period, there is only one multi-institutional study on children, with 29 patients who were treated with calf surfactant.[21] The rest of the studies were carried out on small patient populations.[18–20 22]

Our objective was to administer surfactant in two different groups of patients, one with ARDS secondary to pulmonary or systemic disease, and other in the postoperative period following cardiovascular surgery .

Our results show that surfactant improved oxygenation in 10 of the 13 children with severe ARDS secondary to pulmonary or systemic disease, which was refractory to conventional ventilation. However, in most of our patients the improvement in oxygenation was moderate and the effect on prognosis was probably minimal in all but four of these children.

In cardiac patients, the surfactant did not produce significant changes in oxygenation. The PaO_2/FiO_2 increased significantly from 60 to 93 in one patient only (table 6). Although it has been shown that extracorporeal circulation alters pulmonary surfactant, and that this might contribute to altered respiratory function in the postoperative period of cardiac surgery,[23] a recent study showed that the lecithin to sphingomyelin ratios and surfactant protein A concentrations were reduced in tracheal secretions of children with bacterial pneumonia, viral pneumonia, and ARDS, but not in children on cardiopulmonary bypass.[24] Our results suggest that in these patients surfactant might have a lower efficacy because pulmonary hypertension and pulmonary oedema secondary to cardiac failure might be more important factors in the development of pulmonary damage. Unfortunately, although four of the patients in the postoperative course of cardiac surgery had a catheter in the pulmonary artery, none of them had a Swan-Ganz catheter, and thus we do not know the pulmonary capillary pressure, which is why some of the children in the postoperative course of cardiac surgery might have presented with a mixed ARDS disease with acute cardiac pulmonary oedema. Two studies in which surfactant was administered to adults subjected to extracorporeal surgery, who did not present with ARDS, produced discordant results.[25 26] We have not found any studies on the use of surfactant in children with ARDS secondary to extracorporeal cardiac surgery.

In our patients, we did not find any other previous clinical or respiratory parameter that could predict the response to treatment with surfactant. Experimental studies have found that the response to surfactant depends on the type of pulmonary injury, the degree of alteration, and the presence of surfactant inhibitory serum proteins in the alveoli.[27] Other factors that may play a part in the response to treatment are: (1) the time of administration (the sooner it is administered the greater the effects),[27] (2) the type of surfactant (natural surfactants are more effective than synthetic ones),[28] (3) the form of administration (direct tracheal administration is more effective than an aerosol),[27] (4) the volume of liquid administered,[14 29] and the dose of surfactant and the number of administrations.[14 27] In our study, the patients who received a dose of 200 mg/kg of surfactant had a better response, although this was not significant, perhaps because of the small number of patients treated with this dose. The surfactant was always administered quite late when there was severe hypoxaemia and the patients did not respond to conventional treatment. We have no way of knowing whether earlier administration of the surfactant would have given better results. In any case, surfactant would not be expected to be as effective in ARDS in children and adults as it is in newborns, because the surfactant deficit is only one of the factors that lead to the pulmonary alteration in these patients.[30]

We used the rapid instillation technique as the surfactant delivery method. Several experimental studies have shown that direct instillation through the tracheal tube or through a bronchoscopy is more effective than aerosolised surfactant or the five minute infusion technique.[27 30 31] However, in some patients rapid instillation produces significant decreases in oxygen saturation, heart rate, and blood pressure, as occurred in three of our patients, probably secondary to the transitory disconnection of the respirator.[16 30] These effects can be avoided if the surfactant is given through a tracheal tube without interrupting the mechanical ventilation. Another factor that might limit the use of surfactant is its high cost, especially in older children and adolescents.[32]

Our patients had a high mortality rate despite treatment with surfactant. This might be because of the selection of patients with ARDS who did not respond to conventional treatment, and the inclusion of patients with ARDS in the postoperative course of cardiac surgery in whom pulmonary hypertension and cardiogenic shock were also found. The mortality of patients with ARDS secondary to pulmonary or systemic disease was four of 13, and the mortality of cardiac patients was six of seven. According to our results, the positive response to surfactant could be a prognostic factor in children with ARDS.

We conclude that the administration of intratracheal surfactant moderately improves oxygenation in some children with secondary pulmonary pathology or systemic disease. However, our study does not show whether surfactant changes the prognosis of children with ARDS. Further studies are necessary to determine the time of administration, the dose, the interval, and the specific indications of surfactant in the different pathologies that cause ARDS in childhood.

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