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Early INSURE Therapy Reduces CPAP Failure in Late Preterm Newborns with Respiratory Distress Syndrome

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A B S T R A C T

Background: INSURE (Intubation, Surfactant administration, and Extubation) therapy is controversial in managing respiratory distress syndrome (RDS) in late preterm newborns. This study aims to determine whether the use of the INSURE in late preterm infants with RDS is associated with improved outcomes compared to similar infants managed with CPAP alone.
Methods: A retrospective cohort study compared two different neonatal care units with two different treatments of RDS in late preterm infants in Bucaramanga, Colombia. One cohort used selective bubble CPAP and rescue surfactant, the second cohort used selective bubble CPAP and INSURE within the first hour of life. We included all the newborns with gestational age between 33 - $36^{6/7}$ weeks, born between 2012 to 2017, that developed early RDS and were treated with CPAP.
Results: We recruited 208 patients (57 CPAP and rescue surfactant and 151 CPAP + INSURE). Early INSURE was reported in 117 patients (56.3 %). INSURE therapy was associated with a reduced risk of CPAP failure (RR = 0.50; 95 % CI 0.26 - 0.98); this effect was evident only when surfactant was administered within the first two hours of life (RR = 0.29; 95 % CI 0.12 - 0.69). Early INSURE was associated with a decreased risk of pneumothorax (RR = 0.07; 95 % CI 0.01 - 0.77) and pulmonary hypertension (RR = 0.34; 95 % CI 0.14 - 0.78).
Conclusions: Early INSURE therapy was associated with a reduced incidence of CPAP failure, pneumothorax, and pulmonary hypertension in late preterm infants with moderate to severe RDS. Large, well-powered randomized controlled trials are needed to confirm these observations, but its use is supported by studies with similar results in more premature infants.

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La terapia INSURE temprana reduce la falla de CPAP en pretérminos tardíos con Sindrome de dificultad respiratoria

Keywords:
Continuous Positive Airway Pressure
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R E S U M E N

Introducción: La terapia, Intubación, Surfactante y Extubación (INSURE) se considera de uso controversial en los prematuros tardíos con síndrome de dificultad respiratoria (SDR). El objetivo de este estudio es determinar si el uso de INSURE, en prematuros tardíos con SDR, se asocia con mejores desenlaces, al compararlo con pacientes manejados solamente con CPAP.
Métodos: Estudio de cohorte retrospectivo que comparó el manejo en dos unidades neonatales de Bucaramanga, Colombia. La primera cohorte utilizó CPAP de burbuja y surfactante, solo en caso de rescate. La segunda cohorte, utilizó CPAP y técnica INSURE en la primera hora de vida. Se incluyeron todos los recién nacidos entre 33 y 366/7 de edad gestacional, nacidos entre 2012 y el 2017, que desarrollaron SDR y fueron tratados con CPAP.
Resultados: 208 pacientes fueron incluidos (57 en CPAP y 151 en terapia combinada CPAP + INSURE). La terapia INSURE se asoció con menor riesgo de falla de CPAP (RR = 0.50; IC - 95 % 0.26 - 0.98), este efecto solo fue evidente cuando el surfactante se administraba en las primeras 2 horas de vida (RR = 0.29; IC - 95 % 0.12 - 0.69). INSURE temprana se asoció con un menor riesgo de neumotórax (RR = 0.07; IC – 95 % 0.01 - 0.77) e hipertensión pulmonar (RR = 0.34; IC - 95 % 0.14 - 0.78).
Conclusión: La terapia INSURE temprana se asocia con un menor riesgo de falla de CPAP, neumotórax e hipertensión pulmonar en prematuros tardíos con SDR de moderado a severo. Se necesitan ensayos clínicos controlados, aleatorizados, para confirmar estas observaciones, pero su uso esta soportado por estudios con resultados similares en prematuros tardíos.

Introduction

Preterm birth is a global health problem that requires developing new interventions to decrease this condition's associated mortality, morbidity, and economic impact (1, 2). Among the interventions designed to improve the management and outcome of these patients, surfactant therapy has been one of the leading and most effective interventions implemented at a large scale for the treatment of Respiratory Distress Syndrome (RDS), a significant complication associated with prematurity. Objective prospective data support the use of early selective surfactant in this population of infants, especially in preterm infants with ≤ 34 weeks of gestation (3).

Late preterm infants (34+0 to 36+6 weeks of gestation) account for 6 – 8 % of the total births, representing a heterogeneous group of patients that have been ignored mainly because of their closeness to term gestational age. Nevertheless, the evidence has shown a significantly higher risk of respiratory, metabolic, and neurological morbidity in this population compared to term newborns, highlighting the necessity for additional measures to prevent longstanding sequelae in these infants (4, 5). Regardless of their higher frequency of respiratory morbidity, which occurs in 29 % of the cases as respiratory failure due to RDS, pneumonia, transient tachypnea of the newborn (TTN), pulmonary hypertension (PPHN), apnea, or air leak syndrome, there is scant evidence supporting the use of surfactant in this population, as this population of infants was excluded from the initial surfactant trials (6-12).

In our clinical context, surfactant therapy has been frequently administered to late preterm newborns with clinical suspicion of RDS using the INSURE (intubation-surfactant-extubation) strategy mainly within the first hour of symptoms as a result of our participation in a multicenter randomized controlled trial comparing early selective Bubble Continuous Positive Airway Pressure (BCPAP) with and without the INSURE method in preterm infants ≤ 32 weeks gestation and ≤ 1500 grams (13). Evidence from this trial demonstrated improved outcomes that led to the use of this intervention in late preterm infants at the Hospital Universitario de Santander (HUS), showing favorable results in the short and long term. Another participating center in the initial RCT did not implement the INSURE method in their population of late preterm infants. We designed this multicenter retrospective study to compare two different approaches for managing RDS in late preterm infants to determine whether the use of early selective Continuous Positive Airway Pressure (CPAP) and INSURE improves the outcome of this subpopulation of premature infants.

Patients and Methods

Study design

We performed a multicenter retrospective cohort study in two perinatal centers in Bucaramanga (Colombia).

The first center was Hospital Universitario de Santander (HUS). The standard of care for managing RDS in late preterm infants is selective Bubble Continuous Positive Airway Pressure (BCPAP) and surfactant administration within the first hour of life using the INSURE method.

The second center was Clínica Materno Infantil San Luis (CMISL), where the same population was managed with selective CPAP alone and rescue surfactant. These patients received

surfactant after the first hour of RDS and continued in CPAP until it fails. (See figure 1 for groups distribution).

Inclusion criteria were

Newborns delivered between 33+0 to 36+6 weeks of gestation with clinical evidence of RDS and need of oxygen supplementation during the first hour of life that did not require intubation as part of initial resuscitation. Clinical evidence of RDS was defined as the presence of tachypnea, grunting, intercostal retractions. The Silverman-Anderson scale (SAS) determined the severity of respiratory distress. All infants in both institutions who met the criteria were initially managed with BCPAP to maintain and promote lung recruitment. Preterm infants with diagnoses different from RDS or with major congenital malformations or severe metabolic diseases were excluded.

Electronic medical records from both participating centers were reviewed from January 1, 2012, to December 31, 2017, to identify ICD - 10 codes for RDS and related disorders such as TTN, neonatal pneumonia, prematurity, and exposure to CPAP.

The following variables were then determined the values for all eligible late preterm infants: center of birth, date of birth, gestational age, birth weight, gender, weight, singleton or twin, Apgar score at 1 and 5 minutes of life, time from birth to clinical evidence of RDS, highest Silverman-Anderson score achieved, need for resuscitation in the delivery room, need for intubation in the first 15 minutes of life, need for positive pressure ventilation, need for chest compressions, need for epinephrine, first ventilatory support method initiation of CPAP, initiation of mechanical ventilation, use of surfactant therapy, the time between the beginning of clinical symptoms of RDS and the administration of surfactant, change of the ventilatory support method, development of pneumothorax, development of pulmonary hypertension (PPHN). Maternal and perinatal variables included were: age, diabetes, placental abruption, hypertensive disorders, prolonged premature rupture of membranes, and clinical chorioamnionitis (defined as the presence of fever with one or more of the followings: uterine tenderness, maternal leukocytosis >15,000/ mm3, foul-smelling amniotic fluid or fetal tachycardia), type of delivery, and antenatal steroid treatment.

Relevant clinical data were collected in pre-designed data collection instruments and then stored in a password-protected web-based database, REDCap program (Version 6.14.2 - © 2018 Vanderbilt University), with de-identification capabilities to protect the privacy of participants and their families.

Initial Ventilatory assistance

In both participating institutions, CPAP was installed with a pressure of 4 to 6 cm of H2O and a humidification temperature of 39 °C. The patients were followed until clinical improvement was confirmed. The CPAP was removed, or the infants meet criteria for CPAP failure, which included the presence of at least one of the following: a) Need of a fraction of inspired oxygen > 0.75 (FiO2) for more than 30 minutes to maintain an oxygen saturation between 88 and 92%; b) Persistent or recurrent decrease in saturation below 80 %; c) Breathing with positive pressure by mask; d) Respiratory acidosis (PCO2 > 65 mm Hg and pH < 7.22); e) Presence of recurrent apnea requiring resuscitation through positive pressure-assisted breathing. Patients who must receive mechanical ventilation (MV) by the failure of CPAP were sent to Neonatal Intensive Care Unit (NICU) with subsequent modifications depending on the criteria of the treating physician.

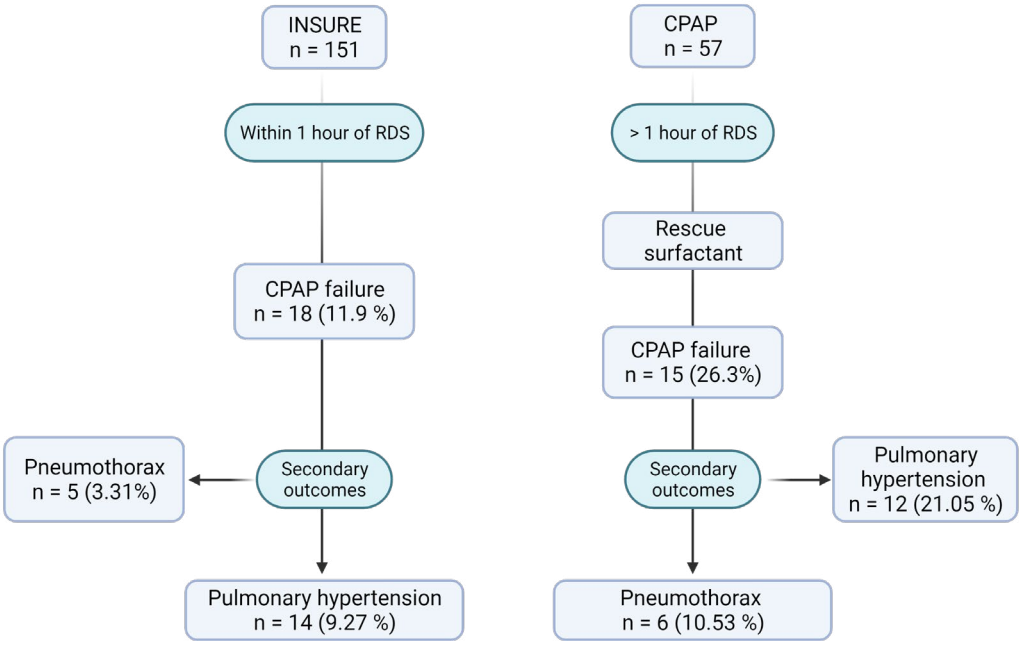

Figura 1. Groups of study

Main outcomes

The outcomes evaluated were the need for mechanical ventilation, the development of pneumothorax or an air leak syndrome, persistent pulmonary hypertension (diagnosis made by heart ultrasound performed by an expert pediatric cardiologist), bronchopulmonary dysplasia (being defined as the need for oxygen treatment > 21 % for at least 28 days), retinopathy of prematurity, necrotizing enterocolitis (NEC) (only the ones that fulfilled the criteria for being classified as Bell's stage II or III), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and exposure to supplemental oxygen (hours).

Ethics in research

The Institutional Review Boards approved this study in both institutions following the Declaration of Helsinki of the World Medical Association guidelines and the Resolution 8430 of 1993 of the Ministry of Health of Colombia. This study was classified as an investigation with minimal risk to participants.

Statistical Analysis

Categorical variables were presented as absolute values with their corresponding percentages. Quantitative variables were summarized as mean and standard deviation when the distribution was normal and median with their interquartile range (IQR) according to the Shapiro-Wilk test when not normally distributed. When exploring differences between patients exposed to CPAP and rescue surfactant versus CPAP plus INSURE, categorical variables were compared using chi-square, student t, or Wilcoxon rank-sum tests according to the type of distribution. Cumulative incidence of the outcomes was analyzed using the relative risk (RR) representing INSURE therapy as the experimental intervention. CPAP failure was evaluated as incidence rate per 1000 days-person; this analysis was completed to estimate incidence rate differences and Kaplan-Meier survival curves. According to Greenland and Morgenstern's recommendations, the variables that appeared to be independently associated with any of the outcomes or had the potential to be a confounder were included in a multivariate binomial model (14). Statistical analyses were performed using Stata/MP™ for Windows™, v. 14.0 (StataCorp LP, College Station, USA).

Results

A total of 208 late preterm newborns fulfilled inclusion criteria; 47.12 % (n = 98) were born in the CMISL and 52.88 % (n = 110) in the HUS. Male infants represented 61.06 % (n = 127) of the total population. The median birth weight of 2 412 (IQR 2117 - 2635) grams. After the initial stabilization with Neopuff™, 57 patients (27.4 %) were treated with CPAP and rescue surfactant. In contrast, 151 (72.6 %) received CPAP with INSURE therapy; of these, surfactant was administered in the first hour of life after clinical evidence of RDS (early INSURE) in 117 patients (56.3%). The clinical and socio-demographic characteristics of the newborns and their mothers are presented in Table 1.

The median maternal age at delivery was 25 years (IQR 20 - 29), preeclampsia was the most common maternal comorbidity observed (24.5 %, n = 51) in this population. The newborns with INSURE therapy had more Intrauterine Growth Restriction (IUGR) (19.2 % vs. 7 %; $p = 0.032$), were more frequently diagnosed with chorioamnionitis (3.3 % vs 0 %; $p < 0.164$) and twin pregnancy (15,9 % vs. 7 %; $p < 0.094$), while gestational diabetes was more common in the CPAP and rescue surfactant group (7.5 % vs 1.99 %; $p = 0.073$).

Of the 208 late preterm infants, only 30.3 % (n = 63) received antenatal steroids and of these, 79.3 % (n=50) received a complete course. SAS severity of RDS for both groups ranged from 1 to 10, with the majority scoring between 4 and 6. Moderate RDS was in 52.7 % of the cases (n = 106), and 39.3 % (n = 79) of the patients had between 7 and 10 points for severe RDS. Eight infants in the CPAP and INSURE group did not have a SAS score.

The CPAP and INSURE group had more severe RDS patients than the CPAP and rescue surfactant group (44.4 % vs. 21.1 %, $p < 0.001$). Only five infants in this cohort required Positive Pressure Ventilation (PPV) and chest compressions (1.9 %). Infants in the CPAP and rescue surfactant group had a higher median initial Positive End Expiratory Pressure (PEEP) compared to infants in the CPAP and INSURE (5 [IQR 5 - 5.5] vs. 4 [IQR 4 – 5]; $p < 0.001$). The initial FiO2 was similar between the two groups (0.6 vs. 0.5; $p = 0.562$).

The CPAP and rescue surfactant group had a higher rate of CPAP failure (26.3 % vs. 11.9 %; $p = 0.011$), pneumothorax (10.5 % vs. 3.3 %; p = 0.038), and pulmonary hypertension (21.4% vs. 9.3 %; p=0.02) compared to the CPAP and INSURE treated newborns (Table 2). These differences were evident for moderate and severe cases, as the sample with SAS between 1-3 was not large enough to evaluate a significant difference. On the other side, supplementary oxygen exposure did not vary among the two groups (Median of 67 hours for CPAP only and 64 hours for INSURE, p = 0.634).

These associations persisted in the binomial regression models with a significant reduction of the CPAP failure risk in infants exposed to CPAP and INSURE therapy (RR = 0.45; 9 5% CI 0.245 - 0.836), even when adjusted by potential confounding variables (RR = 0.50; 95% CI 0.259 - 0.981).

The Kaplan-Meier survival curves (See figure 2) and incidence rate analysis of CPAP failure showed that the patients treated with the CPAP and INSURE strategy exhibited a lower incidence rate of failure (3.7 per 1000 days-person; 95 % CI 24.129 - 60.786) compared with CPAP and rescue surfactant (9.3 per 1000 days-person; 95% CI 5.6 - 15.4), with an incidence rate difference of 5.6 (95 % CI 0.6 - 10.6) per 1000 days-person (p = 0.011).

CPAP and INSURE exposure was associated with a reduction in pulmonary hypertension rate (crude model: RR = 0.44, 95 % CI 0.216 - 0.894; adjusted model: RR = 0.41; 95 % CI 0.217 - 0.801) and pneumothorax risk (crude model: RR = 0.31; 95 % CI 0.099 - 0.991; but not the adjusted model: RR = 0.36; 95 % CI 0.106 - 1.281). No differences regarding NEC and BPD were observed between groups.

Table 1. Baseline Characteristics of the included newborns and their mothers according to the treatment strategy

Variables	CPAP (n = 57)	INSURE (n = 151)	*p*
HUS	3 (5.26 %)	107 (70.86 %)	<0.001
CMISL	54 (94.74 %)	44 (29.14 %)	
Maternal age (years)*	25 (23 to 30)	25 (20 to 29)	0.228
Gestational age (weeks)*	35 (34 to 36)	35 (34 to 36)	0.331
Birth weight (gr)	2495 (2120 to 2670)	2370 (2120 to 2645)	0.206
Male sex	31 (54.39 %)	96 (63.58 %)	0.225
Pregnancy morbidity			
Urinary tract infection	3 (5.26 %)	7 (4.64 %)	0.850
Gestational diabetes	4 (7.0 2%)	3 (1.99 %)	0.073
PROM	11 (19.30 %)	20 (13.25 %)	0.274
Oligohydramnios	3 (5.26 %)	10 (6.62 %)	0.718
Preeclampsia	14 (24.56 %)	37 (24.50 %)	0.993
IUGR	4 (7.02 %)	29 (19.21 %)	0.032
Chorioamnionitis	-	5 (3.31 %)	0.164
Spontaneous premature labor	19 (33.33 %)	54 (35.76 %)	0.743
Drug abuse	-	2 (1.32 %)	0.383
From twin pregnancy	4 (7.02 %)	24 (15.89 %)	0.094
Antenatal Corticoid Therapy			
None	40 (70.18 %)	105 (69.54 %)	
Incomplete	1 (1.75 %)	12 (7.95 %)	0.215
Complete	16 (28.07 %)	34 (22.52 %)	
Vaginal birth	11 (19.30 %)	31 (20.53 %)	0.844
Apgar score 1st min 4 to 6	5 (8.93 %)	23 (15.44 %)	0.227
Apgar score 5th min 4 to 6	1 (1.82 %)	1 (0.6 7%)	0.461
Silverman-Anderson score			
1 to 3 points	12 (21.05 %)	4 (2.78 %)	<0.001
4 to 6 points	33 (57.89 %)	73 (50.69 %)	0.357
7 to 10 points	12 (20.05 %)	67 (46.53 %)	0.011
Not registered	-	7 (4.64 %)	
Resuscitation			
None	47 (82.46 %)	126 (83.44 %)	
PPV only	9 (15.79 %)	22 (14.57 %)	0.972
PPV and chest compressions	1 (1.75 %)	3 (1.99 %)	
Starting PEEP (cm H_2O)	5.0 (5.0 - 5.5)	4.0 (4.0 - 5.0)	<0.001
Starting FiO2	0.6 (0.4 - 0.7)	0.5 (0.4 - 0.7)	0.561

PROM: Premature Rupture of Membranes, IUGR: Intrauterine Growth Restriction, PEEP: Positive End Expiratory Pressure, FiO_2 (Fraction of Inspired Oxygen). PPV: Positive pressure ventilation

Table 2. Outcomes of the RDS According to the Treatment Strategy

Characteristic	CPAP (n = 57)	INSURE (n = 151)	*p*
Primary outcome			
CPAP failure	15 (26.3 %)	18 (11.9 %)	
Secondary outcomes			0.011
Necrotizing enterocolitis	1 (1.75 %)	1 (0.66 %)	
Pneumothorax	6 (10.53 %)	5 (3.31 %)	0.593
Bronchopulmonary Dysplasia	1 (1.75 %)	-	0.038
Pulmonary hypertension	12 (21.05 %)	14 (9.27 %)	0.202
Mild	6 (10.5 %)	7 (4.63 %)	0.020
Moderate	2 (3.5 %)	4 (2.64 %)	
Severe	4 (7.05 %)	3 (1.98 %)	

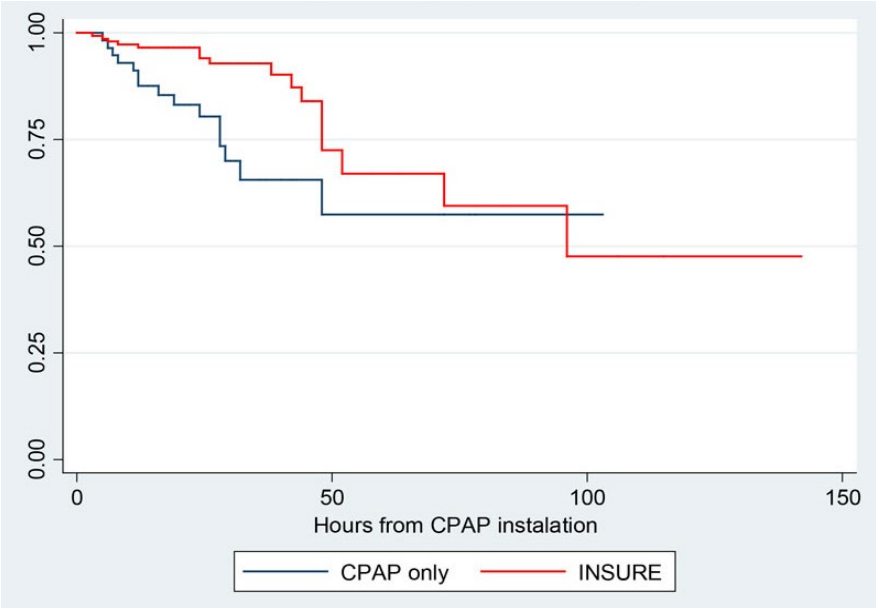

Figura 2. Time to CPAP failure by treatment group.

When the time of delivery of INSURE was analyzed, the associated risk reduction was mainly caused by early INSURE (surfactant administered in the first hour after initiation of RDS symptoms). At the same time, late INSURE showed no beneficial effect for CPAP failure, pneumothorax, and pulmonary hypertension incidence (See table 3).

Both late CPAP and INSURE, and CPAP with rescue surfactant have a similar incidence rate of CPAP failure (7.1 per 1000 per 1000 days-person, 95 % CI 3.6 - 14.2 and 9.3 per 1000 days-person, 95 % CI 5.6 - 15.4; $p = 0.556$) respectively, while early CPAP and INSURE had a shallow rate of CPAP failure (2.7 per 1000 days-person, 95 % CI 1.4 - 5.0; $p = 0.002$). Late CPAP and INSURE patients have a similar incidence of CPAP failures than CPAP and rescue surfactant, but early CPAP and INSURE infants had a lower incidence rate (See figure 3).

Discussion

In the present study, late preterm newborns with moderate to severe RDS exposed to INSURE therapy had a significantly lower incidence of CPAP failure and exposure to mechanical ventilation compared to CPAP-only treated patients (11.9 % vs. 26.3 % p = 0.011). This effect was most significant when surfactant was administered in the first hour of life with clinical evidence of RDS (RR = 0.29; 95 % CI 0.12 - 0.69), even though infants were exposed to CPAP and rescue surfactant had significantly lower Silverman-Anderson scores. Additionally, late surfactant administration was not associated with a lower risk of CPAP failure, suggesting a limited effect of surfactant as the severity of respiratory failure progress.

Table 3. Association between time of INSURE instillation and CPAP failure in the INSURE group

Outcomes	Early INSURE				Late INSURE			
	Crude Model		Adjusted Model		Crude Model		Adjusted Model	
	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI
CPAP failure	0.32	0.15, 0.67	0.29	0.12, 0.69	0.89	0.42, 1.88	1.01	0.58, 2.12
Pneumothorax	0.08	0.01, 0.65	0.07	0.007, 0.77	1.12	0.33, 3.68	1.21	0.39, 3.72
Pulmonary hypertension	0.32	0.14, 0.74	0.34	0.14, 0.78	0.83	0.34, 2.02	0.52	0.23, 1.14

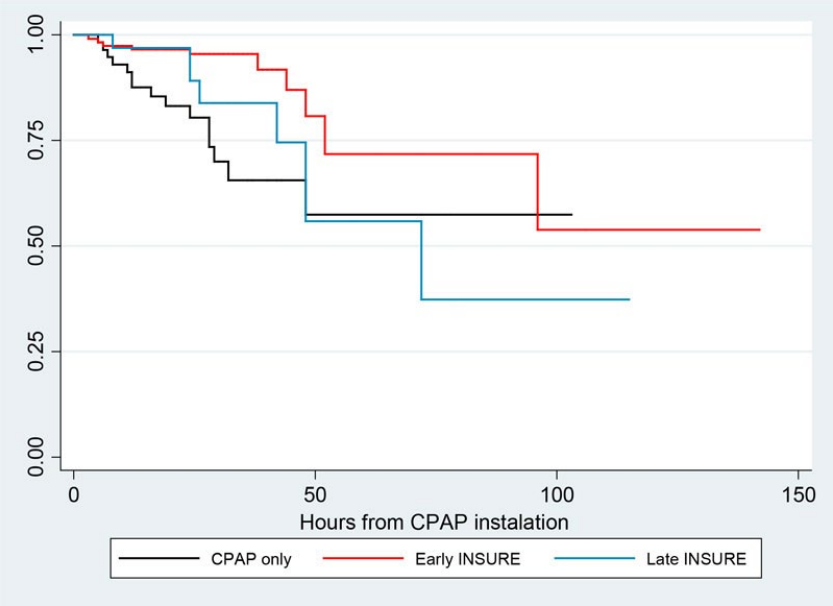

Figure 3. Time to CPAP failure by treatment group, including early or late INSURE treatment.

CPAP and INSURE exposure were also associated with a lower rate of pneumothorax and pulmonary hypertension. However, these benefits have been observed in previous randomized controlled trials comparing these modes of management of RDS in infants < 32 weeks gestation and <1500 grams (13, 15). The present study is the first retrospective study to show a similar benefit in late preterm infants, including a protective effect against pulmonary hypertension. The loss of a protective effect from pneumothorax after controlling for confounders may be explained by the inclusion of infants who received surfactant after the first hour of life (Late Insure). Clinical studies evaluating the time of surfactant administration have confirmed that the earlier surfactant is administered in the course of RDS, the better the outcomes, including pneumothorax (16). When evaluating these outcomes in the multivariate model, the beneficial effects persisted even when adjusting for confounders, highlighting the role and benefit of early surfactant administration in this population.

Recently, Dani et al. (17) published a retrospective cohort study in which surfactant effectiveness was evaluated in 562 late preterm newborns with RDS. They found no significant improvements in respiratory failure or morbidity, even when surfactant exposure was associated with a positive impact on the respiratory function of the patients, based on FiO2, Partial Pressure of Oxygen (PaO2), and Arterial/Alveolar Oxygen Tension Ratio (a/APO2 changes).

Differences in the time of surfactant administration may explain the differences in outcomes between our study and Dani's study. The mean age at which surfactant was administered in Dani's was 18 ± 17 hours compared to approximately 1 hour in our research. From this perspective, Dani et al. evaluated CPAP and rescue surfactant in this population of infants with similar effects to those observed in our control group in the present study (17).

Olivier et al. (18) published a multicenter randomized controlled trial to evaluate the effect of minimally invasive surfactant therapy (MIST) for RDS management in 45 newborns with 32+0 and 36+6 weeks of gestational age. The primary outcome was a composite one, including the need for MV and pneumothorax rate in the first three days after MIST.

In the Olivier study, all participants had a FiO2 of 35 % on nasal CPAP of 6 cm of H2O to maintain saturation ≥ 90 % in the first 24 hours of life. Twenty-one patients were randomized to standard management (surfactant administration based on the attending physician's judgment) and 24 patients to MIST (BeractantTM, 4 mL/kg, 25 mg of phospholipids/mL).

Different non-invasive ventilation strategies were used after randomization in both groups. The incidence of MV need was 7/24 (29.2 %) in the MIST group compared to 18/21 (85.7 %) in the standard group. The incidence of pneumothorax was 1/24 (4.2 %) in the MIST group and 2/21 (9.5 %) in the standard management group. MIST reduced the incidence of the composite primary outcome (relative risk of 0.37, 95 % CI 0.20 - 0.67); absolute risk reduction of 0.53, (95 % CI 0.28 - 0.77), and number needed to treat of 1.9, (95 % CI 1.3 - 3.5; $p < 0.001$).

In our local context, neonatologists have published their experiences in using the INSURE therapy for RDS in preterm newborns. Two relevant studies performed showed that early surfactant had significant benefits in managing this syndrome in newborns under 33 weeks gestation. In one study conducted in 2014, the use of CPAP after early surfactant administration showed a significantly lower incidence of CPAP failure, death, chronic lung disease, intracranial hemorrhage, and sepsis compared to newborns assisted with MV (19).

Moreover, a randomized, controlled trial that evaluated the benefit of early INSURE compared to CPAP and rescue surfactant in infants born between 27 and 31 6/7 weeks of gestation

suggested that early surfactant therapy followed by CPAP decreases the need for subsequent mechanical ventilation and the incidence of the air-leak syndrome (13). The previous studies support the practical benefits of selective CPAP and early INSURE in the population of late preterm infants.

Limitations of our study include its retrospective design with the observed differences between the two comparison groups. Nevertheless, this limitation was compensated by using SAS to guide the administration of surfactant; in both participating institutions, surfactant was only administered when infants developed a Silverman-Anderson score of 4 or greater, minimizing the subjectivity of surfactant administration. Another strength was the different standardized approaches to managing RDS in both institutions, which facilitated creating a comparison group for CPAP and INSURE.

Conclusion

Early selective CPAP and INSURE therapy was associated with a reduced rate of CPAP failure, pneumothorax, and pulmonary hypertension in late preterm infants with moderate to severe RDS, suggesting a potential benefit for its use in this population. Further well-powered randomized controlled trials are required to confirm the findings of this study.

Conflicts of Interest

None to declare

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