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Delivery Room Continuous Positive Airway Pressure/Positive End-Expiratory Pressure in Extremely Low Birth Weight Infants: A Feasibility Trial

Neil N. Finer, MD*; Waldemar A. Carlo, MD‡; Shahnaz Duara, MD§; Avroy A. Fanaroff, MB, BCh‖; Edward F. Donovan, MD¶; Linda L. Wright, MD#; Sarah Kandefer, BSPH**; and W. Kenneth Poole, PhD**, for the National Institute of Child Health and Human Development Neonatal Research Network

ABSTRACT. *Objective.* **Although earlier studies have suggested that early continuous airway positive pressure (CPAP) may be beneficial in reducing ventilator dependence and subsequent chronic lung disease in the extremely low birth weight (ELBW) infant, the time of initiation of CPAP has varied, and there are no prospective studies of infants who have received CPAP or positive end-expiratory pressure (PEEP) from initial resuscitation in the delivery room (DR). Current practice for the ELBW infant includes early intubation and the administration of prophylactic surfactant, often in the DR. The feasibility of initiating CPAP in the DR and continuing this therapy without intubation for surfactant has never been determined prospectively in a population of ELBW infants. This study was designed to determine the feasibility of randomizing ELBW infants of <28 weeks' gestation to CPAP/PEEP or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine DR intubation for surfactant administration, initiating CPAP on neonatal intensive care unit (NICU) admission, and assessing compliance with subsequent intubation criteria.**

Methods. **Infants who were of <28 weeks' gestation, who were born in 5 National Institute of Child Health and Human Development Neonatal Research Network NICUs from July 2002 to January 2003, and for whom a decision had been made to provide full treatment after birth were randomized to receive either CPAP/PEEP or not using a neonatal T-piece resuscitator (NeoPuff). Infants would not be intubated for the sole purpose of surfactant administration in the DR. After admission to the NICU, all nonintubated infants were placed on CPAP and were to be intubated for surfactant administration only after meeting specific criteria: a fraction of inspired oxygen of >0.3 with an oxygen saturation by pulse oximeter of <90% and/or an arterial oxygen pressure of <45 mm Hg, an arterial partial pressure of carbon dioxide of >55 mm Hg, or apnea requiring bag and mask ventilation.**

Results. **A total of 104 infants were enrolled over a 6-month period: 55 CPAP and 49 control infants. No infant was intubated in the DR for the exclusive purpose of surfactant administration. Forty-seven infants were intubated for resuscitation in the DR: 27 of 55 CPAP infants and 20 of 49 control infants. Only 4 of the 43 infants who had a birth weight of <700 g and 3 of the 37 infants of <25 weeks' gestation were resuscitated successfully without positive pressure ventilation, and no difference was observed between the treatment groups. All infants of 23 weeks' gestation required intubation in the DR, irrespective of treatment group, whereas only 3 (14%) of 21 infants of 27 weeks' required such intubation. For infants who were not intubated in the DR, 36 infants (16 CPAP infants and 20 control infants) were subsequently intubated in the NICU by day 7, in accordance with the protocol. Overall, 80% of studied infants required intubation within the first 7 days of life. The care provided for 52 (95%) of 55 CPAP infants and 43 (88%) of the 49 control infants was in compliance with the study protocol, with an overall compliance of 91%.**

Conclusions. **This study demonstrated that infants could be randomized successfully to a DR intervention of CPAP/PEEP compared with no CPAP/PEEP, with intubation provided only for resuscitation indications, and subsequent intubation for prespecified criteria. Forty-five percent (47 of 104) of infants <28 weeks' gestation required intubation for resuscitation in the DR. CPAP/PEEP in the DR did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life. This experience should be helpful in facilitating the design of subsequent prospective studies of ventilatory support in ELBW infants.** *Pediatrics* **2004;114:651–657;** ***premature, ELBW, resuscitation, CPAP, PEEP, intubation, surfactant.***

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ABBREVIATIONS. CPAP, continuous positive airway pressure; VLBW, very low birth weight; DR, delivery room; CLD, chronic lung disease; ELBW, extremely low birth weight; NICU, neonatal intensive care unit; PEEP, positive end-expiratory pressure; PPV, positive pressure ventilation; PIP, peak inspiratory pressure; Spo_2, oxygen saturation by pulse oximeter; Fio_2, fraction of inspired oxygen; $Paco_2$, arterial partial pressure of carbon dioxide.

Gregory et al[1] in 1971 demonstrated that the early use of continuous positive airway pressure (CPAP) in newborn infants with respiratory distress improved oxygenation, and prospective studies thereafter demonstrated improved

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survival in premature infants who were treated with early CPAP.[2] There is an emerging body of opinion that suggests that early CPAP can reduce the need for intubation in a significant number of very low birth weight (VLBW) infants. A review of the use of CPAP in 5 studies of premature infants with respiratory distress, 4 of which were from the presurfactant era, demonstrated reduced mortality and respiratory failure.[3] A number of observational cohort studies have demonstrated that the use of early CPAP, usually initiated within minutes to hours after delivery, has been associated with a decrease in the use of mechanical ventilation, without any corresponding increases in other morbidities, including death, intraventricular hemorrhage, periventricular leukomalacia, and bronchopulmonary dysplasia.[4–6] None of these observations was from prospective controlled trials, and in none was there a contemporaneous control group that did not receive early CPAP.

Verder et al[7] conducted the first prospective evaluation of early CPAP (not necessarily delivery room [DR] CPAP) and short-term intubation for surfactant administration. The primary hypothesis was that use of early CPAP and brief intubation for surfactant administration in infants who meet preestablished criteria would reduce the percentage of infants who require mechanical ventilation from 80% to 40%. Enrollment in this study was stopped after an interim analysis demonstrated a significant benefit for surfactant-treated infants. Verder et al performed a second multicenter, prospective trial that was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within 7 days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days.[8] This study was not a prospective evaluation of early CPAP as all infants received this intervention, beginning at a mean age of 17 minutes.

There are retrospective observations suggesting a benefit for CPAP initiated after delivery. A 1987 survey of 8 neonatology units demonstrated that 1 unit had the lowest rate of chronic lung disease (CLD), defined as the need for oxygen at 36 weeks' postconceptional age.[9] A more recent comparison of practices and outcomes between 2 neonatology units in Boston and the Infants and Children's Hospital unit (Columbia) evaluated VLBW infants who were born from 1991 to 1993. This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation as compared with 29% at Columbia, whereas initial CPAP was used for 63% of infants at Columbia versus 11% at the Boston centers, and Columbia also used less surfactant (10% vs 45%; all $P < .001$).[10] In addition, the rates of CLD were significantly lower at Columbia compared with the other centers (4% vs 22%).

A number of more recent observations and trials have evaluated the use of early CPAP, although none specifically initiated CPAP in the DR. Some of these reports have demonstrated a decrease in the need for mechanical ventilation,[11–13] but none, including 2 randomized trials, noted a significant decrease in CLD at 36 weeks' postconceptional age.

Thus, although there is a substantial body of literature that suggests that early CPAP may be of substantial benefit, none of this information has been obtained from prospective randomized trials in which early, DR CPAP was compared with an appropriate control group of VLBW or extremely low birth weight (ELBW) infants. The term "early CPAP" in the previous studies involved the application of CPAP in the neonatal intensive care unit (NICU) rather than in the DR. In addition, the current guidelines for neonatal resuscitation do not mention the use of CPAP/positive end-expiratory pressure (PEEP).[14] In an effort to evaluate the ability of resuscitation teams to administer CPAP/PEEP at birth, we have now tested the feasibility of randomizing ELBW infants who are at risk for subsequent intubation to CPAP/PEEP versus no CPAP/PEEP in the DR, to be followed by CPAP for all infants subsequent to NICU admission, with intubation and surfactant administration only for infants who meet specified criteria.

METHODS

Infants who were born in the 5 collaborating National Institute of Child Health and Human Development Neonatal Research Network centers were eligible for this study when they had a gestational age of <28 weeks (by best obstetric estimate before delivery), they were delivered and resuscitated in the specially equipped resuscitation room(s), and they were free of known major congenital anomalies, and a decision had been made to provide full resuscitation.

The study was approved by the Institutional Review Boards at each participating institution. A waiver of informed consent was granted at 4 of the 5 centers under federal regulations for research of emergency interventions (Combined Federal Regulations: 45, 46.112.2.3[1–4]). This was to be used when parents were unavailable because of maternal illness, medication that could impair cognition, or lack of adequate time before delivery as allowed. Whenever possible, consent was requested from parents before delivery. All sites agreed to use the waiver only if there was a restricted opportunity to obtain a parental consent. The parents of infants who were entered using the waiver were approached after delivery for discussion and presented with an information sheet explaining the study and indicating to them that the specific medical data obtained from their infant would be used only with their approval. Thirteen of 104 enrolled infants were entered using a waiver.

Study Intervention

The intervention began after birth when the infant was handed to the resuscitation team. CPAP/PEEP and positive pressure ventilation (PPV) were administered via a device called a NeoPuff (NeoPuff Infant Resuscitator; Fisher-Paykel, Auckland, New Zealand). This device is pressure driven and operator cycled using an occlusion valve at the patient T-piece, which allows the resuscitator to set both the peak inspiratory pressure (PIP) and the PEEP or CPAP level and control the rate of ventilation. Initial DR settings were a PIP 15 to 25 cm H_2O and PEEP/CPAP 0 or 5 cm H_2O as determined by the group assignment.

Pulse oximeters were made available in 2 DRs at each site, which were also equipped with the NeoPuff and the video cameras, and the resuscitation teams at each site were encouraged to apply the pulse oximeters immediately after delivery and to use the available oxygen saturation by pulse oximeter (Spo_2) and heart rate information during the resuscitation.

Infants who were randomized to CPAP/PEEP received 100% oxygen by facemask and CPAP or PPV with PEEP if the infant required PPV. Control infants were treated with 100% oxygen and no CPAP. When a control infant required PPV, no PEEP was used.

Other aspects of the resuscitation were managed according to

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the Neonatal Resuscitation Program guidelines[14] and followed current center practice, apart from the restriction that the infant was not to be intubated for prophylactic surfactant administration before 10 minutes of age and that surfactant should be given only after admission to the NICU (not in the DR unless the resuscitators believed that surfactant should be given urgently to stabilize the infant effectively). Thus, earlier intubation was to be performed only for standard Neonatal Resuscitation Program indications, including failure to respond to PPV, with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determined that surfactant should be given urgently. This restriction was based on observations that intubation for surfactant administration up to 15 minutes of age is as effective as earlier administration.[15–17] Delaying surfactant administration until NICU admission would not prohibit early use, also shown to be effective.[18]

Infants from both groups were placed on CPAP 5 to 6 cm H_2O after admission to the NICU using whatever method was typically used in that unit, unless they were stable in room air. Infants could be intubated in the NICU and given surfactant when they met any of the following criteria within the first 7 days after birth: a fraction of inspired oxygen (F_{IO_2}) >0.3 to maintain an Spo_2 >90% or an arterial oxygen pressure >45 mm Hg, an arterial partial pressure of carbon dioxide ($Paco_2$) >55 to 60 with a pH <7.25, and/or apnea requiring bag and mask ventilation. Intubation performed without meeting any of the above criteria was considered a study protocol violation.

The 5 collaborating units performed DR video recordings of neonatal resuscitation following the model of Carbine et al.[19] After completion of the resuscitation, the videotape was removed and placed in a secure location until reviewed and scored. All tapes were reviewed, the scoring sheets completed during the video review were maintained as research data, and the tapes were erased or stored for as long as required by each institution.

Primary Outcome Measure

The primary outcome of this feasibility trial was to determine the percentage of enrolled infants who could be treated according to the study protocol in the DR, received CPAP on NICU admission, and were intubated only after fulfilling stated minimum intubation criteria for a population of 100 infants of <28 weeks' gestation over a 12-month interval.

Assessment of Feasibility

The occurrence of any 1 of the following criteria for an individual patient was considered as a protocol failure:

1. The use of CPAP/PEEP during DR resuscitation in a control infant
2. Intubation before 10 minutes of age for surfactant administration, for resuscitation in the absence of bradycardia (heart rate <100 bpm), and/or cyanosis or an Spo_2 <85% to 90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
3. Failure to place the mask on the infant's face immediately after delivery and stabilization (within 30 seconds of delivery)
4. Failure to use the NeoPuff for resuscitation
5. Failure to initiate CPAP on admission to the NICU
6. Intubation and surfactant administration without meeting stated protocol criteria

Secondary Outcome Measures

Secondary outcome measures included the extent of resuscitation needed as evaluated by the need for DR intubation, the number and duration of intubation attempts in the delivery area, the percentage of infants who required PPV for resuscitation in the DR/resuscitation room, the 5-minute Apgar score assigned at birth, the percentage of infants who required intubation in the NICU, the total duration of mechanical ventilation during the entire NICU stay, and the proportion of infants who received surfactant treatment.

Randomization

Randomization was performed centrally by telephone and by center. Each center was rerandomized to CPAP/PEEP of 0 or 5 cm H_2O every week. Each center was rerandomized on a weekly basis provided that at least 1 infant had been randomized in the previous week. If no infants had been randomized, then the NeoPuff was maintained at its current settings for another week. Before a delivery, an individual at each site was required to set up the NeoPuff with 10 L/min of oxygen flow to deliver the assigned level of CPAP/PEEP, according to the week's randomization assignment.

Statistical Analysis

The primary analysis was to determine whether at least 90% of enrolled infants were treated according to protocol. Enrolling 100 infants would ensure that the 95% confidence limit on the estimated feasibility rate of 90% was 84% to 96%.

For all secondary outcomes, univariate analysis for continuous variables was performed using parametric (eg, *t* tests, analysis of variance) and nonparametric (eg, Mann-Whitney *U*) tests when appropriate; categorical variables including the primary outcome, namely feasibility, were examined by χ^2 analysis. $P < .05$ was considered significant.

RESULTS

A total of 281 infants of <28 weeks were delivered in the study hospitals during the period of the study, 162 of whom were screened by study personnel. Forty-two were determined to be ineligible by the study criteria, and consent was obtained for 104 of the 126 eligible patients, for an enrollment rate of 83%. Consents were obtained from ~110 additional families, but the pregnancies continued beyond 28 weeks; thus, the infants were ineligible at the time of delivery. The demographic compositions of the control and CPAP/PEEP groups were comparable except that the CPAP group had more infants ≤600 g at birth: 11 versus 3 in the control group and 6 infants of 23 weeks' gestational age compared with only a single control infant of 23 weeks. However, none of these differences was significant apart from the receipt of a complete course of antenatal steroids, which was more frequent in the control infants ($P = .029$; Tables 1 and 2). No infant was intubated in the DR for the exclusive purpose of surfactant administration. Only 4 of 43 infants who were <700 g birth weight and 3 of 37 infants who were <25 weeks' gestation were resuscitated without PPV, with no difference observed between the groups. In the DR, 47 infants were intubated: 27 of 55 CPAP infants and 20 of 49 control infants ($P = .40$; Table 3). All infants of 23 weeks' gestational age were intubated in the DR, irrespective of treatment group, whereas only 4 (18%) of 22 infants of 27 weeks' gestation required such intubation (Fig 1). DR intubation varied be-

TABLE 1. Patient Demographics, Apgar Scores, and Antenatal Steroid Use

Patient Description	CPAP ($N = 55$)	Control ($N = 49$)
Birth weight, g (±SD)	756 ± 196	789 ± 196
Male gender, *n* (%)	31 (56)	25 (51)
Gestational age, wk (±SD)	25 ± 1.3	25 ± 1.2
Apgar 1 min <3, *n* (%)	25 (45)	17 (35)
Apgar 1 min <7, *n* (%)	43 (78)	41 (84)
Apgar 5 min <3, *n* (%)	7 (13)	5 (10)
Apgar 5 min <7, *n* (%)	25 (45)	18 (37)
Antenatal steroids given, *n* (%)	54 (98)	48 (98)
Complete steroid course given, *n* (%)	22 (41)*	30 (63)*

* $P = .029$.

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TABLE 2. Treatment by Week of Gestational Age

	GA Group						Total
	23 wk	24 wk	25 wk	26 wk	27 wk	28 wk	
Treatment group							
CPAP	6	14	12	13	9	1	55
%	10.9	25.5	21.8	23.6	16.4	1.8	
Control	1	17	11	8	12	0	49
%	2.0	34.7	22.5	16.3	24.5	0.00	
Total	7	31	23	21	21	1	104

GA indicates gestational age.

TABLE 3. Resuscitation Interventions

Variable	CPAP (N = 55)	Control (N = 49)
Positive pressure in DR	40 (73%)	40 (82%)
PIP in DR, cm H_2O	25 ± 7.2	26 ± 8.4
Intubated in DR	27 (49%)	20 (41%)
Surfactant in DR	7 (13%)	12 (25%)
Average total no. of intubation attempts (±SD)	1.6 ± 0.9	1.9 ± 1.3
Duration of initial intubation attempt, s (±SD)	36 ± 19	32 ± 16

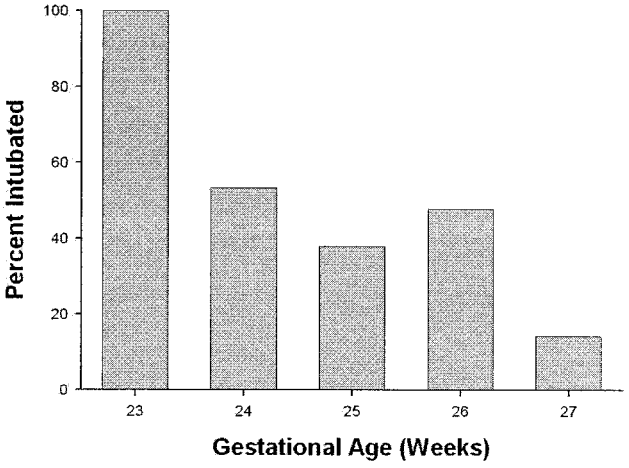

Fig 1. Percentage of infants at each gestational week who were intubated for resuscitation in the DR.

tween 34% and 55% among the 5 sites, and these differences were not significant. When evaluated by birth weight, all 3 infants of <500 g and 6 of 11 infants between 500 and 600 g were intubated in the DR. Surfactant administration in the DR after intubation for resuscitation occurred in 7 of 55 CPAP and 12 of 49 control infants (P = .17).

Video recording of the resuscitation was obtained for 39 of 55 CPAP infants as compared with 32 of 49 control infants. There were 8 instances in which the NeoPuff was replaced with another resuscitation device: 2 infants in the CPAP group and 6 infants in the control group. Only a single infant, in the CPAP group, was intubated for resuscitation in the absence of an ongoing bradycardia or desaturations. A pulse oximeter probe was successfully placed on 69 of 104 infants, and its frequency of use was not different between the CPAP and control infants. All infants were to have CPAP initiated on admission to the NICU, and only 1 control infant did not have CPAP initiated, as this infant was stable in room air.

The CPAP infants had a significantly lower pH and higher $Paco_2$ on admission than the control infants, with a mean (median) of 7.21 (7.25) and 54 mm Hg (52 mm Hg) compared with 7.30 (7.31) and 46 mm Hg (46 mm Hg) for the control infants (P = .003 and .014, respectively). There were no significant differences in the admission arterial oxygen pressure or FIO_2 between groups. For infants who were not intubated in the DR, by day 7, an additional 36 infants were intubated in the NICU: 16 CPAP infants and 20 Control infants (P = .21). Infants in the CPAP group developed criteria for intubation sooner than the control infants, with means and medians of 10.5 and 1.8 hours versus 20.7 and 3.3 hours (P = .41). The age at intubation in the NICU was lowest for the smallest infants, 6 hours for the infants of 500 to 600 g at birth as compared with 82 hours for infants of 900 to 1000 g at birth, although these differences did not reach significance. Overall, 83 (80%) infants required intubation within the first week of life either in the DR or in the NICU.

All CPAP infants who were intubated reached an FIO_2 requirement of >0.3, whereas 3 of 20 control infants were intubated at lesser FIO_2 while meeting other criteria. Three infants in each group had a $Paco_2$ >55 mm Hg at intubation (not significant). There was no difference in the occurrence of apnea as an indication for intubation between groups, noted in 7 CPAP infants compared with 11 control infants.

Overall, the care provided for 52 (95%) of 55 CPAP infants and 43 (88%) of the 49 control infants was in compliance with the study protocol, with an overall compliance of 91%. Death occurred in 21% overall: 27% in the CPAP group versus 13% in the control infants (P = .07). When adjusted for birth weight, these differences did not achieve statistical significance (P = .19). CLD occurred in 29.4% of CPAP infants and 27.9% of control infants, and these differences were not significant. Of the 14 infants who were ≤600 g at birth, 6 (43%) survived, and there were 2 survivors (29%) among the 7 infants who were <24 weeks' gestation: 1 of 6 in the CPAP group. There were no deaths for infants whose birth weight was >900 g. The incidence of pneumothoraces was 13% in the CPAP infants compared with 9% in the control infants, and these differences were not significant. The mean duration of intubation was 17 ± 19 days for control infants as compared with 24 ± 30 days for CPAP infants (not significant). CPAP infants received fewer days of CPAP compared with control infants (8.6 ± 14 days vs 13 ± 18 days; not significant).

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DISCUSSION

This study was designed to test whether the National Institute of Child Health and Human Development Neonatal Research Network could perform a randomized trial that involved the early administration of CPAP, initiated in the DR, as an intervention for infants <28 weeks' gestation, while avoiding early intubation for the exclusive purpose of surfactant administration. All previous descriptions have been retrospective in nature or described trials in which "early" CPAP was started at a variable period of time extending to several hours after birth.[7,8,10–13] Our intent was to evaluate the feasibility of initiating the intervention in the DR to determine whether this approach would be practical for a subsequent definitive trial. Although enrollment reflected only 39% of the total number of infants who were <28 weeks' gestation and delivered in the study hospitals, the consent rate of families who were approached and had infants who were delivered in the gestational age window was 83%. The reasons that more infants within the gestational age window were not enrolled include that the specially equipped DR beds were often in use for other intrapartum patients when potentially eligible patients were admitted to the labor suite and because of decisions to withhold supportive care at delivery. We achieved a protocol compliance of 91%. Most of the protocol violations were related to the use of a device other than the NeoPuff during resuscitation. This trial was not designed to determine the superiority of one resuscitation device over others but rather to attempt to introduce uniformity into the resuscitation process so that we could evaluate the need for intubation in the DR.

de Klerk and de Klerk[11] recently published a 5-year retrospective review of the outcome of sequential cohorts of 1- to 1.5-kg infants ($n = 116$) who were treated with early CPAP versus usual care (delayed CPAP). They reported that early CPAP begun shortly after admission to the NICU decreased endotracheal intubation from 65% to 14% ($P < .001$), surfactant use from 40% to 12% ($P < .001$), and ventilator days from a median of 6 to 2 days ($P < .01$) and reduced oxygen supplementation or death at 28 days from 16% to 3% ($P < .05$).

Sandri et al[13] presented preliminary data from a multicenter, randomized, controlled trial of 155 infants who were 28 to 31 weeks' gestation and randomized to early CPAP within 30 minutes of birth or to CPAP when the F_{IO_2} requirement exceeded 40%. Use of surfactant (22%–21%; not significant) and ventilator support (10%–9%; not significant) were not reduced with early CPAP. More recently, Thomson et al[12] presented the results of a multicenter trial of 237 infants who were from 27 to 29 weeks' gestation and were randomized to 4 treatment groups, namely prophylactic surfactant followed by nasal CPAP using the Infant Flow Driver, early nasal CPAP followed by rescue surfactant, early intermittent positive pressure ventilation with prophylactic surfactant, and conventional management intermittent positive pressure ventilation with rescue surfactant. They reported that CPAP was initiated by 6 hours of age in 76% and 79% of the first 2 treatment groups, and infants in both CPAP groups required the shortest duration of ventilation. However, there were no differences in the incidence of CLD or other neonatal complications. Neither of these studies instituted the use of CPAP in the DR.

This study provided an opportunity to evaluate as a secondary outcome whether DR CPAP/PEEP could reduce the need for intubation for resuscitation. There were no differences in the need for intubation between our CPAP and control infants, although this preliminary study was not powered to detect such a difference. The previous trials of Verder et al[7,8] specifically excluded infants of <25 weeks' gestational age and did not initiate CPAP at delivery. Our observations suggest that infants of <26 weeks' gestation are frequently intubated for resuscitation, even when a decision has been made to delay intubation solely for the administration of surfactant. We believe that this observation is important in designing subsequent intervention trials of respiratory support. We were successful in avoiding intubation for resuscitation in only 14 of 30 infants of 24 weeks' gestation and in 13 of the 21 infants of 25 weeks' gestation, whereas all infants of 23 weeks' gestation received intubation for resuscitation. Lindner et al[20] reported that only 1 of their 11 infants of 24 weeks' gestation was able to avoid intubation in their evaluation of prolonged inflations in the DR. We compared the incidence of DR intubation using the network registry data from January 1, 2002, to December 31, 2002, and found that 1246 (71%) of 1744 of infants who were <28 weeks' gestation required DR intubation compared with 45% for the current study. Excluding infants of 23 weeks' gestation from the network registry data, only 17% of infants of 24 and 25 weeks' gestation avoided intubation in the DR in 2002, as compared with 53% of such infants in the current trial. It is possible that other centers would be able to avoid intubation in such infants during resuscitation, but there is no existing prospective information that would contradict our observations.

Our study used the NeoPuff resuscitator as we wanted to provide the resuscitation team with a simple device that could produce reliable levels of CPAP/PEEP. The NeoPuff allows the presetting of these levels and a user-adjustable PIP that can be changed during resuscitation. Our previous experience demonstrated that a wide variety of operators could deliver specific pressures more reliably with this device than with anesthetic-type devices.[21] All investigators reported that the NeoPuff was easy to use effectively, although for 8 infants, the resuscitation team used a different device. We believe that this reflects the need for more in-service regarding the proper use of this device and the preference of some individuals who have become more comfortable with alternative devices. In addition, it is interesting to speculate whether more control infants were converted to another device because of the lack of CPAP, which contributed to persistent hypoxia secondary to inadequate lung volumes, consistent with previous animal studies.[22]

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We were able to determine adherence to our criteria for intubation in the NICU and found that most infants who were intubated met our minimal criteria, and a minority of our infants had a $Paco_2$ >55 mm Hg at the time of intubation. Our criteria for intubation were minimal as we intended to deliver surfactant to infants with respiratory distress as early as possible, to provide the benefit of prophylactic or early surfactant.[15] Our protocol prohibited early surfactant administration in the first 10 minutes of life in the DR, in an effort to evaluate the need for intubation during resuscitation. We based this approach on the current reviews, which suggest that surfactant administered at 15 minutes of life can be as effective as surfactant given earlier.[23] We believe that more stringent criteria for subsequent intubation and surfactant administration would probably result in fewer infants' requiring such treatment, although no prospective trials have evaluated and compared different criteria. The trend toward a higher mortality in the CPAP infants was largely accounted for by the differences in birth weight between the groups. This study was not powered to evaluate clinical outcomes, and our findings support the need for future definitive and adequately powered trials to evaluate the use of delivery room CPAP in infants of <28 weeks' gestation.

We were interested in evaluating the details of resuscitation for the ELBW infant, as there is no prospective information available for this population. The average duration of intubation attempts was ~30 seconds or greater, and infants required ~1.5 to 1.8 attempts for successful intubation. This is in keeping with our previous observations that 30 seconds is a reasonable guideline for the duration of an intubation attempt.[24]

Our groups were not statistically different by birth weight or gestation, although more infants of <600 g birth weight were assigned to the CPAP group, and this factor is most likely responsible for the longer duration of mechanical ventilation in the CPAP group as compared with the control infants. Our groups were somewhat unbalanced because of the design of the randomization, by week, by center, and the lack of prospective strata. We used this simplified randomization scheme for this preliminary trial because of the ease of use and the estimation that there would probably be no more than 1 infant per week entered from each site. However, this approach led to an imbalance in the groups, and with this experience, we would not recommend this approach in a definitive prospective trial.

Four of the 5 sites obtained a waiver of consent as it was initially believed that for the study to have a representative sample, such a waiver would be required so as to enroll the highest proportion of eligible infants. We were able to argue that current resuscitation practice included both the use of CPAP/PEEP and the absence of such CPAP/PEEP.[25] Nevertheless, the waiver was used for only 11 of the 104 enrolled, demonstrating that adequate enrollment was possible after consent before delivery. We suggest, depending on the intervention, that a waiver may increase enrollments especially of infants who are delivered from acute unpredictable circumstances, who may be especially informative in evaluating any potential therapeutic intervention.

CONCLUSIONS

This study demonstrated that infants could be randomized successfully to a DR intervention of CPAP/PEEP compared with no CPAP/PEEP, with intubation provided only for resuscitation indications and subsequent intubation for prespecified criteria. We have demonstrated that almost half of infants of <28 weeks' gestation are intubated in the DR for clinical resuscitation indications, a percentage that to our knowledge has never been determined prospectively. The use of DR CPAP/PEEP did not significantly decrease the need for such intubations. In addition, the combined high mortality and universal need for DR intubation for infants of 23 weeks' gestation suggests that such infants would not be appropriate for enrollment into a trial to evaluate noninvasive support during resuscitation. Overall, only 20% of our infants of <28 weeks' gestation were able to avoid intubation in the first week of life using our minimal criteria, and we believe that knowledge of these facts is useful in designing subsequent intervention trials for such infants. We are in need of future well-designed and -powered trials to evaluate alternative approaches to the resuscitation and subsequent ventilator support of the ELBW infants, and we believe that the information from this preliminary trial will be useful in designing such interventions.

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APPENDIX. NICHD Neonatal Research Network (2001–2006)

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Indiana University	James A. Lemons, MD	Lucy Miller, RN
Stanford University	David K. Stevenson, MD	Bethany Ball, BS
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University of Cincinnati	Edward F. Donovan, MD	Marcia Mersmann, RN
University of Miami	Shahnaz Duara, MD	Ruth Everett, RN
University of Rochester	Dale L. Phelps, MD	Linda Reubens, RN
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Wake Forest University	T. Michael O'Shea MD, MPH	Nancy Peters, RN
Wayne State University	Seetha Shankaran, MD	Gerry Muran, BSN
Yale University	Richard A. Ehrenkranz, MD	Pat Gettner, RN
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Research Triangle Institute	W. Kenneth Poole, PhD	Betty Hastings
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Delivery Room Continuous Positive Airway Pressure/Positive End-Expiratory Pressure in Extremely Low Birth Weight Infants: A Feasibility Trial

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