RESEARCH PAPER

Early Rescue Administration of Surfactant and Nasal Continuous Positive Airway Pressure in Preterm Infants <32 Weeks Gestation

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Objective: This study reports our institutional experience on the outcome after prophylactic and early rescue endotracheal instillation of surfactant within 20 minutes of birth, followed by extubation and nasal continuous positive airway pressure (NCPAP) in preterm infants <32 weeks gestational age.

Patients and methods: A total of 142 infants were prospectively studied (42, gestational age from 23 to 27 and 100, from 28 up to 32 weeks). All infants were electively intubated for administration of 200mg/kg porcine isolated surfactant (Curosurf, Chiesi Farmaceutici SPA, Parma, Italy) as soon as practicably possible (within 20 min after birth) and NCPAP was then initiated.

Results: Extubation and switch to NCPAP at 6h was successful in 6/42 (14.3%) infants less than 28 weeks gestational age and 75/100 (75%) infants 28-32 weeks gestational age. Out of 81 infants that were successfully extubated, 76 (93.83%) never required re-ventilation. At 96h of age, need for continuing intubation and ventilation was required by 6/38 (15.8%) alive infants <28 weeks gestational age and 8/100 (8%) infants 28-32 weeks gestational age. Mean duration of NCPAP post-extubation was 38±20 hours for infants 23-27 wks and 29±15 hours for infants 28-32 wks gestational age. The mortality rate was 2.81% (4/142).

Conclusion: Implementation of prophylactic or early rescue administration of surfactant with NCPAP in infants at high risk for developing RDS in neonatal ICU is a safe modality of respiratory support in preterm infants.

Key words: *Greece, Management, Nasal continuous positive airway pressure, Outcome, Prematurity, Respiratory distress syndrome, Surfactant.*

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Surfactant replacement therapy in Respiratory distress syndrome (RDS) improves lung function, decreases mortality and also results in a better long-term neurodevelopmental outcome [1,2]. For infants at high risk for RDS, prophylactic intubation within 15 minutes of age for surfactant administration followed by brief mechanical ventilation with planned extubation to nasal continuous positive airway pressure (NCPAP) within one hour has been shown to significantly improve survival and reduce the incidence of bronchopleural dysplasia (BPD) or death [3-5].

We report our institutional experience on the outcome after prophylactic and early rescue endotracheal instillation of surfactant within 20 minutes of birth of followed by extubation to NCPAP in preterm infants of <32 weeks gestational age.

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METHODS

This prospective study was conducted in a level III neonatal intensive care unit (NICU) following approval by the local ethics committee, between June 2006 and May 2008. All babies born between

23 and 31 weeks of gestational age were eligible for entry. Infants with structural cyanotic congenital heart disease, severe congenital malformations, pulmonary hypoplasia, pneumothorax and Apgar scores less than 3 at 5 min were excluded. Infants under or equal to 27 weeks gestation received prophylactic surfactant within 15 minutes of birth. In infants at risk of RDS with gestational age between 28 and to 32 weeks, surfactant was administered if a FiO_2 ≥40 was needed to reach SpO_2 between 85 and 93% or they exhibited signs of moderate to severe respiratory distress at age 20 min (early rescue surfactant treatment). Infants who were administered surfactant either prophylactic or as early rescue treatment were then switched to NCPAP as early as possible depending on their respiratory condition.

After parental consent was obtained (either prenatally or early postnatally), infants were electively intubated for administration of 200 mg/kg porcine isolated surfactant (Curosurf, Chiesi Farmaceutici SPA, Parma, Italy) through the tracheal tube as soon as practicably possible (within 20 min after birth). An umbilical artery access was gained and a chest *X*-ray performed. They were extubated within one hour of birth to NCPAP. Weaning strategies for ventilation involved a peak inspiratory pressure (PIP) ≤18cm H_2O, FiO_2 <40% and rates of 10-20 breaths per minute. The NCPAP was given through nasal prongs using the Medin Medijet NCPAP generator (Medin Innovations GmbH, Germany). The initial pressure of CPAP was 6cm H_2O increasing up to a maximum of 8cm H_2O if required aiming to recruit the maximum number of alveoli. The NCPAP was continued unless any of the following criteria was met (FiO_2 >70%, pH<7.2, PaO_2<50mmHg, significant apnea). Echocardiography was performed in all infants at 24-72 hours of life. Cranial ultrasonography was performed within the first 48 hours of life and repeated at 7 days.

The primary outcome in this study was the need for mechanical ventilation at 6 hours of birth. Secondary outcomes included the incidence of bronchopulmonary dysplasia (BPD) defined as need for oxygen at 28 days of age, the incidence of chronic lung disease (CLD) (need for oxygen at 36 weeks postmenstrual age), death before discharge, incidence of airleak syndromes (pulmonary interstitial emphysema, pneumothorax), intraventricular hemorrhage, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP) [6,7]. All infants were followed up for a maximum of two years.

Clinical characteristics and data are described as median values and range, and as rates and percentages. Data were stored and analyzed using the SPSS 11.5 statistical software (SPSS, Chicago, Illinois).

RESULTS

A total of 398 infants of 23-32 weeks gestation were admitted during the study period. Of these, 256 were not eligible (***Fig.* 1**). Remaining 142 infants were categorized into two subgroups, gestational age from 23 to 27 weeks (*n*=42) and from 28 up to 32 weeks (*n*=100). The demographic and clinical characteristics of all infants enrolled in the study are depicted on ***Table* I.**

Extubation and switch to NCPAP at 1h was successful in 3/42 (7.1%) infants less than 28 wk gestation and in 72/100 (72%) infants 28-32 wk gestational age. At 6h the proportion of extubated infants was 6/42 (14.3%) and 75/100 (75%) respectively. Out of 81 infants that were successfully extubated at 6h, 76 (93.83%) never required re-ventilation. A total of 5 infants required reintubation. Two infants (one 27 wks gestational age and one 31 wks) required re-ventilation within the first 12h for recurrent apnea. Three infants >28 wks gestational age required re-ventilation after more than 48h due to septicemia. Four extremely premature infants (<25 wks gestational age) died within the first 48h of life, 3 due to sepsis and 1 due to cardiopulmonary failure.

At 96h of age, 6/38 (15.8%) alive infants <28 wks gestational age and 8/100 (8%) infants 28-32 wk required continuing intubation and ventilation. Mean duration of NCPAP post-extubation was 38 ± 20 hours for infants 23-27 wks and 29 ± 15 hours for infants 28-32 wks gestational age. All infants who remained intubated at 96h had received antenatal steroid therapy and almost half of them 6/14 (42.8%) were exposed to chorioamnionitis. Supplemental surfactant was administered in 8/14 infants who

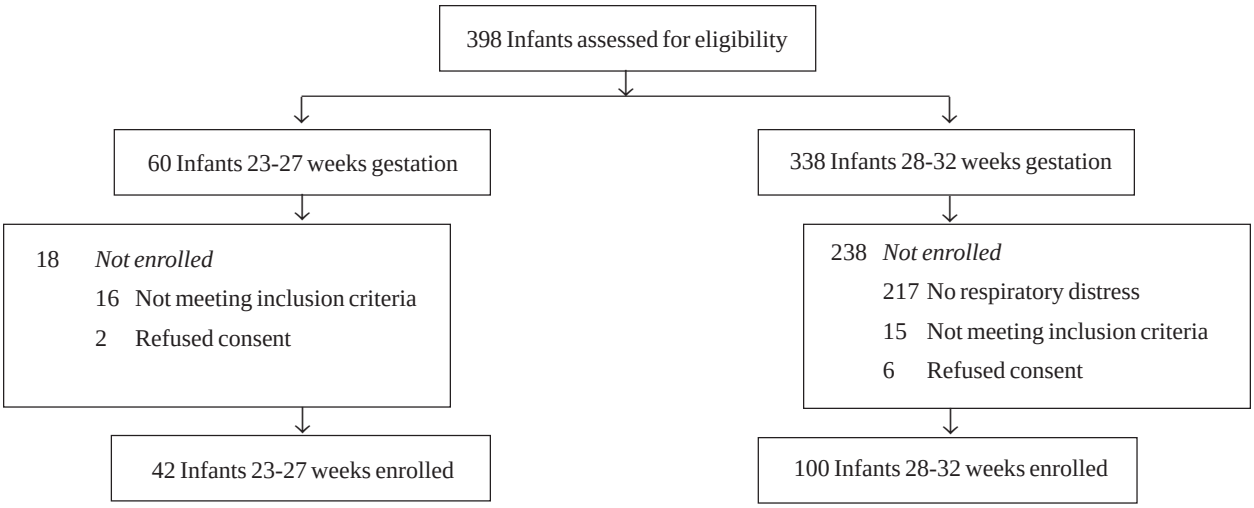

FIG. 1 *Study flow chart.*

remained intubated at 96h. Perinatal asphyxia was evident in one 27-week-old infant who remained intubated at 96h and received additional dose of surfactant. Neonatal sepsis was the main reason for reintubation or death and was proved in 16/142 (11.2%) infants. Secondary adverse outcomes for both groups are presented in ***Table* II**.

DISCUSSION

In this study, we implemented the INSURE (INtubate SURfactant Extubate to CPAP) as prophylactic therapy in infants with gestational age equal or less than 27 weeks and in preterm infants at high risk for developing RDS as early rescue treatment. This proved to be a safe and successful strategy since only 5 out of 81 infants that were successfully extubated at 6h (6.17%) required reintubation. We also showed that the number of infants remaining intubated and ventilated at 24h and 96h of age were low (19.85% and 10.14%, respectively). These results are in agreement with those previously reported with NCPAP [8-12].

TABLE I CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF STUDY INFANTS

Characteristic	Gestational age 23-27 *(n*=42*)*	Gestational age 28-31 *(n*=100*)*
Gender, male	20	52
Birthweight (g)	950 (460-1400)	1350 (900-2080)
Gestational age (wk)	25	30
Antenatal steroids given	38 (90%)	83 (83%)
Peak inspiratory pressure (cm H_20)	18 (14-26)	17 (15-25)
Arterial blood pH at 1h	7.34 (7.12-7.51)	7.33 (7.2-7.46)
FiO_2 at study entry	0.25 (0.21-1)	0.5 (0.4-1)
FiO_2 at 6h	0.22 (0.21-1)	0.25 (0.21-1)
FiO_2 at 24h	0.21 (0.21-1)	0.22 (0.21-1)
Oxygenation index	7.8 (2.9-27.8)	7.9 (3.3-26.6)
Apgar at 1 min	6 (2-9)	7 (2-9)
Apgar at 5 min	8 (2-9)	9 (5-10)
Small for gestational age	7 (16.7%)	14 (14%)

All values expressed as median (range).

TABLE II PRIMARY AND SECONDARY OUTCOMES IN THE STUDY INFANTS

	Gestational age 23-27 wk (*n*=42)	Gestational age 28-31 wk (*n*=100)	Total (*n*=142)
Extubation at 1h	3 (7.1%)	72 (72%)	75 (52.8%)
Extubation at 6h	6 (14.3%)	75 (75%)	81 (57%)
Death	4 (9.5%)	0	4 (2.81%)
Hours ventilated (mean)	47.6	17.6	26.5
Oxygen requirement at 28 d	20 (47.6%)	4 (4%)	24 (16.9%)
36wk post-conceptional age	11 (26.2%)	4 (4%)	15 (10.6%)
Air leak	1 (2.4%)	0	1 (0.7%)
IVH>II	3 (7.1%)	1 (1%)	4 (2.8%)
PVL	0	2 (2%)	2 (1.45)
ROP>II	7 (16.7%)	0	7 (4.9%)
PDA	2 (4.7%)	4(4%)	6 (4.2%)
NEC	0	1 (1%)	1 (0.75)

IVH: intraventricular hemorrhage; PVL: periventricular leucomalacia; ROP: retinopathy of prematurity; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; All values are presented as numbers (percentage).

An important aspect of this study was the successful application of INSURE treatment in very small preterm infants. It is encouraging that a significant number of very preterm infants can benefit from this strategy. Our results also confirm that NCPAP is a safe method of ventilation and an important factor in the reduction of aggressive ventilation and prolonged oxygen therapy decreasing the associated risk. This is in concordance with earlier studies [8-10,13,14].

The incidence rate of retinopathy of prematurity (ROP) is low in our study, confirming the reported beneficial result of the combination of prophylactic surfactant with NCPAP on ROP [9]. Apart from gestational age, there are other factors important in the etiology of ROP such as fluctuations of PaO_2, hyperoxia, pneumothorax and time spent on ventilator [15]. Prophylactic and early administration of surfactant with NCPAP results in reduced need for mechanical ventilation, thereby avoiding fluctuations in PaO_2 and development of air leak syndromes in premature infants. Moreover, the incidence of PDA is lower in our study compared with other studies [8,11,16]. This can be attributed to the short duration of mechanical ventilation and its effects, confirming the advantages of the application of NCPAP. Similarly, the reported incidence of PVL in our study was low and similar to earlier studies [16].

The neonatal mortality rate in our study is 2.8%, that is in accordance with similar studies reporting on prophylactic surfactant therapy [8-10]. This outcome might also reflect the low incidence of NEC and III-IV grade IVH, which constitute major causes of death in premature infants.

Our results regarding oxygenation at 6h and 24h after the prophylactic use of surfactant indicate that there was consistently low requirements for supplemental oxygen and low incidence of severe RDS. Moreover, the incidence of pneumothorax and pulmonary emphysema air leak syndromes is very low in our study (0.7%) which is an expected result of elimination of mechanical ventilation. These findings are in accordance with trials reporting on improvement of gas exchange and the severity of RDS as well as for air leak syndromes after prophylactic surfactant compared with rescue therapy [17].

In conclusion, implementation of prophylactic or early rescue administration of surfactant with NCPAP in infants at high risk for developing RDS in

WHAT IS ALREADY KNOWN?

- Prophylactic or early rescue administration of surfactant and NCPAP are beneficial in reducing lung injury.

WHAT THIS STUDY ADDS?

- Prophylactic or early rescue administration of surfactant and nasal continuous positive airway pressure in preterm infants is an effective strategy without adverse effects on outcome and can be applied to the majority of very preterm infants.

neonatal ICU provides a significantly favorable outcome.

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