

Early or later prophylactic INSURE in preterm infants of less than 30 weeks' gestation

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We aimed to determine whether an early prophylactic INSURE strategy combined with early nasal continuous positive airway pressure (nCPAP) treatment could decrease the subsequent need for mechanical ventilation (MV) compared to the administration of surfactant prophylaxis later, at the 15th minute after birth, combined with early nCPAP. Infants born at <30 weeks' gestation were randomized to receive surfactant prophylaxis immediately or at the 15th minute after birth. All infants received 100 mg/kg poractant alpha, were ventilated with a T-piece resuscitator and were extubated to nCPAP if they had sufficient respiratory drive. Forty infants were analyzed in each group. Ten (25%) infants in the early prophylactic INSURE group, and 13 (32.5%) infants in the later prophylactic INSURE group could not be extubated after surfactant administration in the delivery room. Among the infants who were initially extubated to nCPAP after surfactant administration, 6 in the early prophylactic INSURE group and 4 in the later prophylactic INSURE group needed intubation for MV within the first 3 days of life (20% vs. 16.7%; P=0.73). The duration of total respiratory support (CPAP plus MV) of infants who were intubated within the first 3 days of life was shorter in the early prophylactic INSURE group than in the later prophylactic INSURE group (median: 96 h vs. 309 h; P=0.038). The incidence of all neonatal morbidities and mortality and the duration of hospitalization were similar between the groups. Our study did not demonstrate superiority of early surfactant prophylaxis combined with early nCPAP to the later administration of prophylactic surfactant with early nCPAP; however, it did detect an absolute difference in the primary outcome: need for MV within the first 3 days of life.

Key words: mechanical ventilation, premature infants, prophylaxis, respiratory distress syndrome, surfactant.

Surfactant, continuous positive airway pressure (CPAP) and mechanical ventilation (MV) are the mainstays in the management of respiratory distress syndrome. Surfactant replacement treatment has decreased the incidence of death, pneumothorax and intraventricular hemorrhage, and improved survival of preterm infants.¹ A systematic review of studies that compared intubation and early surfactant therapy followed by extubation to CPAP (INSURE) with later selective surfactant treatment followed by MV showed a reduced need for MV, and a lower incidence of air leak syndrome and

bronchopulmonary dysplasia (BPD).²

All infants must progress quickly from a fluid-filled lung to air breathing at birth. Preterm infants have amplified difficulties with adapting to air breathing and often need assistance for the transition. Respiratory resuscitation of preterm infants in the delivery room within the first 15 minutes of life is one of the factors that can adversely affect the developing lung.³⁻⁵

Preterm lungs ventilated rapidly without surfactant will be injured. Surfactant treatment prior to initiation of ventilation will prevent

much of the injury through a variety of mechanisms.^{6,7} It has been shown in animal studies that surfactant is distributed more uniformly to the lung when administered at birth because it mixes with fetal lung fluid, which increases the volume and negates gravity, and thus the process takes place more rapidly. It has also been shown that the use of positive end-expiratory pressure (PEEP) during initiation of ventilation improves recruitment of functional residual capacity and oxygenation.^{8,9} Thus PEEP and surfactant use are two relevant clinical variables that should decrease lung injury from the initiation of ventilation in the surfactant-deficient preterm lung.

In a previous multicenter trial, which compared immediate bolus and delayed postventilatory aliquot strategies for surfactant prophylaxis, similar survival rates to discharge to home were demonstrated, but beneficial effects of postventilatory aliquot strategy on prolonged oxygen requirement were also seen.¹⁰

We decided to investigate an intervention involving the early administration of prophylactic INSURE immediately after birth. Our primary aim was to let the surfactant mix with the fetal lung fluid and reach the alveoli before the potential onset of lung injury created by the initial administration of positive pressure ventilation in the delivery room (DR).

This study was designed to determine whether the early prophylactic INSURE procedure could decrease subsequent need for intubation and mechanical ventilation (MV). The clinical outcomes of these patients were compared with those of a group of patients who were administered later prophylactic INSURE, at the 15th minute after birth.

Material and Methods

Study design

This prospective randomized trial was conducted in a single neonatal intensive care unit (NICU) between December 2009 and December 2011. Our unit is a level III NICU with 20 incubators and 400 annual admissions.

Infants born <30 weeks' gestation were enrolled. We excluded outborn infants and infants with lethal malformations. Parental consent was obtained for potential study participants before delivery.

The study protocol was approved by the Ethics Committee of the Ankara University Faculty of Medicine. The study has been registered at www.clinicaltrials.gov, as NCT01294852.

Randomization

Infants were assigned by randomization to receive surfactant prophylaxis early, with the first breath, or later, at the 15th minute after birth. Study group assignments were placed in opaque, numbered, sealed envelopes that were opened by research personnel. Due to the nature of the intervention, we could not blind the timing of surfactant administration. Therefore, the team doing the treatment was aware of the group assignment.

Study intervention/procedures

Enrolled infants assigned to the early prophylactic INSURE group were briefly intubated for surfactant administration as soon as possible after birth; infants assigned to the later prophylactic INSURE group received surfactant at the 15th minute after birth. Natural surfactant [porcine (Curosurf; Chiesi Farmaceutici, Parma, Italy)] was administered in a dose of 100 mg/kg in one aliquot. Positive pressure ventilation was administered with a T-piece system (Neopuff Infant Resuscitator; Fisher and Paykel Healthcare, Auckland, New Zealand). After completion of surfactant administration, infants in both groups were extubated to nasal CPAP (nCPAP) through binasal prongs using a flow-dependent system (IFD-Infant Flow Driver; Electro Medical Equipment Ltd, Brighton, Sussex, UK), provided they had sufficient respiratory drive. Extubation failure was defined as occurring when an infant could not be extubated due to lack of sufficient respiratory drive.

A neonatology attending physician or fellow and a senior pediatric assistant attended the delivery of all infants included in the study. Sedation was not used prior to intubation.

Initial CPAP pressure was 5 cm of H₂O. CPAP pressure was titrated according to the effort of breathing and the oxygen requirements, with an oxygen saturation target of 85% to 92%. Maximum acceptable settings were CPAP pressure of 7 cm of H₂O along with a fraction of inspired oxygen (FiO₂) of 0.4.

In both groups, a second dose of surfactant

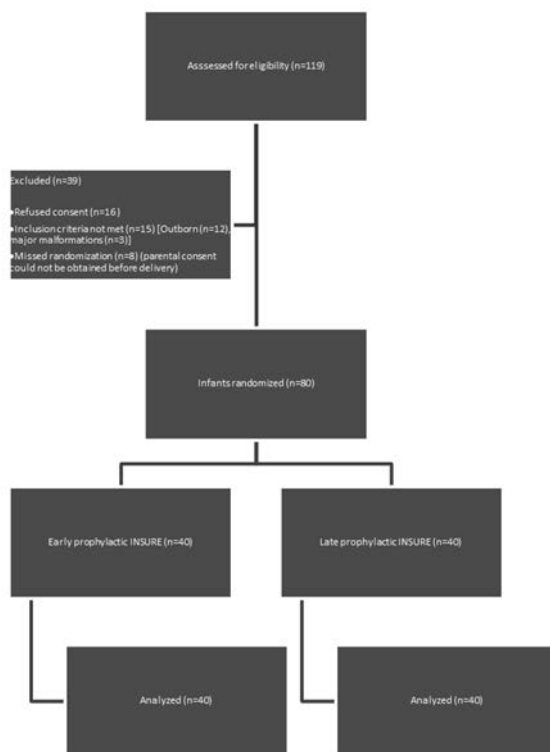


Fig. 1. Trial profile.

of 100 mg/kg was given 6 hours after the first application upon clinical deterioration (respiratory acidosis, FiO_2 of >0.4).

Outcomes

The primary outcome was the need for MV within the first 3 days of life. Indications for intubation and MV were: requirement of CPAP pressure of >7 cm of H_2O , and /or FiO_2 of >0.4 to maintain oxygen saturation between 85% to 92%; respiratory acidosis, defined as partial pressure of carbon dioxide >65 mmHg and pH <7.2 on arterial blood gas sample;

recurrent/severe apnea defined as >4 episodes per hour; or need for bag mask ventilation >2 times per hour.

Secondary outcomes included neonatal mortality, pneumothorax, pulmonary hemorrhage, patent ductus arteriosus (PDA) requiring medical or surgical treatment, necrotizing enterocolitis (stage 2 or greater according to modified Bell's staging), intraventricular hemorrhage ($>$ grade 2 according to the Papille classification), retinopathy of prematurity greater than stage 2 as defined in the international classification, postnatal use of systemic corticosteroids, BPD diagnosed on the basis of the National Institutes of Child Health and Development diagnostic criteria¹¹, duration of total respiratory support and length of hospitalization. Duration of respiratory support was defined as the duration of nCPAP or MV or MV plus nCPAP that infants received.

Statistical analysis

The historical data of our unit from the period January 2008-September 2009 revealed that 53% of infants of <30 weeks' gestation who received prophylactic surfactant within 15 minutes after birth and could be extubated in

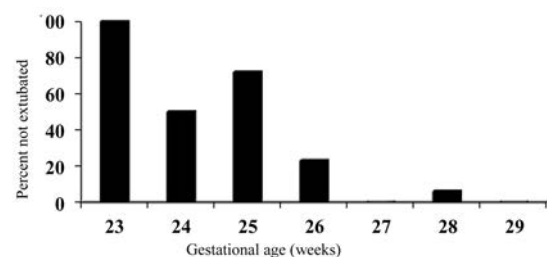


Fig. 2. Percentage of infants at each gestational week who could not be extubated to nCPAP in the DR.

Table I. Baseline Demographic and Clinical Characteristics of the Infants

	Early prophylactic INSURE (n=40)	Late prophylactic INSURE (n=40)	P
Gestational week, mean $\pm$ SD	26.9 $\pm$ 1.9	27 $\pm$ 2.2	0.83
Birth weight, g, mean $\pm$ SD	958 $\pm$ 283	915 $\pm$ 316	0.52
Male gender, n (%)	24 (60)	20 (50)	0.36
Antenatal steroids, n (%)	29 (72.5)	25 (62.5)	0.34
Cesarean delivery, n (%)	30 (75)	29 (72.5)	0.79
Multiple births, n (%)	22 (55)	22 (55)	1.0
5-minute Apgar, median (min-max)	8 (5-9)	8 (3-10)	0.1
Chorioamnionitis, n (%)	15 (37.5)	12 (30)	0.6

Table II. Infants Extubated/Not Extubated to nCPAP after Surfactant Administration in the DR

	Early prophylactic INSURE (n=40)	Late prophylactic INSURE (n=40)	P
Extubated to nCPAP after surfactant, n (%)	30 (75)	27 (67.5)	0.4
Gestational week, mean $\pm$ SD	27.6 $\pm$ 1.5	28.3 $\pm$ 1.5	0.08
Birth weight, g, mean $\pm$ SD	1040 $\pm$ 257	1050 $\pm$ 291.3	0.8
Not extubated after surfactant, n (%)	10 (25)	13 (32.5)	0.6
Gestational week, mean $\pm$ SD	25 $\pm$ 1.7	24.4 $\pm$ 1	0.3
Birth weight, g, mean $\pm$ SD	711 $\pm$ 212	633 $\pm$ 118	0.2

DR. delivery room

the DR were intubated in first 3 days of life, using criteria similar to those in this study. We calculated a sample size on the assumption that early prophylactic surfactant administration with the first breath would decrease this outcome to 20%. With 80% power and a 2-sided significance level of 0.05, 40 infants would be needed in each group.¹²

Clinical characteristics of two groups were described using mean and standard deviation values, and rates and percentages. Categorical variables were compared using the χ^2 test, while continuous variables were analyzed using Student's t test for normal distributions and the Mann-Whitney test for skewed distributions. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 15 for Windows; statistical significance was set at a two-sided P value of 0.05.

Results

During the study period, 119 infants with a gestational age of <30 weeks were assessed for eligibility. Eighty infants were enrolled, 40 in the early prophylactic INSURE group and 40 in

the later prophylactic INSURE group (Fig. 1). Baseline characteristics were similar between the two groups (Table I).

Two neonatologists and four neonatal fellows attended the delivery of all study infants for successful administration of surfactant and DR interventions in each case. We did not record any intubation failures on the first attempt, or any adverse events during intubation or surfactant administration.

Ten (25%) infants in the early prophylactic INSURE group and 13 (32.5%) infants in the later prophylactic INSURE group could not be extubated after surfactant administration in the DR because of insufficient respiratory drive. The gestational ages and birth weights of those infants were significantly younger/lower than those of the extubated infants in the DR ($p<0.001$) (Table II).

Irrespective of the time of prophylactic surfactant administration (early or later), 100% of the infants of 23 weeks' gestational age, 50% (2 of 4) of the infants of 24 weeks' gestational age, 72% (8 of 11) of the infants of 25 weeks' gestational age, 23% (3 of 13)

Table III. Clinical Characteristics of Infants Needing MV in the First 3 Days of Life

	Early prophylactic INSURE (n=6)	Late prophylactic INSURE (n=4)	P
Gestational week, mean $\pm$ SD	26.7 $\pm$ 2.1	27.5 $\pm$ 1	0.4
Birth weight, g, mean $\pm$ SD	830 $\pm$ 263	799 $\pm$ 272	0.6
Male gender, n (%)	2 (33)	2 (50)	1.0
Delivery type, cesarean, n (%)	2 (33)	3 (75)	0.2
5-minute Apgar, median	8	8	0.8
Antenatal steroids, n (%)	3 (50)	4 (100)	0.2
Intubation time, hours, median (range)	24 (6-42)	54 (6-64)	0.1

Table IV. Respiratory Support in the Study Group

	Early prophylactic INSURE	Late prophylactic INSURE	P
Infants extubated in the DR	n=24	n=23	
Duration of CPAP, h, median (range)	9 (1-144)	12 (2-144)	0.69
Infants not extubated in the DR	n=10	n=13	
Duration of MV, h, median (range)	50 (4-144)	54 (4-720)	0.64
Infants extubated in the DR and intubated in the first 3 days of life	n=6	n=4	
Duration of CPAP plus MV, h, median (range)	96 (36-216)	309 (140-480)	0.038
Infants receiving a second dose of surfactant, n (%)	8 (20)	11 (27.5)	0.4

DR: delivery room, CPAP: continuous positive airway pressure, MV: mechanical ventilation,

Table V. Secondary Outcomes among the Infants

	Early prophylactic INSURE (n=40)	Late prophylactic INSURE (n=40)	P
Pneumothorax, n (%)	0	0	-
Pulmonary hemorrhage, n (%)	2 (5)	3 (7.5)	0.6
Patent ductus arteriosus, n (%)	9 (22.5)	12 (30)	0.4
Necrotizing enterocolitis, n (%)	8 (20)	8 (20)	1.0
Intraventricular hemorrhage, n (%)	4 (10)	7 (17.5)	0.3
Retinopathy of prematurity, n (%)	3 (7.5)	5 (12.5)	0.7
Postnatal systemic steroids, n (%)	3 (7.5)	4 (10)	0.6
Bronchopulmonary dysplasia, n (%)	5 (12.5)	3 (7.5)	0.4
Hospitalization duration, d, mean $\pm$ SD	50 $\pm$ 18	49 $\pm$ 20	0.8
Mortality, n (%)	16 (40)	15 (37.5)	0.4

of the infants of 26 weeks' gestational age and 6% (1 of 16) of the infants of 28 weeks' gestational age could not be extubated in the DR. All infants of 27 and 29 weeks' gestational age could extubated to nCPAP (Fig. 2).

Among the infants who were extubated to nCPAP after surfactant administration, 6 infants in the early prophylactic INSURE group and 4 infants in the later prophylactic INSURE group needed MV in the first 3 days of life (20% vs. 16.7%; $P=0.73$). The clinical characteristics of these infants were similar. The time from birth to intubation was 24 hours (range 6-42 h) in the early group and 54 hours (range 6-64 h) in the later group (Table III).

The duration of CPAP in infants who were extubated in the DR after surfactant

administration and the duration of MV in infants who could not extubated to nCPAP in the DR were similar in both groups. The duration of total respiratory support (CPAP plus MV) for infants who were intubated in the first 3 days of life was shorter in the early prophylactic INSURE group than in the later prophylactic INSURE group (median: 96 h vs. 309 h; $P=0.038$). The percentage of infants receiving a second dose of surfactant was similar in both groups (Table IV).

The incidences of morbidities and mortality and the duration of hospitalization were similar in both groups (Table V).

Discussion

In this randomized trial, early prophylactic

surfactant administration, with the first breath, in combination with early nCPAP, shortened the duration of total respiratory support, with similar clinical outcomes among infants born before 30 weeks' gestation, when compared with administration of surfactant at the 15th minute after birth

The immature lungs of preterm infants may be particularly vulnerable at birth, not only because they lack surfactant but also because they are filled with fluid, leaving little room for air entry.¹³ The study performed by Björklund et al¹⁴ demonstrated that manual ventilation, with a few large breaths, administered to immature lambs at birth may cause lung injury and inhibit the effect of subsequently instilled natural surfactant on lung mechanics. In animal studies, it has been shown that the use of PEEP during the transition period from fetus to newborn decreases lung injury, and that surfactant administration at birth has additional benefits. It has been also demonstrated that PEEP is necessary for optimal response to surfactant, improving uniformity of distribution. Furthermore, surfactant administered before ventilation at birth has an additional protective effect.^{9,15-20}

Based on the data from all animal and clinical studies, we designed our study so that infants were administered prophylactic surfactant either immediately at birth, with the first breath, or at the 15th minute after birth, while they were receiving PEEP supplied by a T-piece device, which provides more uniform PEEP than does bag-mask ventilation (an issue addressed by the Neonatal Resuscitation Program).^{21,22} Kendig et al.¹⁰ found that immediate surfactant prophylaxis, before the first breath, resulted in significantly better survival than rescue treatment in very premature infants. Another study from the same group showed even better survival when prophylaxis was postponed until respiration was established.²³ In these two multicenter studies, an anesthesia bag was used for positive pressure ventilation during resuscitation and surfactant administration; also, all infants enrolled in the studies were mechanically ventilated, which is known to be injurious to preterm lungs. In our study, infants in both groups were ventilated with a T-piece resuscitator during resuscitation and prophylactic surfactant administration,

and infants with sufficient respiratory drive were immediately extubated to nCPAP after surfactant administration.

Although intubation is associated with some morbidities, such as right main stem bronchus intubation, pneumothorax, esophageal perforation, accidental extubation, obstruction of the tube, apneic events, transient hypoxia, oxygen saturation and bradycardia, endotracheal instillation is the only current means of surfactant delivery.²⁴ We did not experience any complications related to intubation during resuscitation and surfactant administration in our study, which might be due to the presence of a skilled team in the DR. In the case of infants born outside level III units, intubation is likely to be performed by a provider infrequently exposed to the procedure, and risks related to intubation may increase.

Recently, several noninvasive approaches have been studied in randomized controlled trials to avoid MV, lung injury and MV-related adverse effects in premature infants.²⁵⁻²⁸ Our study did not compare the use of early nCPAP or prophylactic surfactant. The main question our study addressed was, if prophylactic surfactant was to be used, was earlier administration better, or not? The primary outcome need for MV within the first 3 days of life was chosen because of its importance in the context of medical care systems in which resources are limited. Thus, a reduction in the need for MV was felt to be of value even if this benefit did not result in the reduction of long-term adverse outcomes. In this study, administration of prophylactic surfactant immediately at birth did not avoid subsequent intubation and MV, and did not decrease the incidence of NICU morbidities. It did, however, reduce the duration of total respiratory support. Although duration of MV and respiratory support has been reported as one of the most important risk factors for BPD^{29,30}, the incidence of BPD was similar in both groups in our study. Inclusion of infants of the earliest gestational ages (i.e., 23-25 weeks) may be the reason for the higher rates of some morbidities and mortality in our study. But the incidences of air leak, PDA and BPD were lower than reported³¹ by other groups who studied infants born before 28 weeks' gestation.

Observational studies have suggested that

treating very preterm infants with nCPAP during resuscitation is possible and might reduce the rate of intubation and the incidence of BPD without increasing morbidity.³²⁻³⁵ Some studies have suggested that CPAP might be started at birth for most infants born after 25 weeks' gestation.³⁶ One randomized trial involving 104 infants showed the feasibility of the early use of CPAP but was not designed to evaluate its safety and efficacy.³⁷ An additional implication of our study results is that, regardless of the time of surfactant administration, it is difficult to extubate infants of less than 26 weeks' gestational age to nCPAP in the DR.

In this study, infants born before 30 weeks' gestation-moderately-sized preterm infants, for whom surfactant prophylaxis is not currently recommended were administered prophylactic surfactant, because that was the recommendation of the American Academy of Pediatrics³⁸ at the time we designed the study. Also, we were unable to blind the intervention, and the study was conducted over a relatively long period of time. However, there was uniformity in implementing and adhering to the study protocol.

In conclusion, our study did not demonstrate superiority of early surfactant prophylaxis combined with early nCPAP to later administration of prophylactic surfactant combined with early nCPAP; however, the number of patients included in this study was sufficient to give it the power to detect an absolute difference of 30% in the primary outcome, need for MV within the first 3 days of life.

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