ORIGINAL ARTICLE

Early CPAP versus Surfactant in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

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BACKGROUND

There are limited data to inform the choice between early treatment with continuous positive airway pressure (CPAP) and early surfactant treatment as the initial support for extremely-low-birth-weight infants.

METHODS

We performed a randomized, multicenter trial, with a 2-by-2 factorial design, involving infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation. Infants were randomly assigned to intubation and surfactant treatment (within 1 hour after birth) or to CPAP treatment initiated in the delivery room, with subsequent use of a protocol-driven limited ventilation strategy. Infants were also randomly assigned to one of two target ranges of oxygen saturation. The primary outcome was death or bronchopulmonary dysplasia as defined by the requirement for supplemental oxygen at 36 weeks (with an attempt at withdrawal of supplemental oxygen in neonates who were receiving less than 30% oxygen).

RESULTS

A total of 1316 infants were enrolled in the study. The rates of the primary outcome did not differ significantly between the CPAP group and the surfactant group (47.8% and 51.0%, respectively; relative risk with CPAP, 0.95; 95% confidence interval [CI], 0.85 to 1.05) after adjustment for gestational age, center, and familial clustering. The results were similar when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks (rates of primary outcome, 48.7% and 54.1%, respectively; relative risk with CPAP, 0.91; 95% CI, 0.83 to 1.01). Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia (P<0.001), required fewer days of mechanical ventilation (P=0.03), and were more likely to be alive and free from the need for mechanical ventilation by day 7 (P=0.01). The rates of other adverse neonatal outcomes did not differ significantly between the two groups.

CONCLUSIONS

The results of this study support consideration of CPAP as an alternative to intubation and surfactant in preterm infants. (ClinicalTrials.gov number, NCT00233324.)

IT HAS BEEN SHOWN THAT SURFACTANT treatment at less than 2 hours of life significantly decreases the rates of death, air leak, and death or bronchopulmonary dysplasia in preterm infants.[1,2] Overall, prophylactic treatment with surfactant has not been shown to significantly reduce the risk of bronchopulmonary dysplasia alone, whereas studies comparing early with later rescue use of surfactant have shown that there is a decreased risk of chronic lung disease with early use.[2] Several studies have shown that the use of surfactant does not have a significant effect on the risk of subsequent neurodevelopmental impairment,[3] although a recent follow-up assessment of infants involved in a randomized trial showed that early surfactant treatment (at a mean of 31 minutes of age) as compared with later surfactant treatment (at a mean of 202 minutes of age) was associated with a significantly higher rate of increased muscle tone in the infants and a delay in the infants' ability to roll from the supine to the prone position.[4] However, in many of the trials of surfactant treatment, the rate of maternal corticosteroid therapy before delivery — an intervention known to improve neonatal survival[5] and decrease the rate of complications — was not high, and none of the infants in the control group received early treatment with continuous positive airway pressure (CPAP). There is a growing body of observational evidence suggesting that in the case of very preterm infants with respiratory distress who are not treated initially with surfactant, the early use of CPAP may decrease the need for mechanical ventilation without an increase in complications.[6-11]

In a previous study reported in the *Journal*, 610 infants, born between 25 weeks 0 days and 28 weeks 6 days of gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time, were randomly assigned to either intubation and ventilation or CPAP at a pressure of 8 cm of water; infants who were randomly assigned to CPAP were intubated if they met certain criteria for the failure of CPAP treatment.[12] There was no significant reduction in the CPAP group, as compared with the intubated group, in the rate of death or the need for supplemental oxygen at 36 weeks (the primary outcome), and there was a significantly higher rate of pneumothorax in the CPAP group than in the intubated group (9.1% vs. 3.0%); most of the cases of pneumothorax occurred within the first 2 days, which is consistent with the findings of a previous meta-analysis.[13]

We designed the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) to compare early CPAP treatment with early surfactant treatment in extremely preterm infants. Using a factorial design, we also randomly assigned infants to one of two target ranges of oxygen saturation during their exposure to supplemental oxygen.

METHODS

STUDY DESIGN

In this randomized, multicenter trial, we compared a strategy of treatment with CPAP and protocol-driven limited ventilation begun in the delivery room and continued in the neonatal intensive care unit (NICU) with a strategy of early intratracheal administration of surfactant (within 1 hour after birth) followed by a conventional ventilation strategy. In a 2-by-2 factorial design, infants were also randomly assigned to one of two target ranges of oxygen saturation (85 to 89% or 91 to 95%) until the infant was 36 weeks of age or no longer received ventilatory support or supplemental oxygen. The results of this portion of the study are discussed elsewhere in this issue of the *Journal*.[14] Randomization was stratified according to center and gestational-age group, with the use of specially prepared double-sealed envelopes, and was performed before the actual delivery. Infants who were part of multiple births were randomly assigned to the same group. Written informed consent from a parent or guardian for an infant's participation in the trial was required before delivery.

Infants were eligible for inclusion in the study if they were 24 weeks 0 days to 27 weeks 6 days of gestation at birth according to the best obstetrical estimate, if they were born without known malformations at a participating center, if a decision had been made to provide full resuscitation for them, and if written informed consent had been obtained from a parent or guardian. The infants were randomly assigned within each center and within each gestational-age stratum (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days).

The study was conducted as part of the Neonatal Research Network of the Eunice Kennedy

Shriver National Institute of Child Health and Human Development. The study was approved by the human subjects committee at each participating site and at RTI International, which is the data center for the Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for this study.

CPAP GROUP

In the delivery room, CPAP was administered by means of a T-piece resuscitator, a neonatal ventilator, or an equivalent device. CPAP or ventilation with positive end-expiratory pressure (PEEP) (at a recommended pressure of 5 cm of water) was used if the infant received positive-pressure ventilation during resuscitation. CPAP was continued until the infant's admission to the NICU. Intubation was not performed for the sole purpose of surfactant administration in infants who were randomly assigned to the CPAP group, but infants who required intubation for resuscitation on the basis of standard indications specified in the Neonatal Resuscitation Program guidelines[15] were given surfactant within 60 minutes after birth.

In the NICU, infants who were randomly assigned to CPAP could be intubated if they met any of the following criteria: a fraction of inspired oxygen(FIO_2) greater than 0.50 required to maintain an indicated saturation of peripheral oxygen (SpO_2) at or above 88% for 1 hour; a partial pressure of arterial carbon dioxide ($PaCO_2$) greater than 65 mm Hg, documented by a single measurement of blood gases within 1 hour before intubation; or hemodynamic instability, defined as a blood pressure that was low for gestational age, poor perfusion, or both, requiring volume or pressor support for a period of 4 hours or more. Infants who were intubated within the first 48 hours after birth were to receive surfactant. After an infant's admission to the NICU, the unit used its standard method for the delivery of CPAP — that is, a ventilator, a purpose-built flow driver, or a bubble CPAP circuit.

Extubation of an infant in the CPAP group was to be attempted within 24 hours after the infant met all of the following criteria: a $PaCO_2$ below 65 mm Hg with a pH higher than 7.20, an SpO_2 above 88% with an FIO_2 below 0.50, a mean airway pressure of less than 10 cm of water, a ventilator rate of less than 20 breaths per minute, an

amplitude of less than twice the mean airway pressure if high-frequency ventilation was being used, hemodynamic stability, and the absence of clinically significant patent ductus arteriosus. Criteria for reintubation were the same as those for initial intubation. After three intubations, infants in the CPAP group received treatment according to the standard practice in the NICU to which they had been admitted.

SURFACTANT GROUP

All the infants in the surfactant group were to be intubated in the delivery room and were to receive surfactant within 1 hour after birth with continued ventilation thereafter. The infants were to be extubated within 24 hours after meeting all of the following criteria: a $PaCO_2$ of less than 50 mm Hg and a pH higher than 7.30, an FIO_2 of 0.35 or less with an SpO_2 of 88% or higher, a mean airway pressure of 8 cm of water or less, a ventilator rate of 20 breaths per minute or less, an amplitude of less than twice the mean airway pressure if high-frequency ventilation was being used, and hemodynamic stability without evidence of clinically significant patent ductus arteriosus. Once the infants were extubated, they were treated according to the standard practice in the NICU to which they had been admitted.

The criteria for both groups were in effect for the infants' first 14 days of life, after which the infants were treated according to the standard practice in the NICU to which they had been admitted. In the case of both groups, intubation could be performed at any time if there was an episode of repetitive apnea requiring bag-and-mask ventilation, clinical shock, or sepsis, or if surgery was required.

OUTCOMES

The primary outcome was death or bronchopulmonary dysplasia. Bronchopulmonary dysplasia was defined according to the physiological definition, as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen.[16,17] Prespecified secondary outcomes included bronchopulmonary dysplasia as defined by the receipt of any supplemental oxygen at 36 weeks. Prespecified safety

outcomes included death, pneumothorax, intraventricular hemorrhage, and the need for chest compressions or epinephrine during resuscitation.

STATISTICAL ANALYSIS

The sample-size calculations were based on data from the Neonatal Research Network from the year 2000, which showed that the rate of death or survival with bronchopulmonary dysplasia at 36 weeks was 67% and the rate of death or survival with neurodevelopmental impairment at 18 to 22 months was 61%. We hypothesized that with early CPAP there would be a reduction of 10% in the incidence of these complications. We increased the sample size by a factor of 1.12 to allow for infants in multiple births to be randomly assigned to the same treatment, because this introduced a clustering effect into the design, and we increased the sample sizes by an additional 17% to adjust for loss to follow-up after discharge. We increased the sample size further to minimize type I error with the use of a conservative 2% level of significance. The result was a target sample of 1310 infants. We planned to test for an interaction between the two factorial parts of the study, but the study was not powered for that analysis.

Analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percentage of infants in each group who survived to 36 weeks of postmenstrual age without bronchopulmonary dysplasia. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Two-sided P values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. An independent data and safety monitoring committee reviewed the interim safety and efficacy results — including those related to adverse outcomes — four times. Lan–DeMets spending functions with Pocock and O'Brien–Fleming boundaries were used to determine stopping rules for interim safety and efficacy monitoring, respectively.

For the 46 planned analyses of secondary outcomes according to treatment, we would expect no more than 3 tests to have P values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for 36 predefined outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 2 tests per stratum to have P values of less than 0.05 on the basis of chance alone.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

From February 2005 through February 2009, a total of 1316 infants were enrolled, of whom 565 were in the lower gestational-age stratum (24 weeks 0 days to 25 weeks 6 days) and 751 were in the higher stratum (26 weeks 0 days to 27 weeks 6 days) (Fig. 1). There were no significant differences between the two treatment groups with respect to sex, birth weight, or race or ethnic group (Table 1).

Delivery room interventions in the two groups are summarized in Table 2. The rates of intubation in the delivery room and of the use of positive-pressure ventilation or epinephrine to treat persistent bradycardia were significantly lower among infants randomly assigned to CPAP than among those assigned to surfactant treatment. Overall, 32.9% of the infants in the CPAP group did not receive surfactant during their hospitalization.

PRIMARY OUTCOME

After adjustment for gestational age, center, and familial clustering, the rates of the primary outcome of death or bronchopulmonary dysplasia as assessed according to the physiological definition did not differ significantly between the two groups. The results were similar when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks. When components of this composite outcome were analyzed separately, there was no significant between-group difference in the rate of death or the rate of bronchopulmonary dysplasia (Table 3).
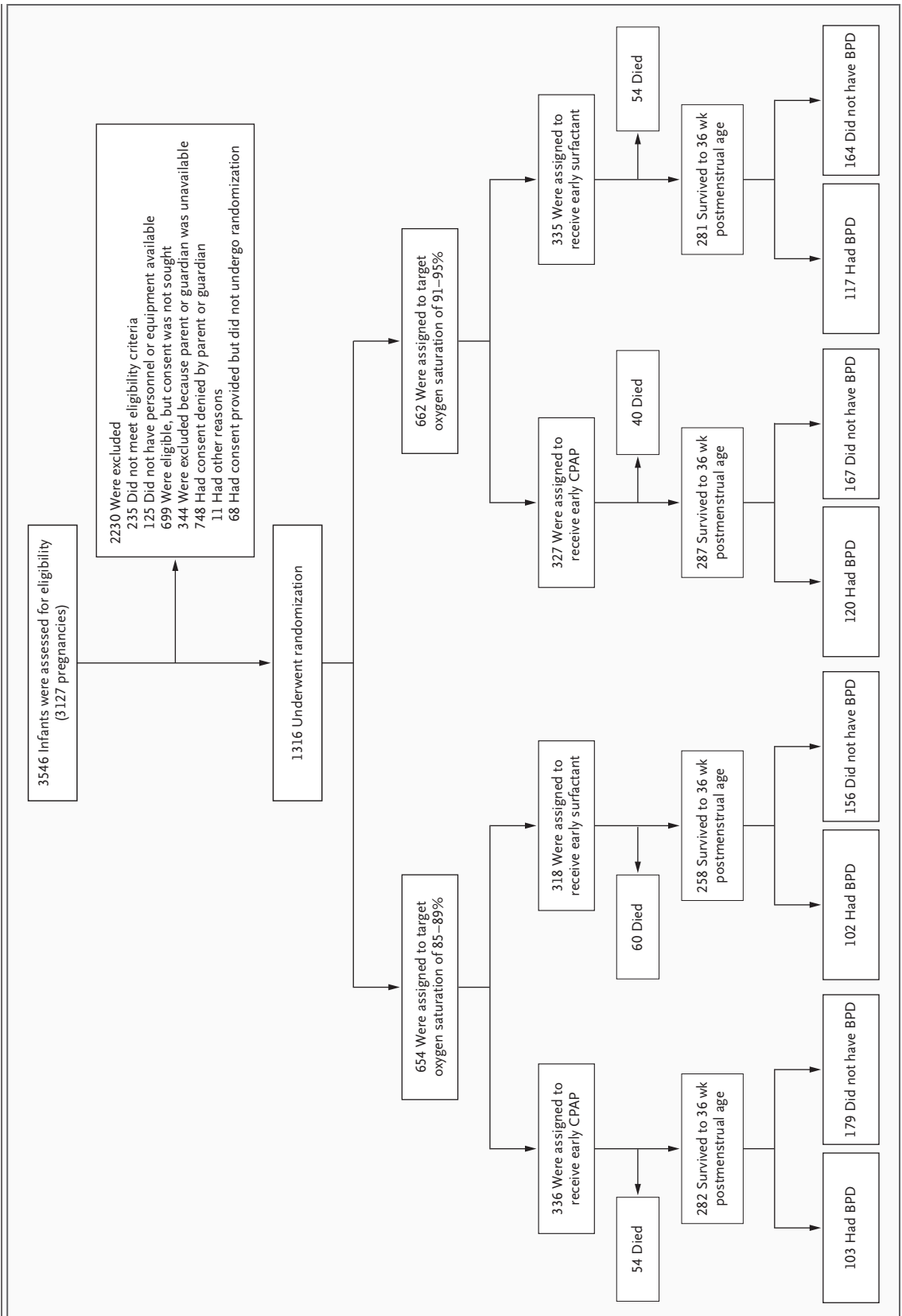
3546 Infants were assessed for eligibility (3127 pregnancies)

2230 Were excluded
  235 Did not meet eligibility criteria
  125 Did not have personnel or equipment available
  699 Were eligible, but consent was not sought
  344 Were excluded because parent or guardian was unavailable
  748 Had consent denied by parent or guardian
  11 Had other reasons
  68 Had consent provided but did not undergo randomization

1316 Underwent randomization

654 Were assigned to target oxygen saturation of 85–89%

662 Were assigned to target oxygen saturation of 91–95%

318 Were assigned to receive early surfactant
  60 Died
  258 Survived to 36 wk postmenstrual age
    156 Did not have BPD
    102 Had BPD

336 Were assigned to receive early CPAP
  54 Died
  282 Survived to 36 wk postmenstrual age
    179 Did not have BPD
    103 Had BPD

335 Were assigned to receive early surfactant
  54 Died
  281 Survived to 36 wk postmenstrual age
    164 Did not have BPD
    117 Had BPD

327 Were assigned to receive early CPAP
  40 Died
  287 Survived to 36 wk postmenstrual age
    167 Did not have BPD
    120 Had BPD

The numbers in the figure exclude infants of women who were screened during pregnancy but whose babies were not subsequently born at a study center between 24 weeks 0 days and 27 weeks 6 days of gestation. Postmenstrual age is defined as the gestational age plus the postnatal age. BPD denotes bronchopulmonary dysplasia according to the physiological definition (receipt of more than 30% supplemental oxygen at 36 weeks, the need for positive-pressure support, or in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen).[16,17]

Table 1. Demographic and Clinical Characteristics of the Study Participants.*

Variable	CPAP (N=663)	Surfactant (N=653)
Gestational age — no. (%)		
24 wk 0 days–25 wk 6 days	285 (43.0)	280 (42.9)
26 wk 0 days–27 wk 6 days	378 (57.0)	373 (57.1)
Assignment to low target oxygen-saturation range in 2-by-2 factorial design — no./total no. (%)		
Gestational age of 24–25 wk	142/285 (49.8)	134/280 (47.9)
Gestational age of 26–27 wk	194/378 (51.3)	184/373 (49.3)
Male sex — no. (%)	342 (51.6)	370 (56.7)
Race or ethnic group — no. (%)†		
Non-Hispanic black	254 (38.3)	235 (36.0)
Non-Hispanic white	250 (37.7)	271 (41.5)
Hispanic	138 (20.8)	121 (18.5)
Other or unknown	21 (3.2)	26 (4.0)
Birth weight — g	834.6±188.2	825.5±198.1
Gestational age at birth — wk	26.2±1.1	26.2±1.1
Maternal use of antenatal corticosteroids — no./total no. (%)		
Any	642/663 (96.8)	623/652 (95.6)
Full course	486/660 (73.6)	453/649 (69.8)
Death of infant in the delivery room — no. (%)	1 (0.2)	5 (0.8)

* Plus–minus values are means ±SD. None of the differences between groups were significant. CPAP denotes continuous positive airway pressure.
† Race or ethnic group was reported by the mother or guardian of each child.

There was no significant interaction between the two interventions assessed in the trial with respect to the primary outcome of death or bronchopulmonary dysplasia as assessed either according to the physiological definition (P=0.59) or according to the need for any supplemental oxygen at 36 weeks (P=0.53). There was no significant interaction between gestational-age stratum and treatment strategy with respect to the primary outcome (P=0.84 with the physiological definition of bronchopulmonary dysplasia and P=0.44 with bronchopulmonary dysplasia defined according to the need for any supplemental oxygen at 36 weeks), and there was no significant between-group difference in the rate of the primary outcome (with either definition of bronchopulmonary dysplasia) in either gestational-age stratum.

SECONDARY OUTCOMES

More infants in the CPAP group than in the surfactant group were alive and free from the need for mechanical ventilation by day 7 (P=0.01), and infants in the CPAP group required fewer days of ventilation than did those in the surfactant group (P=0.03). There were no significant between-group differences in the rates of air leak in the first 14 days, pneumothorax during the hospital stay, necrotizing enterocolitis requiring medical or surgical treatment, patent ductus arteriosus requiring surgery, severe intraventricular hemorrhage, or severe retinopathy of prematurity, as defined according to the new type 1 threshold in the Early Treatment for Retinopathy of Prematurity study (ETROP; ClinicalTrials .gov number, NCT00027222)[18] or according to the need for surgical intervention among survivors. One infant in the surfactant group died in the delivery room at 21 minutes after birth and

was not intubated; 83.1% of the infants in the CPAP group were intubated (P<0.001). The rate of use of postnatal corticosteroids to treat bronchopulmonary dysplasia was lower in the CPAP group than in the surfactant group (P<0.001) (Table 3). The other secondary outcomes are shown in Table 3.

In post hoc stratified analyses of secondary outcomes, among infants who were born between 24 weeks 0 days and 25 weeks 6 days of gestation, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group (rate of death during hospitalization: 23.9% vs. 32.1%; relative risk with CPAP, 0.74; 95% confidence interval [CI], 0.57 to 0.98; P=0.03; rate of death at 36 weeks: 20.0% vs. 29.3%; relative risk, 0.68; 95% CI, 0.5 to 0.92; P=0.01 [see Table A1 in the Supplementary Appendix, available with the full text of this ar-

Table 2. Apgar Scores of Newborns and Interventions in the Delivery Room and NICU.*

Variable	CPAP (N=663)	Surfactant (N=653)	Relative Risk with CPAP (95% CI)	Adjusted P Value
	no./total no. (%)			
Apgar score <3				
At 1 min	154/661 (23.3)	167/653 (25.6)	0.92 (0.76–1.11)	0.38
At 5 min	26/663 (3.9)	32/653 (4.9)	0.82 (0.5–1.34)	0.43
PPV in the delivery room	435/662 (65.7)	606/652 (92.9)	0.71 (0.67–0.75)	<0.001
CPAP in the delivery room	538/663 (81.1)	146/653 (22.4)	3.66 (3.16–4.25)	<0.001
Intubation in the delivery room				
For any reason	227/660 (34.4)	609/652 (93.4)	0.37 (0.34–0.42)	<0.001
For resuscitation	215/660 (32.6)	176/652 (27.0)	1.21 (1.02–1.43)	0.02
Surfactant treatment				
In the delivery room	93/660 (14.1)	335/652 (51.4)	0.28 (0.23–0.34)	<0.001
In the delivery room or NICU	443/660 (67.1)	646/653 (98.9)	0.67 (0.64–0.71)	<0.001
Chest compressions in the delivery room	36/660 (5.5)	40/653 (6.1)	0.86 (0.57–1.31)	0.48
Epinephrine in the delivery room	13/660 (2.0)	27/653 (4.1)	0.48 (0.25–0.91)	0.02

* CI denotes confidence interval, CPAP continuous positive airway pressure, NICU neonatal intensive care unit, and PPV positive-pressure ventilation.

ticle at NEJM.org]); in contrast, there was no significant between-group difference in the rate of death during hospitalization or at 36 weeks among the infants who were born between 26 weeks 0 days and 27 weeks 6 days of gestation (rate of death during hospitalization: 10.8% and 10.2%, respectively; rate of death at 36 weeks: 9.8% and 8.6%, respectively) (see Tables A1 and A3 in the Supplementary Appendix).

DISCUSSION

In this multicenter, randomized trial involving extremely preterm infants, there was no significant difference between a strategy of early CPAP and limited ventilation and a strategy of early intubation and surfactant administration within 1 hour after birth with respect to the rate of the composite primary outcome of death or bronchopulmonary dysplasia. We used the physiological definition of bronchopulmonary dysplasia, since it includes as a specification an attempt to withdraw supplemental oxygen from infants receiving less than 30% oxygen at 36 weeks, in order to confirm their need for supplemental oxygen.[16,17] Plausible results, on the basis of the 95% confidence intervals for the relative-risk estimates, included a risk of death or bronchopulmonary

dysplasia in the CPAP group that was between 85 and 105% of that in the surfactant group. The results were similar in secondary analyses in which bronchopulmonary dysplasia was defined according to the use of any supplemental oxygen at 36 weeks.

We did not include infants who were born at a gestational age of less than 24 weeks, since the results of a pilot trial showed that 100% of such infants required intubation in the delivery room.[19] A retrospective study showed that some infants in this gestational-age group can be treated successfully with early CPAP, but the majority require intubation.[20]

There was a high rate of intubation and surfactant treatment among infants assigned to CPAP, but this was anticipated, given the design of the study, which was to test an initial strategy of early CPAP as compared with early intubation and surfactant, with crossover planned for ethical reasons in the case of infants in whom CPAP treatment was not successful. Our trial differs from the trial of Morley et al.[12] in that we randomly assigned all eligible preterm infants to a treatment group, irrespective of whether they were breathing spontaneously or whether they had respiratory distress that warranted intervention, and in that we included infants who were born as early

Table 3. Selected Prespecified Outcomes.*

Outcome	CPAP (N = 663)	Surfactant (N = 653)	Relative Risk with CPAP (95% CI)	Difference in Means (95% CI)	Adjusted P Value
BPD or death by 36 wk of postmenstrual age — no. (%)					
Physiological definition of BPD†	317 (47.8)	333 (51.0)	0.95 (0.85 to 1.05)		0.30
BPD defined by need for supplemental oxygen	323 (48.7)	353 (54.1)	0.91 (0.83 to 1.01)		0.07
BPD by 36 wk of postmenstrual age — no./total no. (%)					
Physiological definition of BPD†	223/569 (39.2)	219/539 (40.6)	0.99 (0.87 to 1.14)		0.92
BPD defined by need for supplemental oxygen	229/569 (40.2)	239/539 (44.3)	0.94 (0.82 to 1.06)		0.32
Death by 36 wk of postmenstrual age — no. (%)	94 (14.2)	114 (17.5)	0.81 (0.63 to 1.03)		0.09
Need for supplemental oxygen — no. of days‡					0.12
Adjusted mean	62.2±1.6	65.3±1.6		–3.1 (–7.1 to 0.8)	
Unadjusted median	52	56			
Interquartile range	20 to 86	27 to 91			
Need for mechanical ventilation — no. of days‡§					0.03
Adjusted mean	24.8±1.0	27.7±1.1		–3.0 (–5.6 to –0.3)	
Unadjusted median	10	13			
Interquartile range	2 to 32	2 to 36			
Survival without need for high-frequency or conventional ventilation at 7 days — no./total no. (%)	362/655 (55.3)	318/652 (48.8)	1.14 (1.03 to 1.25)		0.01
Any air leak in first 14 days — no. (%)	45 (6.8)	48 (7.4)	0.89 (0.6 to 1.32)		0.56
Necrotizing enterocolitis requiring medical or surgical treatment — no./total no. (%)	83/654 (12.7)	63/636 (9.9)	1.25 (0.92 to 1.71)		0.15
Intraventricular hemorrhage grade 3 or 4 — no./total no. (%)¶	92/642 (14.3)	72/628 (11.5)	1.26 (0.94 to 1.68)		0.12
Postnatal corticosteroid therapy for BPD — no./total no. (%)	47/649 (7.2)	83/631 (13.2)	0.57 (0.41 to 0.78)		<0.001
Severe retinopathy of prematurity among survivors — no./total no. (%)	67/511 (13.1)	65/473 (13.7)	0.94 (0.69 to 1.28)		0.71

* Plus–minus values are means ±SD. BPD denotes bronchopulmonary dysplasia, CI confidence interval, and CPAP continuous positive airway pressure.
† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% supplemental oxygen at 36 weeks, the need for positive-pressure support, or in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of supplemental oxygen.[16,17]
‡ Data are for 1098 infants who survived to discharge, transfer, or 120 days; the maximum follow-up was 120 days.
§ This variable includes high-frequency ventilation and conventional ventilation.
¶ There are four grades of intraventricular hemorrhage; higher grades indicate more severe bleeding.

as 24 weeks of gestation. In the study by Morley et al., surfactant was not administered routinely in the intubation group. Our protocol, which called for early CPAP and a determination of the need for intubation, was based on the findings of previous observational studies showing that Neonatal Research Network sites that had the most experience with CPAP also used a higher threshold for intubation and the initiation of mechanical ventilation than did sites with less experience.[4-6] The infants who were randomly assigned to surfactant treatment in our trial were

treated with a ventilation approach that was used by a majority of the Neonatal Research Network sites before the trial began. We believed that comparing these two methods would provide more clinically relevant results. Data are currently being collected to assess survival without neurodevelopmental impairment at 18 to 22 months.

We found no significant between-group differences in the rates of pneumothorax, intraventricular hemorrhage, or the need for chest compressions or epinephrine in the delivery room, and the rates were similar to those among infants in the Neonatal Research Network population who were born between 2000 and 2004 at similar gestational ages. The rate of air leaks in the first 14 days of life was not increased with the use of early CPAP at a pressure of 5 cm of water, as compared with the use of early surfactant.

In secondary analyses stratified according to gestational age at birth, there was a significant reduction in the risk of death in the CPAP group, as compared with the early-intubation group, among infants born between 24 weeks 0 days and 25 weeks 6 days of gestation but not among infants who were born at a later gestational age. Given the fact that there was no significant interaction between the intervention and gestational age, the post hoc nature of these analyses, and the number of secondary analyses performed, this observation must be interpreted with caution, and further testing should be performed in this immature population.

In summary, we found no significant difference in the primary outcome of death or bronchopulmonary dysplasia between infants randomly assigned to early CPAP and those assigned to early surfactant treatment. In secondary analyses, the CPAP strategy, as compared with early surfactant treatment, resulted in a lower rate of intubation (both in the delivery room and in the NICU), a reduced rate of postnatal corticosteroid use, and a shorter duration of ventilation without an increased risk of any adverse neonatal outcome. These data support consideration of CPAP as an alternative to routine intubation and surfactant administration in preterm infants.

APPENDIX

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