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Early versus delayed surfactant administration in extremely premature neonates with respiratory distress syndrome ventilated by high-frequency oscillatory ventilation

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Abstract *Objective:* To determine whether early surfactant administration is superior to selective delayed treatment in terms of improving survival and/or reducing chronic lung disease in extremely premature neonates with respiratory distress syndrome (RDS) treated by high-frequency oscillatory ventilation (HFOV). *Design:* Prospective randomized clinical trial. *Setting:* Tertiary neonatal intensive care unit (NICU) in the Perinatology Center of Prague. *Patients:* Forty-three extremely premature infants who needed artificial ventilation within 3 h after delivery. *Interventions:* Patients were randomly assigned to either early (n=21) or delayed (n=22) administration of surfactant. All were ventilated by HFOV as the primary mode of ventilation using the high volume strategy aimed at optimizing lung volume. Curosurf at a dose of 100 mg/kg was given as a single bolus via the endotracheal tube within 1 min immediately after intubation in the early group (EARL), or during HFOV only when defined criteria were reached in the delayed (DEL) group. *Measurements and results:* No differences were noted in demographic data between the two groups. Fewer infants randomized to the EARL group required oxygen use or died at 36 weeks (combined outcome 29% vs 64%, p=0.021), and there was a lower incidence of any intraventricular hemorrhage in this group (43 vs 82%, p=0.008). *Conclusions:* When compared to delayed dosing, early administration of surfactant followed by HFOV facilitates and accelerates respiratory stabilization during the acute phase of severe RDS, may reduce the incidence of chronic lung disease or death and may positively influence the incidence of severe intracranial pathology in extremely premature infants with primary surfactant insufficiency.

Keywords Early surfactant · High-frequency oscillatory ventilation · Extreme prematurity · Chronic lung disease · Intraventricular hemorrhage

Introduction

In systematic overviews of trials comparing prophylactic or early administration to surfactant treatment of established respiratory distress syndrome (RDS), infants who received prophylactic or early therapy had a decreased incidence of pneumothorax, pulmonary interstitial emphysema (PIE) and mortality [1, 2, 3]. Unfortunately, prophylaxis with surfactant would overtreat a large number of infants judged at risk for RDS. Early rescue treatment of infants with evolving RDS may offer many of the same advantages as prophylactic therapy with fewer infants treated. More recently, the focus has shifted to optimization of the interaction between artificial ventilation and surfactant during the period shortly after delivery. Even a very short period of inadequate manual ven-

tilation before surfactant administration could adversely influence its efficiency, especially the improvement of compliance of the respiratory system [4]. Furthermore, repeated collapse and re-expansion of alveoli in surfactant-deficient lungs leads to intra-alveolar protein influx and further inactivation of surfactant [5].

The high volume strategy (HVS) during high-frequency oscillatory ventilation (HFOV) appears to decrease recurrent alveolar collapse, as evidenced by studies demonstrating less inflammatory response in the lungs during HFOV in comparison with conventional modes of ventilation [6]. This may also lead to less inactivation of surfactant, as suggested by a lower amount of surfactant required during HFOV in comparison with conventional ventilation (CV) [7, 8]. However, this finding is not direct evidence of a better effect of this mode of ventilation on surfactant metabolism because the administration of surfactant has been determined primarily by oxygenation in clinical practice. Nonetheless, based on the above considerations, the combination of surfactant administration and HVS during HFOV seems to be a very attractive combination therapy for RDS.

In our previous trial we described the positive influence of HFOV followed by surfactant administration on lowering the incidence of chronic lung disease (CLD) [7]. Conventional modes of artificial ventilation were used in most comparable trials concerning surfactant administration timing [1, 2].

The objective of this trial was to determine whether early surfactant administration further optimizes the positive influence of HFOV on the incidence of CLD or death in a group of extremely immature newborn infants in whom surfactant insufficiency is highly likely.

Methods

Patient eligibility and randomization

The trial was conducted in the tertiary regional neonatal intensive care unit (NICU) of the Perinatology Center in Prague from October 1, 1997, to July 15, 1999. Approval to conduct the trial was given by the ethics committee of the First Faculty of Medicine at Charles University.

Eligible newborn infants were characterized by the following criteria: (1) gestational age below 30 weeks of gestation, (2) intubation and assisted ventilation needed within 3 h after delivery for significant RDS and (3) written parental informed consent. Neonates were excluded for any of the following reasons: (1) congenital anomalies, (2) small for gestational age (<10th percentile), (3) 1 min Apgar score 0 and (4) intubation needed for reasons other than RDS. Eligible neonates were selectively intubated in the delivery room if central cyanosis persisted, despite oxygen supplementation and bagging via mask and self-inflating bag with an attached oxygen reservoir, or if sufficient respiratory effort was not evident. Lung volume recruitment was not actively attempted in the delivery room. Those infants who did not require resuscitation and those who responded well to initial bagging were immediately placed on continuous positive airway pressure (CPAP) of 5–6 cmH_2O (nCPAP, The Infant Flow System, E.M.E., England). Subsequently, intubation was indicated if FIO_2 of more than 0.40 was needed in neonates with birth weights less than 750 g, or 0.50 or more in neonates with birth weights of 750 g or more on nasal continuous positive airway pressure (nCPAP) of 6 cmH_2O in order to maintain good oxygen saturation above 87% on pulse oximetry. Intubated patients were randomly assigned to early (EARL) or delayed (DEL) surfactant administration using sealed envelopes before the birth with treatment assignment based on a table of random numbers. HFOV was used as a primary mode of ventilation in all intubated neonates.

Primary end point

The primary end point was CLD (defined as continuous use of oxygen) or death at 36 weeks post conceptional age.

Secondary end points

The secondary end points were: duration of mechanical ventilation, incidence of air leaks, pneumothorax and PIE, radiographic score according to the Toce scale at age 28–30 days and the incidence of other complications of prematurity, such as intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL), retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC).

Additionally, proximal airway distending pressure (PA_wDP), FIO_2, alveolar-arterial difference (A-aDO_2) and $PaCO_2$ were compared during the acute phase of RDS (first 60 h after delivery) between the EARL and DEL groups.

Ventilation management (HFOV – SensorMedics 3100A)

The high volume strategy (HVS) with optimal lung inflation was the main principle of HFOV therapy. Frequency was set at 15 Hz and the inspiratory-to-expiratory time ratio was maintained at 0.33 in all infants throughout the trial. The pressure amplitude (ΔP) was adjusted to achieve adequate vibration of the thorax. The PA_wDP was increased in a stepwise fashion as rapidly as possible to reach optimum lung inflation and alveolar recruitment, as manifested by improvement in oxygenation. Once adequate lung inflation had been achieved and oxygenation optimized, the FIO_2 was weaned to maintain normoxemia (PaO_2 55–80 mmHg). The PA_wDP was adjusted as lung compliance changed using chest radiographs for guidance with the goal of keeping the dome of the right hemi-diaphragm at the 9th rib in the midclavicular line. The chest radiograph was indicated after the initial respiratory stabilization and then occasionally, when FIO_2 of 0.40 or more was needed to maintain normoxemia and did not decrease after the raising of PA_wDP by 15%.

The pressure amplitude was adjusted to the lowest value consistent with normocapnia ($PaCO_2$ 35–45 mmHg). The patients were weaned to nCPAP when the following criteria were fulfilled: (1) PA_wDP 6.5 cmH_2O or less and FIO_2 0.30 or lower and (2) the infant has started to breathe spontaneously with good breath sounds audible during spontaneous breathing. Nasal CPAP of 2–3 cmH_2O with FIO_2 0.25 or lower maintaining normoxemia and PCO_2 55 mmHg or less was the criterion for weaning from nCPAP. Infants were weaned from oxygen supplementation when they were able to maintain oxygen saturation of 89% or more while breathing room air. During the acute phase of RDS, all randomized infants were ventilated by HFOV exclusively. The conventional mode of synchronized intermittent mandatory ventilation (SIMV, Infant Star, Infrasonics, San Diego, California) was only used when reintubation for recurrent apnea or late sepsis was required.

Surfactant administration

Natural porcine surfactant (Curosurf, Chiesi Farmateutici, Parma, Italy) at a dose 100 mg/kg body weight was given as a single bolus via the endotracheal tube within 1 min. Brief manual ventilation was performed after this dose to clear surfactant from the small airways.

Early administration

In this group, the surfactant was given immediately after intubation. Before administration, only 3–5 manual breaths were applied carefully with attention paid to using only the minimal necessary tidal volume, as judged by visual monitoring of chest wall movement. High-frequency oscillatory mode was initiated as soon as possible according to the procedure described above.

Delayed administration

Surfactant was given during HFOV if, after initial respiratory stabilization performed by adjusting the ventilatory parameters according to the HVS, the following criteria were reached: (1) FIO_2 0.35 or more, or (2) PA_wDP greater than 10 cmH_2O. Subsequent doses (up to four) of surfactant were administered if the PA_wDP had increased by at least 15% above the lowest value reached after the previous administration of surfactant and if the FIO_2 had not decreased below 0.35 or had increased more than 15% from the original value after the previous administration.

General care

The infants were moved immediately from the delivery room to the NICU, which is located next to the delivery room. The umbilical or radial artery was cannulated to measure systemic blood pressure and to obtain arterial blood samples. A chest radiograph was obtained to assess lung volume and the extent of lung disease. These procedures, including the initial blood gas determination, had to be completed within 3 h of delivery. Arterial blood samples were taken every 12 h and as clinically indicated in the acute phase of RDS. Pulse oximetry was used primarily to assess oxygenation in order to minimize blood loss in these extremely immature infants. Postnatal dexamethasone was considered when the oxygen requirement increased (FIO_2 0.35 or more) and the chest radiograph revealed dysplastic changes without clinical and laboratory signs of infection in infants older than 10 days. Dexamethasone treatment was started with the dose of 0.4 mg/kg per day divided into two doses and continued in decreasing dosage for 10 days. In some patients this treatment was repeated during the hospitalization period. No infant received more than two courses of steroids. Transcutaneous gas measurement was not used, to avoid the potential skin burns in these extremely premature infants.

Data collection and definitions

Gestational age was based on the obstetrical estimate. Prenatal steroid use was judged to have been completed if at least three doses of 12 mg dexamethasone were administered to the mother before delivery. The diagnosis of chorioamnionitis was made on the basis of histological examination of the placenta, rather than clinical signs and symptoms. All placentas were available for examination.

The duration of assisted ventilation was calculated as the length of time on HFOV and any other periods of assisted ventilation until final extubation. Time on nCPAP was counted separately. The total duration of oxygen supplementation was calculated from the sum of all periods of any technique of oxygen supplementation during the hospitalization and after discharge. The presence and severity of CLD at 28 days of age was evaluated by the radiographic scale of Toce [9]. The radiographs were evaluated by a radiologist unaware of treatment group assignment. Oxygen dependence at 36 weeks post conceptional age was the definition of CLD, our major outcome variable. Chest radiographs documented the occurrence of acute ventilator complications, such as pneumothorax and PIE. The presence of patent ductus arteriosus (PDA) was confirmed by echocardiography and the need for treatment was documented in the medical record. Craniosonography was performed in all patients on days 1, 3 and 10 of life and then weekly to assess the occurrence of IVH and PVL. The Papile classification was used for the grading of IVH [10]. A diagnosis of PVL was made only when cystic echolucencies were found in the cerebral white matter. Final diagnoses were confirmed by two specialists in craniosonography imaging who were not aware of patient group assignment.

Retinopathy of prematurity was classified according to the International ROP classification from 1987 [11]. The diagnosis of NEC was based on modified Bell's criteria (NEC was defined as IIa stage or higher) [12].

Sample size calculation and statistical analysis

On the basis of the data in extremely premature infants on HFOV in our previous trial, we could assume a further reduction of CLD or death at 36 post conceptional weeks from 31% to 10% with the combined early administration of surfactant and HFOV treatment during the acute phase of RDS. Power analysis revealed that an estimated 120 infants were needed to demonstrate this magnitude of difference with a power of 0.80 and significance level of 0.05. We decided to include 130 infants in a 30month period. Two interim analyses were planned when the sample size reached 40 and 80 infants. The stopping criteria were p less than 0.02 for the primary end point and p less than 0.01 for the secondary end points. The analysis was performed on the intention-to-treat principle.

The data were tested for normal and non-normal distribution. Normally distributed data are given as mean ± SD, non-normal data as median and confidence limits. Normally distributed variables (airway pressures, blood gases) were tested by analysis of variance for repeated measures. Non-normal data (duration of artificial ventilation, supplemental oxygen) were analyzed by the Wilcoxon rank sum test. Categorical outcome parameters were compared using the χ^2 test and Fisher exact test and continuous data by Mann-Whitney test. A p less than 0.05 was considered statistically significant for all tests. A logistic regression analysis was performed to investigate possible association between the results of the primary end point (oxygen use or death at 36 weeks) and the following variables: gestational age, birth weight, prenatal steroid use, gender, Apgar score, umbilical artery pH, mode of delivery, prolonged rupture of membranes (PROM) more than 12 h and chorioamnionitis. In addition, we examined a possible correlation between the statistically significant secondary outcome variables and baseline characteristics to eliminate potential sources of bias.

Results

Enrollment into the trial was stopped after the first planned interim analysis, because of a significantly higher rate of major adverse neuro-imaging abnormalities in the DEL group. From October 1997 to July 1999, there were 87 premature newborns with estimated gestational age less than 30 completed weeks of gestation that were

eligible to be entered into the randomized trial. All infants were born in the Perinatology Center of Prague, which is the level III maternity and neonatal center for Prague and Central Bohemia. Of the 87 eligible infants, 36 did not require intubation. Of these infants, 31 were treated with nCPAP and 5 only with supplemental oxygen. Eight infants were excluded: three were intubated later than 3 h after delivery, three were small for gestational age and two had congenital anomalies. Of the remaining 43 infants, 21 were randomly assigned to the early (EARL) group and 22 to the delayed (DEL) group. Seventeen infants in the EARL group and 18 infants in the DEL group needed intubation within 5 min of birth because of rapid development of signs of RDS in the delivery room. The others were intubated within 3 h after delivery. Demographic data of the randomized infants are presented in Table 1.

Gestational age, birth weight, gender, Apgar score, umbilical cord artery pH, percentage of prenatal steroid administration, cesarean sections, breech presentation and chorioamnionitis did not differ significantly between the two groups. The time of intubation was also similar, but the time of the first surfactant dose administration was significantly different between the two groups, consistent with the design of the trial.

Table 1 Demographic data, time of intubation and administration of first surfactant dose (*EARL* early, *DEL* delayed, *PROM* prolonged rupture of membranes)

	EARL group (n=21)	DEL group (n=22)	p value
Gestational age (weeks)	25.7±1.8	25.2±1.2	0.24
Birth weight (g)	734±184	741±130	0.98
Male gender	10/21 (48%)	9/22 (41%)	0.87
Apgar score (5 min)	8 (7.5; 8.5)	7 (6.3; 7.7)	0.06
Umbilical artery pH	7.27±0.03	7.24±0.10	0.34
Prenatal steroid use	10/21 (48%)	9/22 (41%)	0.66
PROM >12 h	7/21 (33%)	7/22 (32%)	0.56
Cesarean section	11/21 (52%)	9/22 (41%)	0.62
Breech position	3/21 (14%)	3/22 (14%)	0.86
Chorioamnionitis	13/21 (62%)	13/22 (64%)	0.75
Age at intubation (min)	3 (0; 27)	3 (0; 18)	0.21
Age at 1st surfactant administration (min)	5 (0; 17.5)	150 (85; 215)	0.014

Data given as means ± SD for parametric tests and medians (5; 95% confidence limits) for non-parametric tests

Pulmonary outcome

There were no significant differences in the number of doses of surfactant between the two groups, although the number of patients with one dose of surfactant was slightly lower in the DEL patients (12/21 vs 7/22, p=0.07) (Table 2). Only 3 (14%) of 22 patients in the DEL group did not receive any surfactant because they had not reached the criteria for its administration. The total duration of mechanical ventilation was similar in the two groups, as was the duration of the HFOV and SIMV periods when examined separately. There were also no significant differences in the duration of nCPAP support and supplemental oxygen use between the two groups. The incidence of air leaks was different (0/21 vs 3/22, p=0.07), but not significantly. Pneumothorax and PIE developed in the same patients of the DEL group. The evaluation of CLD by radiographic score at 28–30 days of life [Toce score of 1.75 (1.6; 1.9) vs 3 (2.8; 3.2), p=0.32] and oxygen use at 36 weeks (21%, 4/19 vs 47%, 7/15, p=0.11) also showed some differences, but these did not individually reach statistical sig-

Table 2 Respiratory and pulmonary outcome (*EARL* early, *DEL* delayed, *HFOV* high-frequency oscillatory ventilation, *SIMV* synchronized intermittent mandatory ventilation, *CPAP* continuous positive airway pressure)

	EARL group (n=21)	DEL group (n=22)	p value
Surfactant			
No. of patients with 1 dose	12/21 (57%)	7/22 (32%)	0.07
No. of patients with 2 doses	9/21 (43%)	11/22 (50%)	0.64
No. of patients with 3 doses	0	1/22 (5%)	0.32
No. of patients who did not receive surfactant	0	3/22 (14%)	0.23
Duration of mechanical ventilation (days)	8 (5; 13)	9 (6; 12)	0.80
HFOV	5 (3.8; 6.2)	5 (4; 6)	0.71
SIMV	0 (0; 2.5)	3 (0.7; 5.3)	0.86
Duration of nasal CPAP (days)	29 (25.5; 32.5)	24.5 (21; 28)	0.50
Supplemental oxygen (days)	57 (53.5; 60.5)	54.5 (48.5; 60.5)	0.36
Postnatal steroids	9/21 (43%)	10/22 (45%)	0.66
Air leaks	0	3/22 (14%)	0.07
Pneumothorax	0	3/22 (14%)	0.07
Pulmonary interstitial emphysema	0	3/22 (14%)	0.07
Chronic lung disease			
Radiographic score in 28–30 days of life (Toce scale)	1.75 (1.6; 1.9)	3 (2.8; 3.2)	0.32
Oxygen use at 36 weeks	4/19 (21%)	7/15 (47%)	0.11
Oxygen use or death at 36 weeks	6/21 (29%)	14/22 (64%)	0.021

Data given as medians (5; 95% confidence limits)

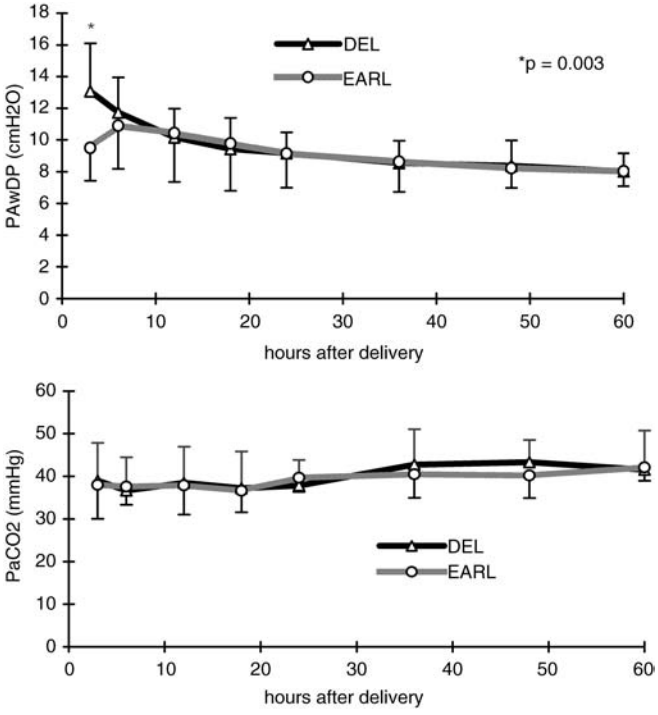

Fig. 1 Proximal airway distending pressure (PA_wDP; top panel) and $PaCO_2$ (bottom panel): comparison between EARL (*circles*) and DEL (*triangles*) groups for 60 h after the first arterial blood gas determination (3rd h after delivery). Values are means ± SD. On the top panel, PA_wDP in EARL group was lower significantly only in the 3rd h after delivery ($p<0.003$), during the next 3 h the difference resolved and in the subsequent 60 h PA_wDPs was the same. Third hour after delivery correlates with the first arterial blood gases determination after delivery. The bottom panel illustrates the normocapnic ventilation in the two groups during the 60 h after delivery

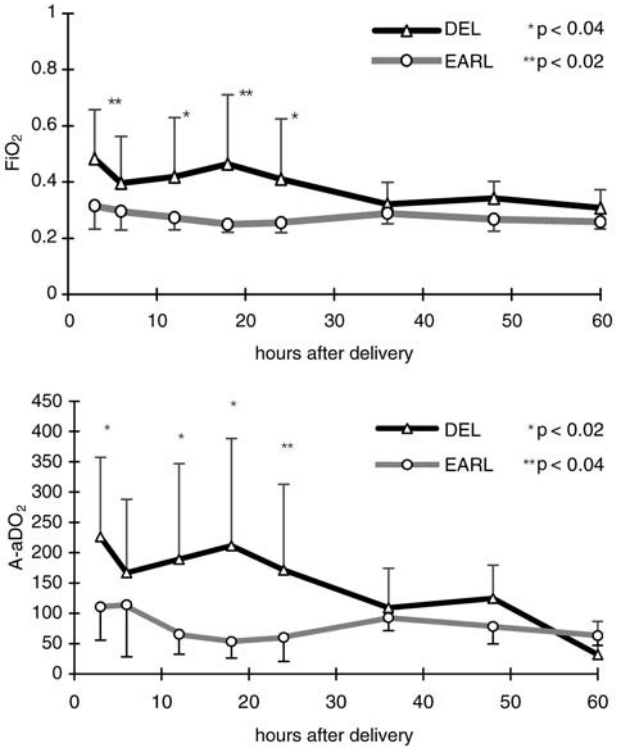

Fig. 2 Comparison of FIO_2 and A-aDO_2 between EARL (*circles*) and DEL (*triangles*) groups for 60 h after the first arterial blood gas determination (3rd h after delivery). The values shown are means ± SD. Lower values of FIO_2 and A-aDO_2, shown in the top and bottom panels, last up to 24th h after delivery, except the 6th h ($p<0.04$). This transitional lowering of both values could correspond to the effect of the first dose of surfactant administration in the DEL group (median is150 min after delivery). In the next evaluating time interval FIO_2 and A-aDO_2 are similar in the two groups

Table 3 Clinical outcome – early and late morbidity (*EARL* early, *DEL* delayed, *PDA* patent ductus arteriosus, *IVH* intraventricular hemorrhage, *PVL* periventricular leucomalacia, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis)

	EARL group (n=21)	DEL group (n=22)	p value
Mortality to discharge	2/21 (10%)	7/22 (32%)	0.13
PDA	9/21 (43%)	9/22 (41%)	1.0
IVH	9/21 (43%)	18/22 (82%)	0.008
IVH grade 1	5/21 (24%)	5/22 (23%)	0.93
IVH grade 2	3/21 (14%)	9/22 (41%)	0.051
IVH grade 3	1/21 (5%)	3/22 (14%)	0.31
IVH grade 4	0	2/22 (9%)	0.16
PVL	0	3/22 (14%)	0.23
IVH grade 1–2	8/21 (38%)	14/22 (64%)	0.10
IVH grade 3–4	1/21 (5%)	5/22 (23%)	0.11
IVH grade 3–4 or PVL	1/21 (5%)	8/22 (36%)	0.012
ROP >stage 2	5/21 (24%)	5/22 (23%)	0.93
Cryotherapy	4/21 (19%)	3/22 (14%)	0.63
NEC ≥ stage 2A	3/21 (14%)	9/22 (41%)	0.09
Hospital days[a]	99 (93.2; 104.8)	105 (99; 111)	0.25

[a] Data are medians (5%; 95% confidence limits)

nificance in this sample size. However, when the primary outcome of oxygen use or death at 36 weeks was compared, the EARL group had a significantly lower incidence of this combined outcome (6/21, 29% vs 14/22, 64%, p=0.021).

Clinical outcome

Unexpectedly, we found significant differences between the two groups in the incidence of IVH (9/21, 43%, in the EARL group vs 18/22, 82% in the DEL group; p=0.008) (Table 3). It was this adverse experience that led to the early termination of the trial. The combination of cranial morbidity, such as IVH grade 3+4 or PVL, (of prognostic significance) was also significantly lower in the EARL group (1/21, 5% vs 8/22, 36%, p=0.011). Furthermore, mortality to discharge (2/21, 10% vs 7/22, 32%; p=0.074) and the incidence of NEC, stage 2A or higher (3/21, 14%, vs 9/22, 41%; p=0.052) also tended to be lower in the EARL group, but this did not reach

statistical significance in this small sample size. The incidence of PDA requiring treatment, ROP higher than stage II, need for cryotherapy and hospital days were similar in the two groups.

Acute phase of respiratory distress syndrome

The impact of the timing of the initial administration of surfactant on ventilatory variables during the acute phase of RDS is illustrated in Figs. 1 and 2. The PA_wDP in the EARL group was lower, compared to the DEL group 3 h after delivery, but the difference disappears after the administration of surfactant in the DEL group. Ventilation in the two groups was comparable and $PaCO_2$ was within the target range. The FIO_2 and A-aDO_2 were lower in the EARL group during the first 24 h after delivery (Fig. 2, top and bottom panels; $p<0.04$).

Regression analysis

The logistic regression analysis did not confirm any possible influence of gestational age and the other independent variables tested (demographic data) on the significantly different dependent variables, such as oxygen use or death at 36 weeks and the incidence of IVH.

Discussion

Routine use of HFOV appears to be safe and effective when a high volume strategy (HVS) and surfactant treatment are used [13]. Early selective surfactant administration given to infants with RDS requiring assisted ventilation leads to a decreased risk of acute pulmonary injury and decreased risk of neonatal mortality and CLD, compared to delayed treatment, especially in premature infants in whom surfactant insufficiency is very likely [1, 2]. In our previous trial, the very early use of HFOV, with surfactant administration only if specific criteria were fulfilled after optimization of ventilatory settings, decreased the incidence of CLD in comparison with the same procedure on conventional ventilation (CV) [7]. In contrast, in Gerstmann's trial, which demonstrated the benefit of HFOV on reducing the incidence of CLD, the surfactant had been administered before the start of HFOV [8].

Although our trial was stopped because of the higher incidence of adverse effects in the DEL arm, the primary outcome variable also came very close to meeting the stopping criterion ($p<0.02$). In the first interim analysis of our present trial, a lower incidence of the combined outcome variable of CLD or death was found in the early surfactant patients in whom surfactant was administered immediately after intubation and before initiation of HFOV with a p of 0.021. Furthermore, the radiographic score at 28–30 days of life tended to be lower in the EARL group. In the acute phase of RDS, higher PA_WDP was required in the DEL group, compared to the EARL group, only during the 6 h after delivery, but the differences in FIO_2 and A-aDO_2 oxygenation lasted nearly 24 h, even though the high volume lung recruitment strategy was employed in both groups with the intention of avoiding overinflation. These findings support the hypothesis that the short period after delivery, during which early surfactant administration can facilitate more rapid optimization of ventilatory settings to reach optimal lung inflation, plays a very important role in the pulmonary outcome of extremely premature neonates. The nearly 24h period of better oxygenation in the EARL group, despite initially lower PA_wDP, could be explained by more homogeneous lung inflation and better ventilation-perfusion matching in this group.

The higher incidence of intraventricular hemorrhage found in the DEL group was unexpected. Because the study was stopped before the projected number of subjects had been enrolled, the results should be interpreted with caution. It is conceivable that the incidence of intraventricular hemorrhage in our DEL group is high coincidentally or is related to some unrecognized difference between the two groups of patients. The incidence of intraventricular hemorrhage grades 3–4 in the DEL group is substantially higher than the HFOV group in our previous comparative trial (23% vs 0%), while the rate of grade 1–2 IVH is similar (64% vs 68%) [7]. The HFOV group in our previous trial was a little more mature and, furthermore, it is likely that the zero incidence of major intraventricular hemorrhage in the earlier trial was fortuitous. Although it appears high, the incidence of IVH grades 3–4 in our DEL patients is nearly the same (23% vs 21%) as in the conventional group in the recent prospective randomized multicenter trial of Moriette et al. when examining the group of less than 28 weeks postmenstrual age, which appears to be similar to our patients [14]. More importantly, the incidence of IVH grades 3–4 was even higher in the HFOV group in the Moriette trial when compared to our DEL group (32% vs 23%). We believe that the relatively high overall incidence of IVH is consistent with the extreme immaturity of this selected study population. Perhaps more impressive is the strikingly low incidence of serious intracranial morbidity, i.e. grade 3–4 IVH or periventricular leucomalacia (PVL) in the EARL group.

The mechanism(s) responsible for the apparent positive influence of early surfactant administration are unclear. The influence of the timing of surfactant administration on the incidence of serious intracranial morbidity has not been elucidated. The Soll and Yost meta-analyses do not support a significant effect on the risk of severe IVH associated with prophylactic or early selective surfactant administration despite the Gortner et al. and Dunn et al. trials, which reported a tendency toward higher oc-

currence of severe IVH with prophylactic or early surfactant administration [1, 2, 15, 16]. On the other hand, other authors have reported opposite results [17, 18]. The data from the multicenter retrospective cohort study by Brown et al. support our findings; using an early treatment strategy resulted in improved survival in patients at risk for developing hyaline membrane disease and appeared to decrease the likelihood of developing severe IVH [19].

The influence of HFOV on the incidence of IVH has been controversial as well. The pre-surfactant era HIFI study, that was criticized for its lack of a well-defined ventilator strategy, reported an increased risk of severe IVH and PVL in HFOV patients [20]. Because of its large size, the study dominates all meta-analyses of HFOV. The meta-analysis of Clark et al., which included nine studies that compared high-frequency and CV in premature neonates suggested that high-frequency ventilation is not associated with an increased occurrence of IVH or PVL [21]. This is further supported by Bhuta and Henderson-Smart's review, in which the studies that employed a high-volume strategy are evaluated separately [13]. The authors concluded that, when the high-volume strategy is used, there was no increase in severe IVH or PVL. There is ample evidence that hypocapnia with or without high-frequency ventilation is strongly associated with a marked increase in severe neuro-imaging abnormalities [22, 23]. However, severe hypocapnia was not present in our study.

Our patients were at high risk for the development of IVH. They were all extremely premature, substantially more so than those in any of the other studies published, and there was a high incidence of chorioamnionitis. Only those who needed early intubation for severe RDS were included, because we manage the less severe cases of RDS with early CPAP. A retrospective evaluation of circulatory status (comparison of vasoactive amine therapy and frequency of volume expansions) showed that there were no significant differences between the two groups during the first 5 days after delivery.

In summary, the results of our small trial suggest that, when compared to delayed dosing, early administration of surfactant followed by HFOV facilitates and accelerates respiratory stabilization during the acute phase of RDS and may reduce the incidence of CLD or death in extremely premature infants with primary surfactant insufficiency. Furthermore, delayed dosing was associated with a greater incidence of serious intracranial morbidity in these extremely premature infants. We speculate that early surfactant administration followed by HFOV can decrease the development of IVH by a more rapid improvement of ventilatory and circulatory status immediately after delivery in extremely premature neonates with severe RDS. The period immediately after delivery may be a very critical time, affecting mortality, morbidity and the long-term development of these infants. However, in view of the early termination because of safety concerns, further studies are required to substantiate these findings.

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