Randomized Trial of Early Bubble Continuous Positive Airway Pressure for Very Low Birth Weight Infants

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Objective To determine whether very low birth weight infants (VLBWIs), initially supported with continuous positive airway pressure (CPAP) and then selectively treated with the INSURE (intubation, surfactant, and extubation to CPAP; CPAP/INSURE) protocol, need less mechanical ventilation than those supported with supplemental oxygen, surfactant, and mechanical ventilation if required (Oxygen/mechanical ventilation [MV]).

Study design In a multicenter randomized controlled trial, spontaneously breathing VLBWIs weighing 800-1500 g were allocated to receive either therapy. In the CPAP/INSURE group, if respiratory distress syndrome (RDS) did not occur, CPAP was discontinued after 3-6 hours. If RDS developed and the fraction of inspired oxygen (FiO_2) was >0.35, the INSURE protocol was indicated. Failure criteria included FiO_2 >0.60, severe apnea or respiratory acidosis, and receipt of more than 2 doses of surfactant. In the Oxygen/MV group, in the presence of RDS, supplemental oxygen without CPAP was given, and if FiO_2 was >0.35, surfactant and mechanical ventilation were provided.

Results A total of 256 patients were randomized to either the CPAP/INSURE group (n = 131) or the Oxygen/MV group (n = 125). The need for mechanical ventilation was lower in the CPAP/INSURE group (29.8% vs 50.4%; P = .001), as was the use of surfactant (27.5% vs 46.4%; P = .002). There were no differences in death, pneumothorax, bronchopulmonary dysplasia, and other complications of prematurity between the 2 groups.

Conclusion CPAP and early selective INSURE reduced the need for mechanical ventilation and surfactant in VLBWIs without increasing morbidity and death. These results may be particularly relevant for resource-limited regions. *(J Pediatr 2012;161:75-80).*

Continuous positive airway pressure (CPAP) was described in 1971 as an alternative form of respiratory support for preterm infants with respiratory distress syndrome (RDS).[1] Several studies in the 1970s and early 1980s concluded that the early use of CPAP reduced the requirement for mechanical ventilation. However, these were small case series studies, enrolling preterm infants with an average birth weight >1500 g.[2-4] Within the last decade, early CPAP in very low birth weight infants (VLBWIs) has regained popularity.[5,6] In retrospective studies, units that favored the use of CPAP over endotracheal intubation and mechanical ventilation had a lower incidence of bronchopulmonary dysplasia (BPD).[7,8] Furthermore, animal studies showed a decrease in markers of lung inflammation in CPAP treatment compared with mechanical ventilation.[9]

At the time that we designed the present study, the majority of published studies using early CPAP were observational retrospective reviews comparing 2 historical periods or very small case series.[10-12] In addition, the most common therapeutic approach for RDS in preterm neonates in our region was early selective surfactant administration with intubation and mechanical ventilation, especially in those with a fraction of inspired oxygen (FiO_2) requirement exceeding 0.35. Infants with lower FiO_2 requirements were managed with an oxyhood. Moreover, most of the units in our network had only limited experience with

BPD	Bronchopulmonary dysplasia	PDA	Patent ductus arteriosus
CPAP	Continuous positive airway pressure	PEEP	Positive end-expiratory pressure
		PIP	Peak inspiratory pressure
FiO_2	Fraction of inspired oxygen	RDS	Respiratory distress syndrome
GA	Gestational age	ROP	Retinopathy of prematurity
INSURE	Intubation, surfactant, extubation	SpO_2	Oxygen saturation
IVH	Intraventricular hemorrhage	VLBWI	Very low birth weight infant
MV	Mechanical Ventilation		

nasal CPAP in preterm infants. Pilot data from the South American Neocosur Network showed that 87% of preterm infants with a birth weight of 500-1000 g and 60% of those with a birth weight of 800-1500 g (VLBWIs) were treated with mechanical ventilation.

A 2005 Cochrane review of prophylactic CPAP therapy identified no conclusive studies to guide clinicians.[13] Two controlled studies using early versus delayed CPAP demonstrated no benefit; in one of these studies, CPAP was used in the first 30 minutes of life,[14] and in the other, CPAP was provided via a nasopharyngeal tube starting shortly after birth.[15]

In 1994, Verder et al[16] reported that early use of surfactant followed by extubation and nasal CPAP, also known as the INSURE (intubation, surfactant, extubation) protocol, reduced the need for mechanical ventilation from 85% to 41% in preterm infants born at 29-30 weeks gestational age (GA). Some 42% of the patients who received CPAP did not require surfactant. These same authors later reported a decrease in intubation rate from 68% to 25% in preterm infants born at 27-29 weeks GA with early versus late treatment.[17]

In light of the high use of mechanical ventilation in our region, which contrasts with the lack of resources in several facilities, the primary objective of the present multicenter collaborative study was to determine whether in VLBWIs a strategy of prophylactic bubble CPAP followed by early selective surfactant using the INSURE protocol could decrease the need for mechanical ventilation without increasing death and morbidity.

Methods

This randomized, controlled, multicenter trial was approved by the local Ethics Committees of each participating center and registered at ClinicalTrials.gov (NCT00368680). The trial was conducted in 12 tertiary neonatal intensive care units from 5 South American countries: Argentina, Chile, Paraguay, Peru, and Uruguay. In all participating centers, at least 2 workshops were conducted to teach staff the correct use of the CPAP equipment.

The inclusion criteria were inborn preterm infants with birth weight 800-1500 g who were spontaneously breathing at 5 minutes of life. Some of the infants had received a brief period of manual ventilation. Immediate postdelivery care was provided under a radiant warmer in accordance with the guidelines of the American Academy of Pediatrics and American Heart Association Neonatal Resuscitation Program. If intermittent positive-pressure ventilation was required, a T-piece resuscitator that allows the setting of predetermined peak inspiratory pressure (PIP) and positive-end expiratory pressure (PEEP) was used (Neopuff; Fisher & Paykel Healthcare, Auckland, New Zealand). Exclusion criteria were major congenital malformations or genetic diseases, 5-minute Apgar score ≤3, the need for ongoing mechanical ventilation at 5 minutes after birth, and lack of informed consent.

Informed parental consent was sought before delivery. If entry criteria were met, at 5 minutes of life and after birth

weight was determined, each infant was randomized to one of two groups (Figure). A computerized randomization system was used, with allocation obscured in a sealed opaque envelope. The infants were stratified by birth weight (800-999 g and 1000-1500 g) and by center.

The primary outcome was any requirement for mechanical ventilation between study enrollment and hospital discharge. Secondary outcomes included death, use of surfactant, pneumothorax, intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), late-onset sepsis, retinopathy of prematurity (ROP), BPD, days of oxygen therapy, days of mechanical ventilation, and length of hospital stay.

In the infants in both groups, oxygen requirement was monitored continuously, with an oxygen saturation (SpO_2) target of 88%-94%. Infants randomized to the Oxygen/MV group who were initially managed with oxygen via nasal cannula were transferred to an oxyhood. A chest X-ray was obtained within the first 2 hours of life if there was clinical evidence of respiratory distress. A data collection form was completed for each child, with predefined diagnostic criteria: RDS based on clinical and radiological features, pneumothorax by X-ray, PDA by clinical diagnosis and echocardiographic confirmation whenever possible, IVH by ultrasonography or autopsy graded using the Papile classification scheme,[18] late-onset sepsis by clinical signs and confirmed by positive blood or cerebrospinal fluid culture, necrotizing enterocolitis by radiologic or surgical findings, ROP by ophthalmologic examination according to the international classification,[19] and BPD by supplemental oxygen usage at 36 weeks postmenstrual age.[20] Data were collected at each center and sent to the Database Unit at Catholic University of Chile, which stored, managed, and analyzed the data.

CPAP/INSURE Group
Infants were given CPAP (as soon as possible after allocation) using a bubble CPAP system (Fisher & Paykel Healthcare) with a distending pressure of 5 cm H_2O. The short binasal prongs included with the CPAP system were used. Before the nasal prongs were inserted, CPAP was maintained at 5 cm H_2O through a mask connected to a T-piece resuscitator, ensuring that the infants in this group were maintained on CPAP from the time of enrollment.

Criteria for Respiratory Support and Surfactant Administration. Infants with an FiO_2 >0.35 to maintain SpO_2 in the target range and X-ray findings compatible with RDS were intubated and given surfactant following the INSURE protocol. Preintubation sedation was provided at the discretion of each center. During surfactant administration, ventilation was provided using a T-piece resuscitator with a PIP of 20 cm H_2O and a PEEP of 5 cm H_2O for 5-10 minutes, after which nasal CPAP was resumed. In 10 of the 12 participanting centers, the surfactant used was the modified natural bovine lung surfactant Survanta (Abbott Laboratories, Abbott Park, Illinois) at a dose of 100 mg/kg. The other 2 centers used a natural bovine surfactant (Surfactante B Richet; Laboratorios Richet, Buenos Aires, Argentina) at
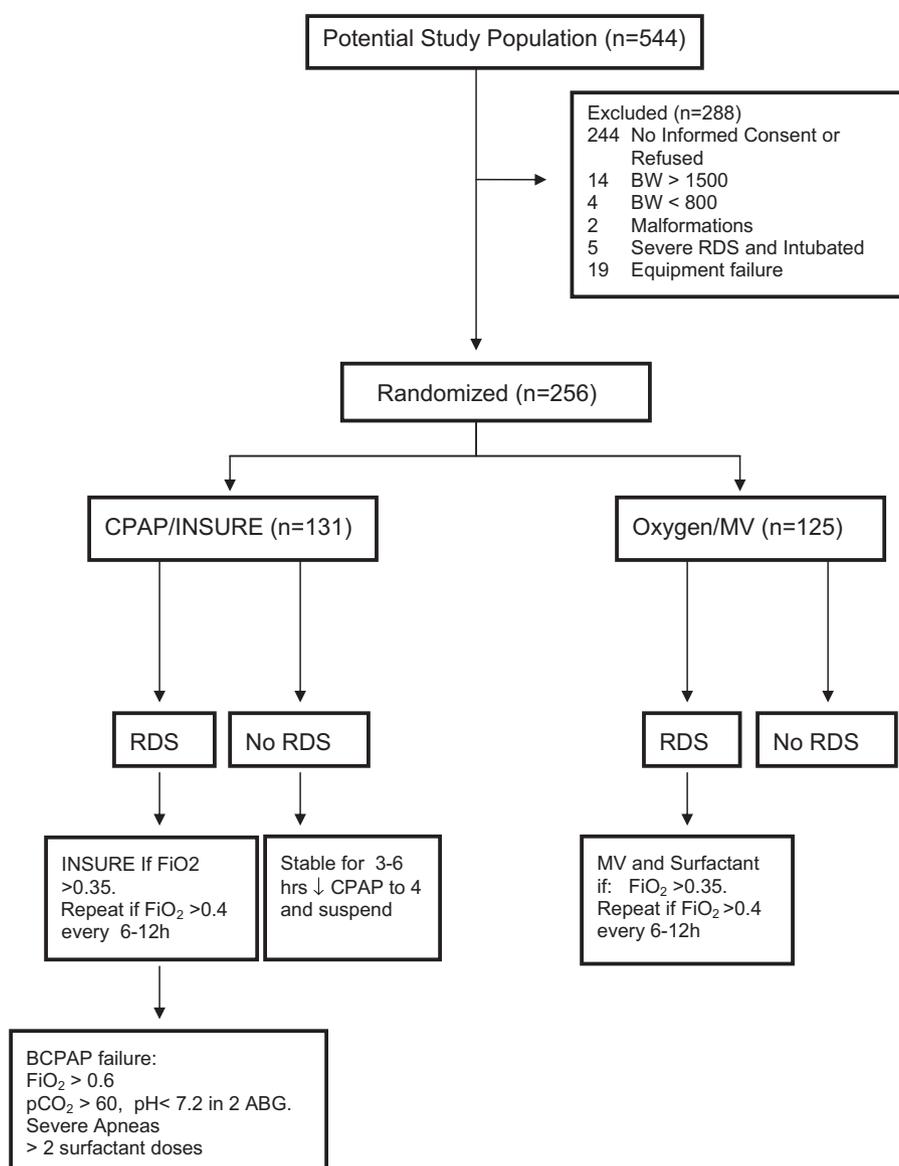
Figure. Patient flow throughout the clinical trial. *BW*, birth weight; *BCPAP*, bubble continuous positive airway pressure; *ABG*, arterial blood gas.

a dose of 100 mg/kg. The CPAP pressure could be increased up to 7 cm H_2O if the FiO_2 requirement increased to >0.50, at the discretion of the attending physician. Surfactant administration was repeated every 6-12 hours if the FiO_2 requirement exceeded 0.40, following the same procedure. If a third dose of surfactant was required, then mechanical ventilation was initiated. The maximum number of surfactant doses administered was 4.

Criteria for CPAP Failure, Intubation, and Mechanical Ventilation. The following criteria were used to define CPAP failure, intubation, and mechanical ventilation: (1) $FiO_2 \geq 0.60$ at least 2 hours after surfactant administration; (2) need for a third dose of surfactant; (3) more than 3 episodes of apnea and bradycardia (heart rate <80/minute)

per hour; and (4) $PaCO_2$ >60 mm Hg with pH <7.20 on consecutive arterial blood gas analyses within 30 minutes.

Criteria for Discontinuation of CPAP. If the newborn had no RDS and did not require oxygen after 3-6 hours, then CPAP was discontinued. If RDS was present, then CPAP could be discontinued once the infant had been stable for 24 hours and the FiO_2 was <0.30 with a CPAP pressure of 4-5 cm H_2O with no signs of RDS. Some patients remained on CPAP longer in accordance with local practices.

Oxygen/MV Group
The infants in this group were monitored for RDS and FiO_2 requirement. Oxygen was administered by an oxyhood or a low-flow nasal cannula as necessary.

Criteria for Intubation, Surfactant Administration, and Ventilation. In infants with RDS and an FiO_2 >0.35 on oxyhood therapy and with compatible X-ray findings, surfactant was administered followed by mechanical ventilation. Surfactant therapy was repeated every 6-12 hours if the FiO_2 requirement was ≥0.40. The maximum number of surfactant doses administered was 4.

Recommendations for Mechanical Ventilation in Both Groups. A noninjurious ventilation strategy was recommended that targeted an SpO_2 of 88%-94% and a $PaCO_2$ of 45-55 mm Hg, using inspiratory pressures as low as possible, short inspiratory times of 0.3-0.35 second, and a PEEP of 5 cm H_2O. The initial respiratory rate was 30-40 cycles/minute, adjusted according to $PaCO_2$ level. Tidal volumes were not measured at all centers; however, when measured, the recommended upper limit was 5 mL/kg.

Ventilator Weaning Criteria in Both Groups. Extubation was attempted if the infant was clinically stable, with blood gas values in the ranges noted earlier and the following ventilator settings: FiO_2 ≤0.30, PIP ≤15 cm H_2O, respiratory rate ≤20 cycles/minute, and PEEP 4-5 cm H_2O. Aminophylline (6 mg/kg) or caffeine (20 mg/kg) was given before extubation.

Sample Size Calculation

Based on the previously reported information from our network, 60% of the VLBWIs received mechanical ventilation. In the present study, a sample size of 256 infants was needed to detect a reduction of at least 30% in the use of mechanical ventilation in the CPAP/INSURE group, using a two-tailed type I error rate of 0.05 and a power of 80%. An interim analysis by an independent monitor was conducted when one-half of the planned sample was recruited and a reason to discontinue enrollment was not identified.

Statistical Analyses

Categorical variables were compared using Pearson χ^2 or Fisher exact tests. Continuous variables were compared using the Student t test or Mann-Whitney U test, the latter when data were skewed. To quantify the magnitude of associations, respiratory rates and 95% CIs were computed. P values <.05 were considered significant. All statistical analysis was performed using SPSS version 17.0 (IBM, Armonk, New York).

Results

Infants were enrolled between November 2, 2006, and September 19, 2009. A total of 256 infants were recruited, 131 in the CPAP/INSURE group and 125 in the Oxygen/MV group (Figure). There were no differences in baseline characteristics between the groups (Table I). The CPAP/INSURE group had significantly lower rates of mechanical ventilation (29.8% vs 50.4%) and surfactant use (27.5% vs 46.4%). There were no differences in the rates of pneumothorax, oxygen therapy at 28 days, BPD, or death

Table I. Perinatal and demographic characteristics

Characteristic	CPAP/INSURE (n = 131)	Oxygen/MV (n = 125)	P value
Body weight, kg, mean ± SD	1196 ± 194.8	1197 ± 189.2	.993
GA, weeks, mean ± SD	29.8 ± 2.4	29.5 ± 2.2	.242
Male sex, %	51.1	51.2	.993
Cesarean birth, %	74.8	73.6	.825
Antenatal steroid use, %	90.8	88.0	.460
Twins, %	21.4	23.2	.726
5-minute Apgar score, median (range)	9 (5-10)	9 (4-10)	.356

(Table II). Of the subgroup that received surfactant, infants in the CPAP/INSURE group received an average of 1.3 doses of surfactant, versus 1.5 in the Oxygen/MV group (P = .262). The percentage of infants receiving only one dose of surfactant was 69.5% in the CPAP/INSURE group and 58.6% in the Oxygen/MV group (P = .29). The median age at first surfactant dose was similar in the 2 groups: 1 hour (range, 0-23 hours) for the CPAP/INSURE group and 2 hours (range, 0-18 hours) for the Oxygen/MV group.

No between-group differences were seen for the incidence of IVH grade III-IV, PDA, ROP, necrotizing enterocolitis, and sepsis; however, nasal lesions were found only in the CPAP/INSURE group (Table III).

The rate of supplemental oxygen use was 73.3% (96 of 131) in the CPAP/INSURE group and 87.2% (109 of 125) in the Oxygen/MV group. There was no difference in the median duration of oxygen therapy: 4 days (range, 0.1-116 days) in the CPAP/INSURE group and 3 days (range, 0.1-144 days) in the Oxygen/MV group (P = .947). For the subgroup that required mechanical ventilation, the median duration of mechanical ventilation was similar in the 2 groups: 2.5 days (range, 0.1-51 days) for the CPAP/INSURE group and 2.0 days (range, 0.1-68 days) for the Oxygen/MV group (P = .767). No significant difference was seen in median length of hospital stay: 48.0 days (range, 1-118 days) in the CPAP/INSURE group versus 50.0 days (range, 0-173 days) in the Oxygen/MV group (P = .796).

Discussion

In VLBWIs with a birth weight of 800-1500 g, the CPAP/INSURE strategy reduced the need for mechanical ventilation

Table II. Respiratory outcomes and mortality

Outcome	CPAP/INSURE (n = 131), %	Oxygen/MV (n = 125), %	RR	95% CI	P value
RDS	50.0	56.0	0.89	0.71-1.13	.337
Mechanical ventilation	29.8	50.4	0.59	0.43-0.81	.001
Surfactant requirement	27.5	46.4	0.59	0.42-0.83	.002
Pneumothorax	3.1	5.6	0.55	0.16-1.82	.315
O_2 at 28 days of life	16.0	24.8	0.65	0.39-1.06	.081
BPD	6.9	9.6	0.72	0.31-1.64	.426
Death	8.4	9.6	0.87	0.40-1.91	.737
BPD/death	13.7	19.2	0.72	0.41-1.25	.238

RR, relative risk.

Table III. Secondary outcomes

Outcome	CPAP/INSURE (n = 131), %	Oxygen/MV (n = 125), %	RR	95% CI	P value
PDA	34.4	30.4	1.13	0.79-1.61	.500
IVH total	25.2	20.2	1.25	0.79-1.98	.338
IVH grade III-IV	4.6	6.4	0.72	0.26-2.00	.522
NEC	15.3	13.6	1.12	0.62-2.04	.705
ROP	13.0	16.8	0.77	0.43-1.39	.309
Sepsis	2.3	1.6	1.43	0.24-8.42	.999
Nasal damage	8.4	0.0	-	-	.001

NEC, necrotizing enterocolitis.

compared with treatment with an oxyhood and early selective surfactant administration followed by mechanical ventilation. The effect of this strategy on mechanical ventilation use and surfactant requirement—reductions of 40.8% and 40.7%, respectively—is very valuable in a region with limited resources. Our results suggest a more benign evolution of RDS in the infants treated with early CPAP, and consequently lower surfactant and mechanical ventilation requirements, although the higher threshold for mechanical ventilation in this group might have contributed to this latter outcome.

A 2002 Cochrane review[12] concluded that CPAP reduced respiratory failure when compared with less invasive support, such as the oxyhood. However, most of the studies in that review were decades old, and the infants had higher birth weight and GA and were older than those currently treated for RDS. In addition, the studies do not reflect current practice, including extensive use of prenatal steroids and postnatal surfactants. Our findings confirm that the results of those older studies still hold in today's prenatal steroid/surfactant era.

Several controlled studies of early CPAP treatment in developed countries have been published recently[21-24]; however, those studies are not comparable with the present study, because our control group received only oxyhood therapy. In brief, the studies showed that the infants receiving early CPAP required less surfactant and had fewer days of mechanical ventilation and less postnatal steroid use. In one of these studies, infants born at 24-25 weeks GA who received early CPAP had significantly lower mortality than those given early mechanical ventilation.[24]

A recent study from Colombia randomized 279 preterm infants born at 27-31 weeks GA with RDS in the first hour of life to either an INSURE to CPAP protocol or only CPAP.[25] The INSURE to CPAP group had lower mechanical ventilation requirements and less pneumothorax. Compared with the present study, the onset of CPAP was later, in the first hour of life.

In the present study, up to 2 doses of surfactant could be given to infants in the CPAP/INSURE group to reduce the use of mechanical ventilation. We found no previous reports of repeat use of the INSURE technique. Some 30.5% of infants received a second dose of surfactant when the FiO_2 requirement was >0.40. This strategy can further reduce the need for mechanical ventilation, although this may depend on the FiO_2 criterion for subsequent surfactant doses. A third dose of surfactant was required for 5.5% of the infants, and mechanical ventilation was indicated by protocol.

The most recent Cochrane review[26] concluded that the INSURE protocol reduces the use of mechanical ventilation, with a resulting lower incidence of alveolar rupture and BPD. However, whether these positive effects are secondary to the use of CPAP or the early surfactant is unclear.

This study used bubble CPAP and these results may not apply to other positive-pressure devices. It is also likely that results of early CPAP will vary according to birth weight and GA. The data published by Ammari et al[27] in one of the most experienced centers with CPAP, show that >80% of infants >900 g of birth weight did not required mechanical ventilation when CPAP was used. However, in newborns less than 700g the treatment success was only 25%.

Consistent with recent studies,[22-25] the present study found no reduction in BPD with the early use of CPAP, although the study was not powered for that purpose. Nonetheless, there were trends toward decreasing incidences of pneumothorax, BPD, and death in the CPAP/INSURE group that did not reach statistical significance. Nasal lesions were present only in the CPAP/INSURE group, but all cases were minor. No other adverse effects were found.

Our study has several limitations. This was not a blinded study, although management was rigidly defined in both groups. We enrolled only 55% of the total potential study population. One of the study's strengths is the inclusion of infants from 12 diverse centers throughout South America.

Our findings demonstrate the feasibility of successfully using less invasive ventilator strategies in VLBWIs in our region. For clinicians managing preterm neonates in the developing world, with few ventilators and a short supply of surfactant, early provision of nasal CPAP administered through an inexpensive system can significantly reduce the need for mechanical ventilation and surfactant without increasing death or morbidity. ∎

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