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Early versus Late Surfactant Replacement Therapy in Severe Respiratory Distress Syndrome

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Abstract. 26 preterm infants with severe respiratory distress syndrome (RDS) have been treated at different ages with a single dose of natural porcine surfactant (Curosurf, 200 mg/kg). Criteria for treatment included clinical and radiological signs of severe RDS (grade III–IV), requirement of artificial ventilation and an $FiO_2 \geq 0.6$. Nineteen neonates have been subjected to early treatment (2–15 h of age, mean birth weight SD: 1201 ± 387 g) and 7 patients to late treatment (>15 h to 48 h of age, birth weight SD 1624 ± 649 g). Average FiO_2 before treatment was 0.88 in early-treated patients and 0.8 in late-treated patients, age at treatment was 4.6 h and 36 h, respectively (median). Both early- and late-treated infants exhibited an improvement in oxygenation (more than twofold increase of the PaO_2/FiO_2 ratio) within 5 minutes after initiation of therapy. Average duration of intermittent pressure ventilation was 15 days in the early treatment group and 19 days in the late treatment group. Total exposition to >21% oxygen was 21 days in early-treated and 48 days in late-treated infants. Pneumothorax occurred in none of the patients. All early treated infants survived without signs of severe bronchopulmonary dysplasia (BPD >21% O_2, >90 days plus radiological changes). However, two out of seven late-treated infants developed severe BPD; one patient died as a consequence of cardiopulmonary deterioration. Two patients in the early treatment group died of nonpulmonary complications. We conclude that surfactant replacement therapy should probably be initiated as soon as possible after manifestation of severe RDS.

Key words: Respiratory distress syndrome—Surfactant replacement therapy.

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Introduction

There is now convincing evidence that the severity of respiratory distress syndrome (RDS) can be reduced by either prophylactic treatment with surfactant [1–5] or surfactant replacement in infants with established disease [6–14]. In all randomized trials surfactant substitution resulted in improvement in oxygenation and reduced ventilatory requirements. Two prevention trials [1, 3] and two rescue trials [8, 14] demonstrated a decrease in mortality of treated infants; a reduced combined incidence of mortality and bronchopulmonary dysplasia (BPD) was found in three additional trials [5, 6, 9].

In this observational study we provide some evidence that in severe RDS, the risk of prolonged oxygen dependency and, hence, BPD is higher if the baby is treated later (>15 h of postnatal age) rather than during early in the course of the disease.

Patients and Methods

Surfactant replacement therapy was performed in 26 patients with severe RDS consecutively treated at the neonatal intensive care unit, Department of Pediatrics, University of Göttingen, between May 1987 and April 1988. These babies did not belong to the population randomized in previous [14] or ongoing controlled multicenter trials. Preparation and characterization of Curosurf has been described in detail elsewhere [14, 15]. Criteria for surfactant therapy were: 1) birthweight 700–2,000 g; 2) clinical and radiological findings typical of neonatal RDS; 3) artificial ventilation; 4) $FiO_2 \geq 0.6$ (FiO_2 = fraction of inspiratory oxygen); 5) no complicating disease; 6) age of treatment 2–15 h ("early treatment") or >15–48 h ("late treatment"). All infants assigned to "late treatment" were transferred from peripheral pediatric hospitals with signs of severe RDS at an age >15 h; treatment was initiated within two hours after admission. In general, anemia, hypotension, hypoglycemia, and acidosis were treated by appropriate measures before surfactant replacement. All infants were mechanically ventilated with an FiO_2 of 0.6 to 1.0, a frequency of 40–60 breaths/min and a positive inspiratory pressure (PIP) of <40 cm H_2O; positive end-expiratory pressure (PEEP) was 3–5 cm H_2O, inspiration to expiration ratio was 1 : 1 to 1 : 2. A total dose of surfactant (Curosurf: 200 mg/kg = 2.5 ml/kg) was divided into two portions and instilled into each dependent bronchus. Following each instillation, the infants were ventilated manually for one minute; details of the instillation technique have been recently published [14, 16]. After the period of manual ventilation the patient was reconnected to the ventilator; the FiO_2 and ventilator setting were immediately adjusted to the patient's clinical response to maintain adequate blood gases (PaO_2 50–70 mm Hg, $PaCO_2$ 40–45 mmHg, pH >7.3) with the lowest possible level of FiO_2 and PIP. Early-treated infants and late-treated patients were compared with respect to various parameters: FiO_2, PaO_2/FiO_2 ratio, PIP, $PaCO_2$, arterial pH. In addition, the two study groups were compared for the frequency of pulmonary and nonpulmonary complications and duration of mechanical ventilation as well as exposure to supplemental oxygen. Radiologic examinations of the lungs were obtained immediately before treatment as well as 12 h and 10 days after initiation of therapy and whenever clinically indicated. Cranial ultrasound was performed serially, intraventricular hemorrhage was classified according to Papile et al. [17]. Sequential echocardiograms were obtained every 24 h to determine patency of the ductus arteriosus. BPD was defined as an oxygen requirement greater than 21% at 28 days of life plus typical findings in chest films as judged by a pediatric radiologist. Severe BPD was diagnosed in patients who required more than 21% inspiratory oxygen at 90 days of life and had characteristic radiological changes [18]. The trial was approved by the ethical committee of the University of Göttingen; informed consent was obtained from the patients prior to treatment. Statistical analysis was evaluated by Wilcoxon-Mann-Whitney test and by the Chi-square test; the limit level of statistical significance was defined as $p < 0.05$.

Table 1. Characteristics of patients who had been subjected to early or late surfactant replacement therapy; early therapy: 2–15 h, late therapy: >15–48 h

Characteristics	Early therapy (N = 19)	Late therapy (N = 7)
Gestational age (week)*	29.6 ± 1.9	31.0 ± 2.5
Birth weight (g)*	1,201 ± 387	1,624 ± 649
<1000 g (N)	9	2
Age at treatment#	3 (2–12)	36 (22–48)
FiO_2 before treatment*	0.88 ± 0.11	0.80 ± 0.15

* Mean ± SD
\# Median (10^{th}–90^{th} percentile)

Results

Characterization of Patients

The characteristics of the patients who had been subjected to early or late surfactant replacement therapy are shown in Table 1. Although the differences between the groups were not statistically significant, the late-treated infants tended to be more mature, with a higher birth weight and a slightly lower average FiO_2 before treatment. Other characteristics that were determined soon after birth (multiple birth, sex, Apgar-Score, pH of the umbilical cord artery) did not differ between both groups.

Clinical Observations

As demonstrated in Fig. 1, surfactant treatment resulted in a rapid improvement of oxygenation, without statistically significant differences between the groups; as a consequence, mean FiO_2 could be lowered within 15 minutes in early-treated infants from about 0.89 to 0.38 and in late-treated patients from about 0.80 to 0.37. Correspondingly, a more than twofold increase of the PaO_2/FiO_2 ratio was observed in both group of patients. During the first ten days reduction of the average FiO_2 showed a parallel pattern in both groups; the same was true for the increase of the PaO_2/FiO_2 ratio. The PIP was similarly reduced in both groups within one hour after surfactant therapy; however, from two hours to 10 days peak insufflation pressure was slightly higher in late-treated infants (NS). Average values for respirator frequency, PEEP, and inspiration to expiration ratio were not different between the groups.

Outcome

The outcome data are summarized in Table 2. Average duration of intermittent positive ventilation was similar in both groups. However, the time of total

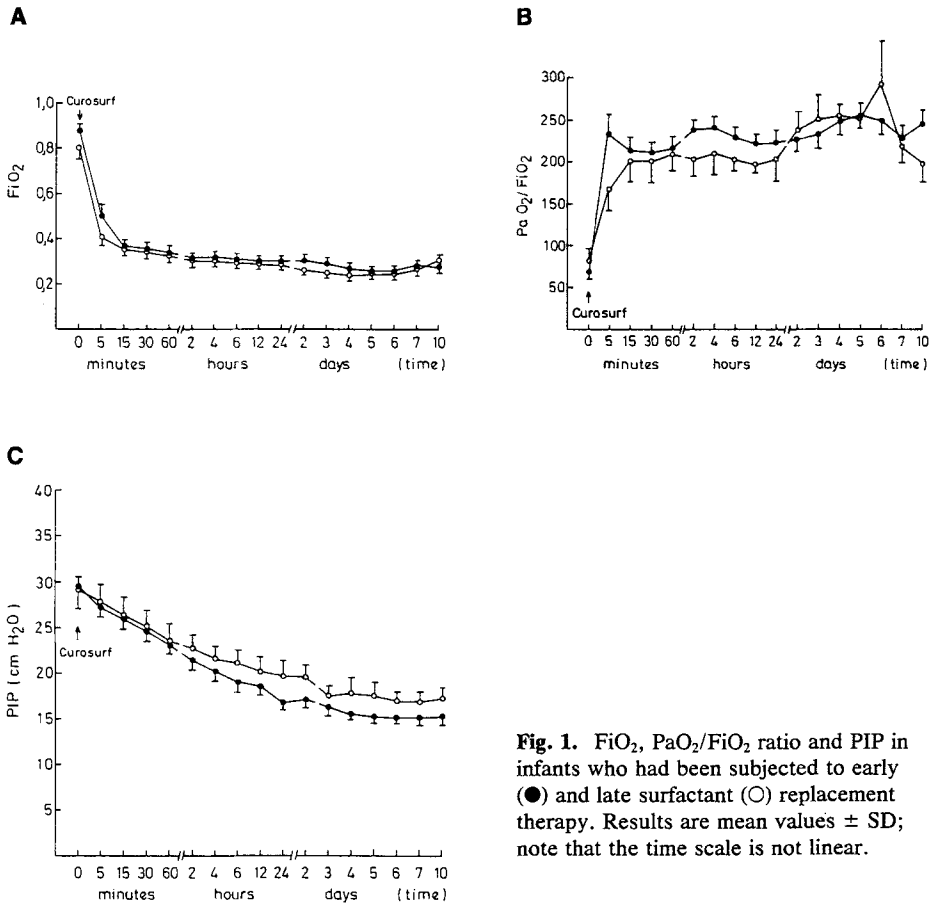

Fig. 1. FiO_2, PaO_2/FiO_2 ratio and PIP in infants who had been subjected to early (●) and late surfactant (○) replacement therapy. Results are mean values ± SD; note that the time scale is not linear.

exposition to supplemental oxygen was significantly longer in late-treated infants ($p < 0.01$). Only two out of 19 early-treated patients developed interstitial emphysema after surfactant substitution; this finding was prominent in 4 of 7 late-treated patients. None of the infants of both groups developed a pneumothorax; mild BPD was present in 6 of the early-treated and 3 of late-treated infants. However, in the late treatment group two patients developed severe BPD; one child died after 4 month of life following deterioration of pulmonary and cardiac function. In the early-treated group, one patient died from septicemia, and another from acute expansion of an intracerebral hemorrhage (grade III–IV) following ligation of a patent ductus arteriosus. Overall mortality in both groups of patients with severe RDS was 11.5% (3/26). Although the differences were not statistically significant, the incidence of extrapulmonary complications like cerebral hemorrhage and persistent ductus arteriosus was somewhat higher in the group of early-treated infants, perhaps reflecting the greater number of more immature infants in this group.

Table 2. Duration of IPPV, time of exposition to oxygen and outcome

Parameters	Early therapy (N = 19)	Late therapy (N = 7)
Duration of IPPV in survivors (days)*#	6 (3–40)	7.9 (3.8–50)
Exposition to oxygen		
≥60% (h)#**	4.0 (2–12)	30.0 (20–50)
≥21% (days)#**	15.0 (3–50)	14.0 (3.2–170)
Complications		
Pulmonary interstitial emphysema	2	4
Pneumothorax	0	0
Persistent ductus arteriosus	11	2
Intracerebral hemorrhage		
all grades	5	1
grade III–IV	1	0
Bronchopulmonary dysplasia		
mild	6	3
severe	0	2
Mortality	2[1]	1[2]

\# Median (10^{th} and 90^{th} procentile)

[1] Both patients died of extrapulmonary complications (day 5, day 11)

[2] Death at the age of 4 months caused by severe BPD

Discussion

In this clinical observational study we document that surfactant replacement therapy in severe RDS has an immediate effect on gas exchange even if treatment is initiated at a comparatively late stage of the disease. Early and late surfactant substitution resulted in an identically rapid improvement of gas exchange reflected by a significant increase in the PaO_2/FiO_2 ratio; the initial reduction of the FiO_2 showed a corresponding pattern in both groups of patients. The total exposition to oxygen, however, was longer in patients who had been subjected to late surfactant substitution. None of the infants developed a pneumothorax; a reduction in the incidence of pneumothorax has been reported in prevention [3–5] as well as rescue trials [7, 9, 13, 14]. The incidence of mild bronchopulmonary dysplasia was similar in both groups. However, two out of seven late-treated patients developed severe bronchopulmonary dysplasia, one of these patients died as a consequence of cardiopulmonary deterioration. It is likely that in these patients severe parenchymal injury of the lungs was already induced during the prolonged period of mechanical ventilation prior to surfactant replacement. The bronchiolar and alveolar epithelium tends to disrupt soon after initiation of mechanical ventilation in patients with RDS probably leading to increased permeability of the lungs to macromolecules and to accumulation of proteinaceous edema in the airspaces. In addition, des-

quamated necrotic epithelium mixed with coagulated proteins may cause physical plugging of the airways [19], and proteolytic enzymes and toxic oxygen radical metabolites, generated by the inflammatory response, may contribute further to chronic pulmonary damage.

Our data suggest that surfactant replacement therapy should be initiated as soon as possible after manifestation of severe RDS. Future controlled clinical studies should aim at identifying the optimal dose of exogenous surfactant for treatment of neonatal RDS and the number of doses and treatment intervals required for a therapeutic response with the lowest possible incidence of chronic lung disease and extrapulmonary complications.

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