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KEY WORDS
premature, resuscitation, surfactant, CPAP, randomized controlled trial

ABBREVIATIONS
RDS—respiratory distress syndrome
BPD—bronchopulmonary dysplasia
nCPAP—nasal continuous positive airway pressure
PS—prophylactic surfactant
ISX—intubate-surfactant-extubate
FIO_2—fraction of inspired oxygen
CI—confidence interval
COIN—Continuous Positive Airway Pressure or Intubation at Birth

This trial has been registered at www.clinicaltrials.gov (identifier NCT00244101).

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WHAT'S KNOWN ON THIS SUBJECT: Intubation with prophylactic surfactant administration protects preterm infants from the complications of respiratory distress syndrome. From recent studies it was suggested that initial respiratory support with continuous positive airway pressure and later selective surfactant treatment might be an acceptable alternative.

WHAT THIS STUDY ADDS: Preterm neonates managed with early nasal CPAP or prophylactic surfactant with rapid extubation to nasal CPAP had outcomes similar to those treated with prophylactic surfactant followed by mechanical ventilation. Early CPAP might obviate the need for mechanical ventilation and/or surfactant.

abstract

OBJECTIVE: We designed a multicenter randomized trial to compare 3 approaches to the initial respiratory management of preterm neonates: prophylactic surfactant followed by a period of mechanical ventilation (prophylactic surfactant [PS]); prophylactic surfactant with rapid extubation to bubble nasal continuous positive airway pressure (intubate-surfactant-extubate [ISX]) or initial management with bubble continuous positive airway pressure and selective surfactant treatment (nCPAP).

DESIGN/METHODS: Neonates born at 26⁰⁄₇ to 29⁶⁄₇ weeks' gestation were enrolled at participating Vermont Oxford Network centers and randomly assigned to PS, ISX, or nCPAP groups before delivery. Primary outcome was the incidence of death or bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age.

RESULTS: 648 infants enrolled at 27 centers. The study was halted before the desired sample size was reached because of declining enrollment. When compared with the PS group, the relative risk of BPD or death was 0.78 (95% confidence interval: 0.59–1.03) for the ISX group and 0.83 (95% confidence interval: 0.64–1.09) for the nCPAP group. There were no statistically significant differences in mortality or other complications of prematurity. In the nCPAP group, 48% were managed without intubation and ventilation, and 54% without surfactant treatment.

CONCLUSIONS: Preterm neonates were initially managed with either nCPAP or PS with rapid extubation to nCPAP had similar clinical outcomes to those treated with PS followed by a period of mechanical ventilation. An approach that uses early nCPAP leads to a reduction in the number of infants who are intubated and given surfactant. *Pediatrics* 2011;128:e1069–e1076

The majority of neonates born at <30 weeks' gestation require respiratory support after birth to facilitate transition and ensure adequate gas exchange.[1] The best approach to the initial respiratory management of these infants is uncertain.

Endotracheal administration of exogenous surfactant decreases complications of respiratory distress syndrome (RDS) in premature infants.[2] Both prophylactic treatment, in which surfactant is administered shortly after birth to infants at high risk of developing RDS,[3] or selective therapy, in which surfactant is administered to infants only after they have exhibited evidence of significant RDS,[4] have been proven to be effective. Meta-analysis of 8 trials to compare these approaches revealed that prophylactic surfactant led to reduced rates of pneumothorax, neonatal mortality and the combined outcome of death or bronchopulmonary dysplasia (BPD).[5] However, several aspects of these trials deserve closer examination to determine their relevance to current clinical practice. Infants enrolled in these studies had low rates of exposure to antenatal steroids. If randomly assigned to receive prophylactic surfactant, infants were generally ventilated for a significant period of time after treatment and most infants in the selective treatment groups were on mechanical ventilation before surfactant treatment.

In 1987, Avery et al[6] reported that the application of early nasal continuous positive airway pressure (nCPAP) was associated with reduced rates of BPD. Over the past decade, many trials have demonstrated the feasibility and apparent benefits of providing early nCPAP,[7–11] and studies have also revealed that surfactant can be effectively administered to many infants initially managed with nCPAP with a brief period of endotracheal intubation followed by rapid extubation back to nCPAP.[12] Our trial was designed to compare the effect of 3 distinct approaches to the initial respiratory management of very preterm infants on the incidence of death or BPD.

METHODS

Study Design

The Delivery Room Management Trial was a multicenter randomized trial conducted at participating Vermont Oxford Network centers. To participate, study centers must have demonstrated competency in the use of bubble nCPAP by successfully completing a Web-based educational program and effectively using it in at least 20 infants. Each center obtained approval to conduct the study from their institutional review boards. Expectant parents were approached for informed consent if considered at high risk of having a preterm delivery at 26⅐ – 29⅐ weeks' gestation. Women who were carrying a fetus with a potentially life-threatening anomaly or condition were excluded. Random assignment took place when it was deemed that delivery was imminent. Infants could be excluded after randomization only if found to be stillborn or to have a previously unrecognized life-threatening congenital anomaly. Investigators randomly allocated infants to 1 of the 3 treatment arms by drawing a card contained within a sealed envelope. Stratification and block randomization was according to center and according to gestational age. Infants from multiple gestation pregnancies were randomly assigned as individual subjects.

Study Interventions

Infants were randomly allocated to 1 of 3 groups:

1. prophylactic surfactant (PS): infants were to be intubated 5 to 15 minutes after birth for the purposes of surfactant administration, then stabilized on mechanical ventilation for a minimum of 6 hours after which time they could be extubated to nCPAP;
2. intubate-surfactant-extubate (ISX): infants were to be intubated 5 to 15 minutes after birth for the purposes of surfactant administration. Infants who required a fraction of inspired oxygen (F_{IO_2}) < 0.6 without severe respiratory distress or apnea were to be extubated to nCPAP 15 to 30 minutes after surfactant instillation; or
3. nCPAP: infants were to be supported with nCPAP within 15 minutes after birth and intubated only if meeting 1 or more of the following criteria: (*a*) >12 episodes of apnea that required stimulation or more than 1 episode that required bagging in a 6-hour period; (*b*) P_{CO_2} > 65 mm Hg on arterial or capillary blood gas; or (*c*) requirement for F_{IO_2} of >0.4 to maintain oxygen saturation of 86% to 94%. Intubation was discretionary if F_{IO_2} was 0.4 to 0.6 and mandatory if F_{IO_2} > 0.6. After intubation, infants requiring supplemental oxygen were to be treated with surfactant.

Decisions regarding subsequent management with ongoing mechanical ventilation or extubation to nCPAP were at the discretion of the clinical team. All infants who required mechanical ventilation and F_{IO_2} of >0.30 for >6 hours after receiving surfactant were eligible for retreatment.

Patients who received nCPAP were initially supported with a pressure of 5 cm H_2O, which could be increased to a maximum of 7 cm H_2O. Short, binasal prongs were used as the interface. CPAP was generated by continuous gas flow delivered through a heated, humidified circuit with the end submerged to an appropriate depth in a water-filled bottle. We attempted to maintain infants on bubble nCPAP for

at least 72 hours after extubation and until 1 week of age if requiring supplemental oxygen. After the first week, the degree and method of respiratory support were determined by the clinicians caring for the infant.

Extubation was attempted when an infant on mechanical ventilation remained stable for a 6 hour period with a mean airway pressure of ≤7 cm H_2O and an F_{IO_2} of ≤0.30. Clinicians could extubate from higher ventilator settings if deemed appropriate. Use of methylxanthines before extubation was encouraged but not mandated.

Primary and Secondary Outcomes

The primary outcome was death or moderate to severe BPD at 36 weeks' postmenstrual age.[13] An infant was deemed to have BPD if on mechanical ventilation, CPAP, or required supplemental oxygen to maintain an arterial oxygen saturation of ≥88%.[14] Infants who required <30% oxygen via head box or 250 mL/minute of oxygen via nasal cannula were subjected to a oxygen saturation test to confirm the need for supplemental oxygen. Secondary outcomes included the number of infants who received surfactant, number of surfactant doses, use of postnatal steroids, growth, days on assisted ventilation, days on nCPAP, and days on supplemental oxygen. Other outcomes included the incidence of common complications of prematurity and mortality.[15]

Long-term outcomes including health and neurodevelopmental status as determined by questionnaire at 2 years' corrected age will form the basis of a future report.

Statistical Analysis

The primary analysis was performed by comparing each of the 2 "experimental" groups (ISX and nCPAP) to the "standard management" group (PS). Analysis was performed on an intention to treat basis. χ^2 test for categorical variables and analysis of variance for continuous variables were used. Relative risks and 95% confidence intervals (CIs) were calculated to compare outcomes of ISX and nCPAP groups to the PS group. Logistic regression was used to assess the effect of study group on the primary outcome, adjusting for gender, birth weight, antenatal steroid administration, mode of delivery, multiple birth, and chorioamnionitis.

Planned sample size was based on a 30% reduction in the number of infants with BPD per death from 36% to 25% ($\alpha = 0.05$; $\beta = 0.2$). Baseline incidence of BPD/death for infants born at 26⅐ to 29⅐ weeks' gestation was determined from the Vermont Oxford Network database. A total of 876 infants were to be enrolled with 292 in each arm of the study.

RESULTS

Three interim analyses for efficacy and safety were performed at scheduled intervals and revealed no safety concerns or significant differences between groups in the primary outcome. An additional analysis was requested in January 2009 to assess the effect of declining enrollment on study viability. The Data Safety Monitoring Committee recommended to the steering committee that recruitment be halted in March 2009 before the desired sample size was reached.

A total of 648 infants from 27 Vermont Oxford Network centers were enrolled between September 2003 and March 2009. During this time frame, 3335 infants within the eligible gestational age range were born at participating centers. Centers enrolled a median of 8 patients (range: 2–167). 55% of the infants were recruited from the top 3 enrolling centers. There were 301 infants of 26⅐ to 27⅐ and 347 of 28⅐ to 29⅐ weeks' gestation. Eight infants who were randomly assigned were not subsequently enrolled (Fig 1). Enrolled infants had a mean birth weight of 1053 g and mean gestational age of 28⅐ weeks. There were no significant differences in demographics or population characteristics between groups other than fewer male infants in the nCPAP group ($P < .05$, PS versus nCPAP group) (Table 1).

Adherence to assigned treatment protocol was assessed by examining support provided to study infants in the first hour after birth (Table 2). More than 98% of infants in both the PS and ISX groups were intubated and given surfactant. Of infants in the ISX group, 83.3% were successfully extubated, and 82.1% of infants in the nCPAP group were managed without intubation during this interval.

The rates of the primary outcome are shown in Table 3. There were no statistically significant differences between groups in the combined outcome of BPD or death at 36 weeks' postmenstrual age. The relative risk of BPD or death was 0.78 (95% CI: 0.59–1.03) for the ISX group and 0.83 (95% CI: 0.64–1.09) for the nCPAP group compared with the PS group. Adjustment of the rates using logistic regression analysis failed to alter the conclusion (death or BPD: ISX versus PS, OR: 0.68 [95% CI: 0.43–1.08]; nCPAP versus PS, OR: 0.82 [95% CI: 0.52–1.29]). Results were similar when the analysis was performed, excluding 21 infants in whom status using physiologic criteria for BPD was not clearly coded. Mortality and rates of death or BPD analyzed according to gestational age strata did not differ between groups.

Within the first week after birth, 100 of 222 (45.1%) of the infants in the nCPAP group were intubated, and all of them received surfactant. Number of surfactant doses received by infants in each group is shown in Fig 2. Of the infants in the ISX group, 111 of 216 (51.4%) had

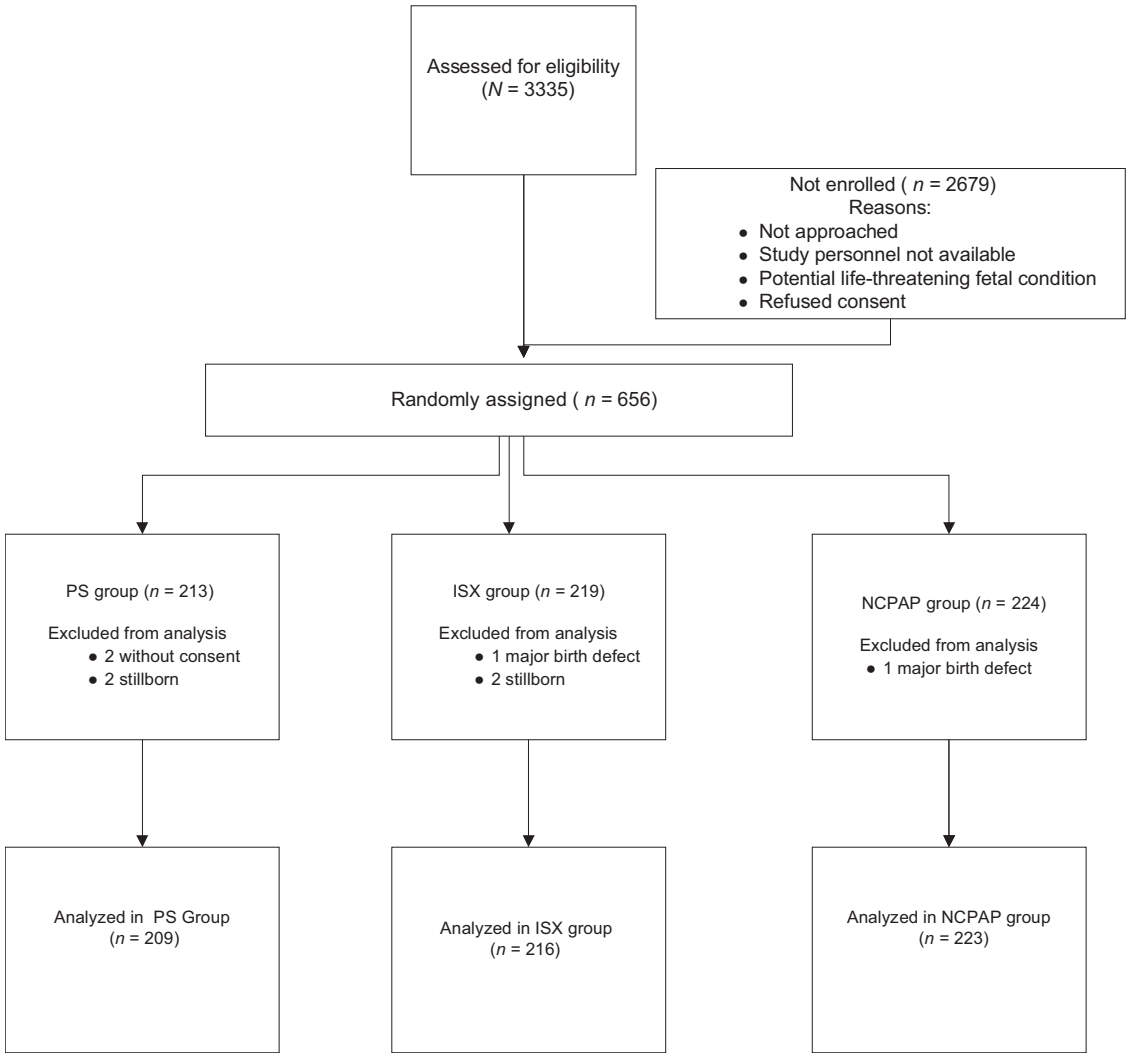

FIGURE 1
Consort diagram.

TABLE 1 Baseline Group Characteristics

	PS (n = 209)	ISX (n = 216)	nCPAP (n = 223)
Maternal characteristics, n/N (%)			
Prenatal care	206/209 (98.6)	214/216 (99.1)	221/223 (99.1)
Any antenatal steroids	206/209 (98.6)	213/216 (98.6)	220/223 (98.7)
Vaginal delivery	57/209 (27.3)	70/216 (32.4)	61/223 (27.4)
ROM >24 h	48/208 (23.1)	49/216 (22.7)	52/223 (23.3)
Clinical chorioamnionitis	14/209 (6.7)	24/216 (11.1)	24/222 (10.8)
Neonatal characteristics			
Birth weight, mean ± SD, kg	1040 ± 244	1066 ± 270	1053 ± 252
Gestational age, mean ± SD, wk	28.0 ± 1.1	28.1 ± 1.3	28.1 ± 1.1
Male, n/N (%)	118/209 (56.5)	115/216 (53.2)	99/223 (44.4)
White race, n/N (%)	154/206 (74.8)	164/213 (77.0)	151/218 (74.8)
Maternal education less than high school, n/N (%)	26/205 (12.7)	32/211 (15.2)	29/213 (13.6)
Multiple birth, n/N (%)	77/209 (36.8)	63/216 (29.2)	76/223 (34.1)
Median Apgar score			
At 1 min	6	6	7
At 5 min	8	8	8

an endotracheal tube at some point within the first week after birth but after the first hour. Of those that had been successfully extubated in the first hour, 75 of 180 (41.7%) required reintubation. Overall, 128 of 216 (59.3%) of the infants in this group received mechanical ventilation at some point during their hospitalization. The corresponding number for the nCPAP group was 116 of 222 (52.3%), which indicates that almost half of the infants managed with nCPAP initially were able to completely avoid endotracheal intubation. Other than differences in the rates of mechanical ventilation, there were no significant differences

TABLE 2 Respiratory Support in First Hour of Life

Intervention	PS ($n = 209$)	ISX ($n = 216$)	nCPAP ($n = 223$)
NCPAP, *n*/*N* (%)	11/209 (5.3)	167/216 (77.3)	203/223 (91.0)
Intubated, *n*/*N* (%)	207/209 (99.0)	213/216 (98.6)	40/223 (17.9)
Age at intubation, median (quartile), min	3.5 (2.0–5.0)	4.0 (2.0–6.0)	4.5 (3.0–11.5)
Surfactant administration, *n*/*N* (%)	206/209 (98.6)	212/216 (98.2)	33/223 (14.8)
Extubation, *n*/*N* (%)	1/209 (0.5)	180/216 (83.3)	5/223 (2.2)

TABLE 3 Status at 36 Weeks' Postmenstrual Age

	PS	ISX	RR (95% CI)	NCPAP	RR (95% CI)
All, *N*	209	216	—	223	—
Death, %	7.2	7.0	0.97 (0.49–1.94)	4.1	0.57 (0.25–1.27)
Death or BPD, %	36.5	28.5	0.78 (0.59–1.03)	30.5	0.83 (0.64–1.09)
Gestational age 26–27⅐ wk, *N*	98	101	—	102	—
Death, %	11.2	10.1	0.90 (0.40–2.02)	5.9	0.53 (0.20–1.38)
Death or BPD, %	53.1	43.4	0.82 (0.61–1.10)	40.6	0.77 (0.57–1.03)
Gestational age 28–29⅐ wk, *N*	111	115	—	121	—
Death, %	3.6	4.4	1.20 (0.33–4.34)	2.5	0.69 (0.16–3.03)
Death or BPD, %	21.8	15.7	0.72 (0.41–1.25)	21.9	1.00 (0.61–1.64)

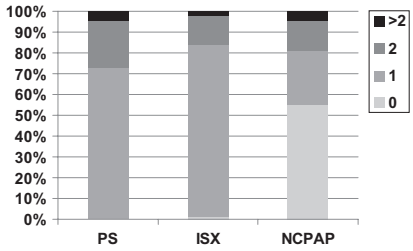

FIGURE 2
Surfactant dosing.

in type or duration of various forms of respiratory support provided to infants in the 3 groups (Table 4).

Other secondary outcomes are detailed in Table 5. There were no statistically significant differences between the groups except in the incidence of PDA. Although PDA was less common in the ISX group, the rates of surgical ligation were not different. Of note, the incidence of pneumothorax was similar between groups. There were also no differences in rates of weight gain or time to full feeds between groups (data not shown).

DISCUSSION

In this study, infants born at 26⅐ to 29⅐ weeks' gestation whom investigators attempted to initially support with nCPAP or those given prophylactic surfactant followed by rapid extubation to nCPAP seemed to have similar clinical outcomes to those treated with prophylactic surfactant followed by mechanical ventilation. The study was stopped after recruitment reached 74% of the projected sample size because of difficulties with enrollment. It is possible that statistically significant differences in outcome might have been demonstrated if the full sample size had been attained.

Early application of nCPAP in very preterm infants at high-risk of RDS seems to be safe and might lead to improved outcomes compared with elective intubation and ventilation. Even if considered equivalent, many would advocate using this approach as a means of providing a less invasive method of support. A significant number of infants stabilized with nCPAP shortly after birth can avoid intubation, ventilation, and surfactant treatment altogether. In this study, 48% of the infants in the nCPAP group were ultimately managed without intubation, and 54% were managed without the use of surfactant.

It is interesting to compare our study with the other recently reported randomized trials examining initial respiratory management of very preterm infants. The COIN trial (Continuous Positive Airway Pressure or Intubation at Birth) compared routine intubation to management with early nCPAP in spontaneously breathing preterm infants born between 25 and 28 weeks' gestation.[16] Results were equivocal, which suggests that clinicians should be comfortable using either approach and should expect comparable outcomes. In the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trial, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network examined a similar question.[17] They found that the outcomes of infants managed with either early nCPAP or intubation and prophylactic surfactant were similar. In the subgroup of infants born at 24 to 25 weeks' gestation, outcomes seemed to be improved if initial management with nCPAP was attempted. The European CURPAP study compared initial

TABLE 4 Respiratory Support

	PS ($n = 209$)	ISX ($n = 216$)	NCPAP ($n = 223$)
Time on O_2[a], mean ± SD, d	30.3 ± 26.5	26.0 ± 24.7	29.2 ± 28.3
Received nCPAP, *n*/*N* (%)	202/209 (96.7)	212/216 (98.2)	219/222 (98.7)
Time on nCPAP, mean ± SD, d[a]	17.0 ± 14.3	15.2 ± 13.0	16.1 ± 14.7
Received any mode of ventilation, *n*/*N* (%)	200/209 (95.7)	128/216 (59.3)	116/222 (52.3)
Time on any mode of ventilation, mean ± SD, d[a]	7.7 ± 12.4	9.2 ± 13.8	12.5 ± 14.1
Received HFV, *n*/*N* (%)	41/209 (19.6)	30/216 (13.9)	34/222 (15.3)
Time on HFV, mean ± SD, d[a]	7.7 ± 9.7	7.1 ± 10.3	9.3 ± 11.1
Nasal cannula >1 L/min, *n*/*N* (%)	51/175 (29.1)	45/178 (25.3)	55/181 (30.4)
Time on nasal cannula >1 L/min, mean ± SD, d[a]	13.0 ± 9.7	16.3 ± 11.5	11.7 ± 9.1

HFV indicates high-frequency ventilation.
[a] After first hour, only for infants who received the intervention.

TABLE 5 Complications of Prematurity

	PS, *n*/*N* (%)	ISX, *n*/*N* (%)	RR vs PS (95% CI)	NCPAP, *n*/*N* (%)	RR vs PS (95% CI)
Pneumothorax	10/209 (4.8)	7/216 (3.2)	0.68 (0.26–1.75)	12/222 (5.4)	1.13 (0.50–2.56)
Pulmonary hemorrhage	6/209 (2.9)	7/216 (3.2)	1.13 (0.39–3.30)	3/222 (1.4)	0.47 (0.12–1.86)
PDA	92/208 (44.2)	74/216 (34.3)	0.77 (0.61–0.98)	101/222 (45.5)	1.03 (0.83–1.27)
NEC	14/209 (6.7)	16/216 (7.4)	1.11 (0.55–2.21)	18/222 (8.1)	1.21 (0.69–2.54)
NEC surgery	9/209 (4.3)	7/215 (3.3)	0.75 (0.29–1.98)	12/222 (5.4)	1.25 (0.54–2.90)
Gastrointestinal perforation	10/209 (4.8)	6/216 (2.8)	0.58 (0.21–1.57)	7/221 (3.2)	0.66 (0.26–1.71)
Sepsis					
Late-onset bacterial infection[a]	27/205 (13.2)	25/214 (11.7)	0.89 (0.53–1.48)	17/220 (7.7)	0.59 (0.33–1.04)
Coagulase-negative staphylococcus	18/205 (8.8)	17/214 (7.9)	0.90 (0.48–1.71)	16/221 (7.2)	0.82 (0.43–1.57)
Late-onset fungal infection	3/205 (1.5)	3/214 (1.4)	0.96 (0.20–4.69)	1/221 (0.5)	0.31 (0.03–2.95)
Received cranial ultrasound	203/209 (97.1)	207/216 (95.8)	0.99 (0.95–1.02)	218/222 (98.2)	1.01 (0.98–1.04)
With any IVH, %	46/203 (22.7)	43/206 (20.9)	0.92 (0.64–1.33)	47/218 (21.6)	0.95 (0.66–1.36)
With severe IVH, %	12/203 (5.9)	8/206 (3.9)	0.66 (0.27–1.57)	6/218 (2.8)	0.47 (0.18–1.22)
PVL	2/190 (1.1)	6/204 (2.9)	2.79 (0.57–13.68)	3/206 (1.5)	1.38 (0.23–8.19)
Any ROP	65/183 (35.5)	61/180 (33.9)	0.95 (0.72–1.27)	85/192 (44.3)	1.25 (0.97–1.60)
Severe ROP	7/183 (3.8)	4/180 (2.2)	0.58 (0.17–1.95)	13/192 (6.8)	1.77 (0.72–4.34)

PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.
[a] All bacterial pathogens, including coagulase-negative staphylococcus.

management with nCPAP to prophylactic surfactant followed by rapid extubation to nCPAP in infants born at 25 to 28 weeks' gestation.[18] The investigators found similar outcomes between these groups and concluded that early application of nCPAP shortly after birth followed by selective surfactant treatment should be the preferred management strategy because many infants will be able to avoid intubation and surfactant treatment.

The COIN trial, SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial), and our study compared infants managed with elective intubation and ventilation versus early application of nCPAP. The findings from these 3 studies are remarkably consistent. Although entry criteria and indications for intubation and surfactant administration were different and no single trial was able to demonstrate a statistically significant difference, each study showed a lower relative risk of death or BPD when infants were managed initially with nCPAP.

Our study included a third treatment arm in which infants were intubated, given surfactant, and rapidly extubated to nCPAP. In theory, this might be the best approach because it allows the established benefit of prophylactic surfactant while avoiding exposing infants to ventilator induced lung injury. The Colombian Neonatal Research Network studied infants born at 27 to 31 weeks' gestation with signs of RDS at less than 1 hour of age who were randomly assigned to treatment approaches similar to our nCPAP and ISX groups.[19] Rates of mechanical ventilation and pneumothorax were reduced with very early surfactant administration without mandatory ventilation. However, there were no differences in rates of mechanical ventilation or BPD in their lower gestational age stratum of 27 to 29 weeks, consistent with the findings of our trial.

The 2 arms in the CURPAP study are also similar to the nCPAP and ISX groups of our study. Although there are some differences in entry criteria and study protocol, results are similar. Neither trial found a statistically significant advantage to either approach with respect to clinical outcomes. In both studies, approximately half of the infants placed electively on nCPAP shortly after birth were able to avoid intubation and surfactant treatment.

There are risks inherent to prophylactic surfactant administration. Even a short period of endotracheal intubation with positive pressure ventilation can lead to lung injury.[20] Furthermore, surfactant is not an inexpensive therapy, and some infants will deteriorate during the instillation process.[21] Prophylactic treatment results in a significant number of infants receiving treatment who seem to be able to do just as well without it, particularly those exposed to antenatal steroids.[22] However, attempts to provide initial respiratory support with nCPAP should not result in infants with significant RDS being disadvantaged by having surfactant withheld or administration delayed.

Several systematic reviews have been performed to examine timing of surfactant treatment in preterm infants with or at risk for RDS. Although studies included in these reviews did not generally include infants managed with nCPAP from shortly after birth, the reviews consistently conclude that outcomes are improved if surfactant is given earlier rather than later.[5,12,23] The increased rate of pneumothorax seen in the nCPAP group of the COIN trial might be in part because of the low percentage of these very preterm infants being given surfactant expeditiously. In the COIN study, the oxygenation criterion for intubation was a requirement for F_{IO_2} of >0.60 and, even with intubation, surfactant treat-

ment was not mandated. Verder et al[24] found that, when evaluating the INSURE approach (Intubation, Surfactant, Extubation) to surfactant treatment in preterm infants initially managed with nCPAP, those who were treated earlier with less severe disease had better outcomes than those treated only after requiring higher levels of supplemental oxygen. In the systematic review by Stevens et al,[12] infants selectively treated with surfactant at a lower F_{IO_2} threshold (<0.45) had fewer complications than those treated at a higher F_{IO_2}. We chose an oxygen requirement of >0.4 to prompt clinicians to strongly consider intubation and surfactant treatment. Using this criterion, only 45% of the nCPAP group was treated with surfactant, and there was no increase in rate of pneumothorax. The CURPAP study used similar criteria for selective surfactant treatment in the nCPAP group and did not demonstrate an increase in pneumothorax. If nCPAP is to be used to stabilize very preterm infants after birth, it is likely to be optimal if selective surfactant treatment is provided early in their course, as soon as infants have clear evidence of respiratory distress syndrome.

Because this study could not be blinded, there was a possibility of bias influencing the outcomes if providers managing the infants did not follow strict guidelines. However, the assigned treatment strategy was successfully applied in the majority of randomly assigned infants. Fewer than 20% of the infants in the ISX and nCPAP groups were unable to be managed as intended. Clinicians choosing to adopt either approach can expect successful application in most cases when managing infants born at 26 to 29 weeks.

CONCLUSIONS

We have shown that preterm neonates born at 26⁶⁄₇ to 29⁶⁄₇ weeks' gestation who are initially managed with either nCPAP or prophylactic surfactant with rapid extubation to nCPAP seem to have similar clinical outcomes to those treated with prophylactic surfactant followed by a period of mechanical ventilation. An approach that uses early nCPAP leads to a reduction in the number of infants who are intubated and receive surfactant. Because there seems to be no negative effect to applying an elective early nCPAP approach to these infants, it may be recommended as a less invasive and potentially less expensive method of management.

PARTICIPATING CENTERS

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Randomized Trial Comparing 3 Approaches to the Initial Respiratory Management of Preterm Neonates

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