VARIABLES ASSOCIATED WITH THE EARLY FAILURE OF NASAL CPAP IN VERY LOW BIRTH WEIGHT INFANTS

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Objective To identify risk factors and neonatal outcomes associated with the early failure of "bubble" nasal continuous positive airway pressure (CPAP) in very low birth weight (VLBW) infants with respiratory distress syndrome (RDS).

Study design Following resuscitation and stabilization at delivery, a cohort of 261 consecutively inborn infants (birth weight ≤1250 g) was divided into three groups based on the initial respiratory support modality and outcome at 72 hours of age: "ventilator-started" group, "CPAP-failure" group, and "CPAP-success" group.

Results CPAP was successful in 76% of infants ≤1250 g birth weight and 50% of infants ≤750 g birth weight. In analyses adjusted for postmenstrual age (PMA) and small for gestational age (SGA), CPAP failure was associated with need for positive pressure ventilation (PPV) at delivery, alveolar-arterial oxygen tension gradient (A-a DO_2) >180 mmHg on the first arterial blood gas (ABG), and severe RDS on the initial chest x-ray (adjusted odds ratio [95% CI] = 2.37 [1.02, 5.52], 2.91 [1.30, 6.55] and 6.42 [2.75, 15.0], respectively). The positive predictive value of these variables ranged from 43% to 55%. In analyses adjusted for PMA and severe RDS, rates of mortality and common premature morbidities were higher in the CPAP-failure group than in the CPAP-success group.

Conclusion Although several variables available near birth were strongly associated with early CPAP failure, they proved weak predictors of failure. A prospective controlled trial is needed to determine if extremely premature spontaneously breathing infants are better served by initial management with CPAP or mechanical ventilation. *(J Pediatr 2005;147:341-7)*

Respiratory distress syndrome (RDS) is an important cause of morbidity and mortality in preterm infants.[1-3] Intermittent positive pressure ventilation (PPV) and prophylactic administration of replacement surfactant are the standard treatments for infants with moderate or severe disease.[3] However, mechanical ventilation is invasive and has the potential to injure the airways and lung parenchyma. Ventilator-induced lung injury may be associated with alveolar structural damage, pulmonary edema, inflammation, and fibrosis.[4] Avoidance of mechanical ventilation is an effective way to reduce the incidence of chronic lung injury.

Gentle ventilation strategies have been suggested as a way to improve pulmonary outcomes for very preterm infants.[5-6] Although nasal continuous positive airway pressure (CPAP) has been associated with a lower incidence of newborn chronic lung disease (CLD) when used as the initial respiratory support modality in very low birth weight (VLBW) infants with RDS,[1,7] not all extremely premature infants with RDS are candidates for initial treatment with CPAP, and not all those who are given CPAP can be successfully managed with this modality. Infants who fail CPAP may suffer the consequences of delayed surfactant administration and other adverse outcomes that may be related to early CPAP failure.

We undertook this retrospective analysis of the hospital course of inborn, VLBW infants ≤1250 g at our institution to try to answer the following questions: (1) Are there perinatal/neonatal variables that distinguish infants who are successfully managed with

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A-a DO_2	Alveolar-arterial oxygen tension gradient	PPROM	Preterm premature rupture of membranes
CLD	Chronic lung disease	PPV	Positive pressure ventilation
CPAP	Continuous positive airway pressure	RDS	Respiratory distress syndrome
IVH	Intraventricular hemorrhage	ROP	Retinopathy of prematurity
PDA	Patent ductus arteriosus	SGA	Small for gestational age
PMA	Postmenstrual age	VLBW	Very low birth weight

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CPAP from those who fail CPAP? and (2) Can we predict which infants are likely to fail CPAP?

METHODS AND DESIGN

"Bubble" nasal CPAP is routinely used at the Children's Hospital of New York, Columbia University as an initial respiratory support modality in spontaneously breathing VLBW infants with RDS. Following resuscitation (if needed) and stabilization at delivery, VLBW infants are immediately carried to the transitional nursery within the delivery suite, where CPAP is applied to those with spontaneous respiratory effort within 5 to 10 minutes of birth.[1] The initial respiratory support modality for infants without spontaneous respiratory effort, including those who have required prolonged PPV at birth and those with severe cardiorespiratory instability, is mechanical ventilation via an endotracheal tube. Administration of exogenous surfactant (Survanta®) is not routine with either modality of ventilatory support. When used as late rescue it is reserved for infants with endotracheal intubation requiring a fraction of inspired oxygen (FIO_2) >0.60 to maintain arterial oxygen tension between 50 and 70 mmHg or oxygen saturation between 90% and 95%.

We performed a retrospective analysis of the prenatal histories, clinical courses, and laboratory data of all inborn admissions to the neonatal intensive care unit between June 1999 and July 2002, to determine which variables might be associated with failure of bubble nasal CPAP in VLBW infants ≤1250 g at birth. Data sources included maternal and infant medical records, laboratory data, procedure logs, and initial chest radiographs.

Respiratory Care Groups

Infants were categorized into one of three respiratory care groups based on the respiratory care modality used during the first 72 hours of life. Respiratory modalities used during delivery room resuscitation and stabilization, although noted, were not included in the categorization scheme. Categorization was as follows: infants were first divided into two groups, the "ventilator-started" group included infants whose initial respiratory support modality at birth was endotracheal intubation and mechanical ventilation; the "CPAP-started" group consisted of infants begun on nasal CPAP following delivery. This designation was made during stabilization in the transitional nursery and usually (but not always) corresponded to management within the delivery room. Infants in the CPAP-started group were subsequently subdivided into a "CPAP success" group that included infants who were successfully treated with CPAP for at least 72 hours and a "CPAP failure" group that included those who required endotracheal intubation for respiratory failure within the first 72 hours of life. For the purpose of the study, "failure" of CPAP occurred when oxygenation was worsening (FIO_2 requirement exceeded 0.6) or ventilation was inadequate (arterial pH dropped below 7.20 and $PaCO_2$ exceeded 65 mmHg) or infants had frequent episodes of apnea requiring repeated stimulation or bag-and-mask ventilation despite adequate CPAP delivery and oxygenation during the first 72 hours of life. CPAP failure beyond 72 hours of age is uncommon and rarely related to the initial respiratory disease or to severe recurrent apnea. Infants failing CPAP received endotracheal intubation and mechanical ventilation with or without surfactant.

The maternal variables examined included multiple birth, pregnancy-induced hypertension, diabetes mellitus, preterm premature rupture of membranes (PPROM) >18 hours, cesarean section, fetal distress, meconium-stained amniotic fluid, maternal medications (corticosteroids, indomethacin, magnesium sulfate, antibiotics, and terbutaline), and clinical chorioamnionitis (defined as the presence of fever with one or more of the following: maternal leukocytosis >15,000/mm^3, uterine tenderness, fetal tachycardia, or foul-smelling amniotic fluid).[8]

Infant variables included birth weight, postmenstrual age (PMA), presence of small for gestational age (SGA; weight for PMA below 10th Lubchenko percentile),[9] Apgar scores, delivery room management (PPV via a bag and mask or via an endotracheal tube), indices of severity of the respiratory distress (severity of RDS on the initial chest x-ray, PaO_2/FIO_2 ratio, alveolar-arterial oxygen tension gradient [A-a DO_2] at the time of the first arterial blood gas [ABG]), the duration of oxygen therapy, and neonatal morbidities: pneumothorax, patent ductus arteriosus (PDA; by echocardiography), germinal matrix-intraventricular hemorrhage (IVH; by cranial ultrasonography typically performed at 24-48 hours, 7 days, 3-4 weeks, and 6-8 weeks of age), severe IVH (grades III-IV), presence of retinopathy of prematurity (ROP; any grade by 32 weeks PMA with weekly or bi-weekly follow-up), severe ROP (requiring photocoagulation), necrotizing enterocolitis (clinical and surgical diagnoses), CLD, moderate-severe CLD, and mortality. For the purposes of these comparisons, CLD was defined according to the new classification, which differentiated three groups of preterm infants with CLD <32 weeks gestation.[10,11] Mild CLD was defined as the treatment with supplemental oxygen for ≥28 days but not at 36 weeks PMA; moderate CLD was defined as treatment with supplemental oxygen for ≥28 days and treatment with <30% oxygen at 36 weeks PMA, and severe CLD was defined as treatment with supplemental oxygen for at least 28 days and treatment with >30% oxygen and/or positive pressure (PPV or nasal CPAP) at 36 weeks PMA. The severity of RDS on the initial chest x-ray was graded as mild, moderate, or severe according to standard classification by our pediatric radiologist (CR-S) who was blinded to failure as an outcome.[12]

Clinical and laboratory data included the ABG and FiO_2 at the time of admission and at the time of CPAP failure. Only about half of the study infants had umbilical venous cord gas results available for analysis; results of these did not differ among groups. Indices of severity of RDS (PaO_2/FIO_2 ratio, arterial to alveolar oxygen tension ratio, and A-a DO_2) were calculated at the time of first blood gas. Rates of neonatal morbidities (see above) were calculated only for those infants whose duration of survival placed them at risk for that particular morbidity; otherwise the data were treated as missing.

Table I. Distribution of infants (n (%)) into respiratory care groups by birth weight

Respiratory care group/Birth weight (g) [no. of infants]	<500 [14]	500-599 [23]	600-699 [42]	700-799 [31]	800-899 [34]	900-999 [25]	1000-1099 [34]	1100-1199 [37]	1200-1250 [21]	≤1250 [261]
Ventilator-started (% of total)	7 (50)	9 (39)	5 (12)	6 (19)	3 (9)	1 (4)	0 (0)	1 (3)	0 (0)	32 (12)
CPAP-started (% of total)	7 (50)	14 (61)	37 (88)	25 (81)	31 (91)	24 (96)	34 (100)	36 (97)	21 (100)	229 (88)
CPAP-failure (% of CPAP-started)	3 (43)	8 (57)	21 (57)	8 (32)	5 (16)	3 (13)	4 (12)	2 (6)	1 (5)	55 (24)
CPAP-success (% of CPAP-started)	4 (57)	6 (43)	16 (43)	17 (68)	26 (84)	21 (87)	30 (88)	34 (94)	20 (95)	174 (76)

STATISTICAL ANALYSIS

To characterize the risks for early CPAP failure, three comparisons were made based on the infant's initial and eventual respiratory care group: ventilator-started versus CPAP-started; ventilator-started versus CPAP failure; and CPAP failure versus CPAP success. Because many of the variables used are not normally distributed, median values and their corresponding 95% CI for each group are reported.[13] *P* values for post hoc comparisons were obtained from individual comparisons using Mann-Whitney test. To compensate for multiple comparison artifacts in post hoc testing, we used a rejection *P* value of .019 for the individual comparisons, equivalent to an overall *P* value of .05 for the three comparisons being made for each variable.[14]

For multivariate analyses of possible associations between maternal variables and failure we used logistic regression with CPAP failure as the dichotomous dependent variable and adjusted for the effects of PMA, infant gender, and SGA. We also used logistic regression models to control for PMA, presence of SGA, and presence of severe RDS on initial chest x-ray to examine possible associations between mortality and morbidity indicators among the three groups. Nonsignificant terms were removed sequentially from logistic models and the results recalculated at each removal.

Prediction of Early CPAP Failure

We used three variables strongly associated with early CPAP failure (birth weight, PMA, and A-a DO_2), available at birth or immediately thereafter (when early management might be altered by their results) to construct models that might predict early CPAP failure. The variables were first dichotomized at the intersection point between the sensitivity and specificity of the test (CPAP failure vs birth weight at 100-g intervals, CPAP failure vs PMA at 1-week intervals, and CPAP failure vs A-a DO_2 at 100-mmHg intervals) yielding cut-points for birth weight (≤750 g), PMA (<26 weeks), and A-a DO_2 (>180 mmHg). We assessed the positive predictive value of these variables alone and in combination.

RESULTS

Respiratory Care Groups

Following initial resuscitation and stabilization in the delivery room and the transitional nursery, 229 (88%) infants were placed on nasal CPAP (the CPAP-started group) and 32 (12%) infants were started on mechanical ventilation (the ventilator-started group) as initial respiratory support modalities. Of ventilator-started infants, 29 of 32 (91%) underwent endotracheal intubation in the delivery room; the remaining three infants underwent endotracheal intubation on admission to the transitional nursery. Five of 229 (2%) infants in the CPAP-started group (two CPAP successes and three CPAP failures), who needed endotracheal intubation and ventilation during initial resuscitation, had their endotracheal tubes removed on admission to the transitional nursery. Among the infants in the CPAP-started group, 174 (76%) infants were successfully treated with CPAP for at least 72 hours (the CPAP-success group), and 55 (24%) required the placement of an endotracheal tube for respiratory failure within the first 72 hours of life (the CPAP-failure group).

Maternal Risk Factors

In multivariate analyses controlled for PMA, SGA, and infant gender, none of the following maternal risk factors was associated with early CPAP failure: multiple birth, pregnancy-induced hypertension, diabetes mellitus, PPROM, clinical chorioamnionitis, cesarean section, fetal distress, meconium-stained amniotic fluid, and maternal medications (corticosteroids, indomethacin, magnesium sulfate, antibiotics, and terbutaline). In these analyses both PMA and SGA were significantly associated with early CPAP failure (adjusted odds ratio [95% CI] = 0.53 [0.43, 0.65] for every week's increase in gestational age and 2.77 [1.21, 6.34] when infants were SGA) and infant gender was not.

Infant Risk Factors and Characteristics

There was no significant difference between the number of male and female infants in each of the three respiratory support groups. Table I shows the distribution of infants by respiratory care groups in 100-g birth weight increments. Infants <500 g were included in this study (n = 14). Among infants with birth weight ≤750 g, 73.9% (68/92) were initially begun on CPAP and 50% (34/68) failed and required mechanical ventilation. The CPAP success rates for weight groups 751 to 1000 g (n = 77) and 1001 to 1250 g (n = 92) were 80% (56/70) and 92.3% (84/91), respectively. Among infants ≥26 weeks PMA, 2.8% (5/174) were initially begun on mechanical ventilation and 12.6% (22/169) of those started on

Table II. Distribution of infants (n (%)) into respiratory care groups by weeks of PMA

Respiratory care group/PMA (wk) [no. of infants]	23 [13]	24 [35]	25 [39]	26 [39]	27 [26]	28 [41]	29 [31]	30 [15]	31 [8]	32 [7]	33 [5]	34 [2]	≤34 [261]
Ventilator-started (% of total)	7 (54)	10 (29)	10 (26)	2 (5)	2 (8)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	32 (12)
CPAP-started (% of total)	6 (46)	25 (71)	29 (74)	37 (95)	24 (92)	40 (100)	31 (100)	15 (100)	8 (100)	7 (100)	5 (100)	2 (100)	229 (88)
CPAP-failure (% of CPAP-started)	3 (50)	12 (48)	18 (62)	12 (32)	3 (13)	3 (8)	4 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	55 (24)
CPAP-success (% of CPAP-started)	3 (50)	13 (52)	11 (38)	25 (68)	21 (87)	37 (92)	27 (87)	15 (100)	8 (100)	7 (100)	5 (100)	2 (100)	174 (76)

Table III. Comparison of infant characteristics by respiratory care group (continuous variables)

	Median [95% Confidence Interval]*				Post hoc comparisons**		
	Ventilator-started A	CPAP-started B+C	CPAP-failure B	CPAP-success C	A:(B+C)	A:B	B:C
Gestational age (wk)	24 [23.1, 24.9]	27 [26.2, 27.8]	25 [24.5, 25.5]	28 [27.7, 28.3]	<.001	.004	<.001
Birth weight (g)	622.5 [457, 692]	900 [843, 957]	669 [610, 727]	973 [907, 1034.7]	<.001	.06	<.001
Apgar (1 min)	2 [0.4, 3.6]	6 [5.3, 6.7]	6 [5.0, 7.0]	7 [6.0, 8.0]	<.001	<.001	.002
Apgar (5 min)	7 [6.0, 8.0]	8 [8.0, 8.0]	8 [7.6, 8.4]	8 [8.0, 8.0]	<.001	<.001	.002
First arterial blood gas values							
pH	7.21 [7.17, 7.25]	7.29 [7.27, 7.31]	7.28 [7.26, 7.30]	7.30 [7.28, 7.32]	<.001	<.001	.20
pCO_2	48 [40.9, 55.1]	47 [45.1, 48.9]	49 [46.7, 51.3]	46 [44.0, 47.9]	.11	.38	.39
pO_2	63.5 [45.3, 78.7]	86 [77.2, 94.8]	87 [62.1, 111.9]	85.5 [75.6, 94.4]	<.001	.005	.08
Base excess (mmol)	−7 [−8.5, −5.5]	−3 [−3.6, −2.4]	−4 [−5.1, −2.9]	−3 [−3.5, −2.5]	<.001	<.001	.20
paO_2/FIO_2	0.75 [0.42, 0.98]	2.25 [2.02, 2.48]	1.76 [1.34, 2.17]	2.45 [2.20, 2.68]	<.001	<.001	<.001
A-a DO_2	559.5 [492, 627]	154 [133, 176]	235.5 [189, 281]	118 [98, 137]	<.001	<.001	<.001

*95% confidence intervals for median obtained using Maritz Jarrett estimate of standard error.
**P values for post hoc comparisons obtained using Mann-Whitney test. Rejection P value of .019, based on studentized critical values for the three comparisons made for each variable.

CPAP failed. There were no CPAP failures after 29 weeks gestation (Table II).

Infants who succeeded on CPAP were about 3 weeks more mature and weighed about 300 g more than those who failed (Table III). Median 1-minute Apgar scores were significantly lower in the ventilator-started group than in the CPAP-started group (2 vs 6) but median 5-minute scores were similar (7 vs 8). The decision to apply mechanical ventilation (vs starting nasal CPAP) was made during the first several minutes of life (probably within the first minute) and was based mainly on the degree of depression of the newborn rather than on size or maturity. Results of the first ABG, usually performed within the first hour of life, differed sharply between those who were initially ventilated and those who were started on CPAP but not between those who succeeded and those who failed CPAP. However, the level of respiratory support required to obtain these gases was not the same: the medians of PaO_2/FIO_2 and A-a DO_2 differed significantly in a continuum between groups.

Ventilator-started infants were about 30 times more likely to have received positive pressure, via a bag and mask, at delivery than infants who were started on CPAP (91% vs 24%; OR = 29.9, 95% CI [8.8, 102]). Those who had endotracheal intubation and ventilation at delivery were overwhelmingly more likely to remain in the ventilator-started group (91% vs 2%, OR = 433, 95% CI [98, 1908]). The proportion of infants judged to have radiographic evidence of severe RDS was significantly higher for infants who were ventilator-started than for infants who were CPAP-started (63% vs 25%, OR = 4.9, 95% CI [2.3, 10.7]). Eighty-one percent (47/58) of cases of severe RDS in the CPAP-started group occurred among those who ultimately failed CPAP. The mean and median times to early CPAP failure were 18.4 hours (±SD 14.0 hours) and 16 hours, respectively. The mean and median

Table IV. Adjusted odds ratios for mortality and morbidities by respiratory care groups

	Ventilator-started: CPAP-failure		CPAP-failure: CPAP-success	
Outcome factor	**AOR [95% CI]**	***P* value**	**AOR [95% CI]**	***P* value**
Pneumothorax	2.06 [0.82, 5.15]	.06	5.23 [1.60, 17.12]	.003
CLD (any severity)	1.83 [0.85, 3.94]	.06	2.77 [1.50, 5.11]	<.001
CLD (moderate-severe)	0.83 [0.19, 3.68]	.91	2.32 [0.69, 7.83]	.09
PDA (Symptomatic)	0.40 [0.22, 0.75]	.002	0.95 [0.58, 1.57]	.42
PDA (ligation)	0.88 [0.39, 2.01]	.38	1.36 [0.71, 2.59]	.17
Necrotizing enterocolitis (clinical diagnosis)	0.82 [0.27, 2.47]	.36	1.35 [0.53, 3.45]	.27
ROP (All grades)	0.78 [0.32, 1.88]	.29	1.25 [0.68, 2.32]	.24
ROP (photocoagulation)	0.44 [0.10, 1.90]	.14	0.96 [0.36, 2.54]	.47
IVH (all grades)	1.83 [1.03, 3.47]	.03	1.79 [1.03, 3.12]	.02
IVH (grade III-IV)	2.71 [1.29, 5.67]	<.001	2.20 [1.03, 4.69]	.02
Death	4.50 [2.08, 9.71]	<.001	7.21 [2.55, 20.45]	.001

Only survivors to eligibility of complication included in counts. Logistic model of outcome factor regresses against respiratory support modality controls for PMA, SGA, and presence of severe RDS on initial chest x-ray.
AOR, adjusted odds ratio.

FIO_2 requirement at the time of CPAP failure were 0.66 (SD 0.2) and 0.67, respectively. Mean ABG values at the time of failure for infants failing CPAP were pH = 7.15 (SD 0.10), $PaCO_2$ = 69 mmHg (SD 19), PaO_2 = 57 mmHg (SD 22). A blood culture taken at birth was positive in two infants successfully maintained on CPAP and two infants in the ventilator started group.

In a multivariate analysis controlling for PMA and SGA, the adjusted OR and 95% CI for association with early CPAP failure were 2.37 [1.02, 5.52] for PPV at delivery, 2.91 [1.30, 6.55] for A-a DO_2 >180 mmHg, and 6.42 [2.75, 15.0] for severe RDS on the initial chest x-ray.

Mortality and Morbidities

Death occurred in 21 of 32 (66%) of ventilator-started infants and 20 of 229 (9%) of CPAP-started infants. Mortality in the CPAP-failure group was 18 of 55 (33%), and the mortality in the CPAP-success group was 2 of 174 (1%). Periventricular leukomalacia was noted only in one survivor, an infant in the CPAP failure group. Among survivors, the median duration of oxygen therapy differed significantly between the ventilator-started and the CPAP-started groups (50 days [17, 83] vs 3.0 days [2.1, 3.9], respectively, P = .003) but not between the ventilator-started group and the CPAP failure group (35 days [20, 51], P = .863).

The adjusted OR for the logistic regression models with mortality and morbidity variables as outcomes are given in Table IV. The models were controlled for PMA, SGA, and presence of severe RDS on the initial chest x-ray. Only infants who survived to eligibility for the complication were included in the analyses. CLD and IVH (any grades) were progressively more likely to be associated with ventilator-started than CPAP-failing infants and CPAP-failing than CPAP-succeeding infants. PDA was more common among CPAP-started than ventilator-started infants. Significantly higher rates of mortality, pneumothorax, CLD (all grades), IVH (all grades and grades 3 and 4) were associated with CPAP failure compared with CPAP success.

Surfactant Administration

No infant who succeeded on CPAP in the study received replacement surfactant. The proportion of infants who received surfactant in the ventilator-started group was equal to that in the CPAP failure group (53% vs 51%, OR = 1.1, 95% CI [0.5, 2.6]). Those infants with severe RDS by chest x-ray were more likely to receive surfactant (OR = 4.5, 95% CI [1.8, 11.4]). Infants in the CPAP failure group who received surfactant were those who failed earlier (11.8 hours [SD 10.3] vs 25.1 hours [SD 14.3], P <.001). There was no positive or negative significant association between receipt of surfactant and any of the adverse outcomes, including mortality, pulmonary hemorrhage, PTX, CLD, PDA requiring ligation, IVH, severe IVH, ROP (any grade), severe ROP (requiring photocoagulation), necrotizing enterocolitis, or the duration of oxygen therapy. The power to detect possible associations between surfactant administration and any these complications within each respiratory care group was insufficient.

Prediction of Early CPAP Failure

The dichotomous variables birth weight ≤750 g, PMA <26 weeks, and A-a DO_2 >180 mmHg maximized the specificity and sensitivity of birth weight, PMA, and A-a DO_2 to predict early CPAP failure. Early CPAP failure rates for these variables were 50%, 55%, and 51%, respectively. Only 53% of CPAP-started infants with radiographic evidence of severe RDS failed CPAP. These failure rates are equivalent to the positive predictive values of the individual tests. There was no improvement in positive predictive values when these criteria were used in combination.

DISCUSSION

Progress in neonatal intensive care is closely related to improvements in the management of respiratory failure in small infants. Current modalities of ventilatory assistance range from CPAP to various modes of mechanical ventilation.

The advent of less invasive methods of delivering CPAP to infants with RDS is associated with reduced need for intubation and mechanical ventilation and a lower incidence of CLD.[1,15-16] The clinical outcomes for infants who succeed on CPAP are excellent, with low rates of mortality, IVH, ROP requiring photocoagulation, and lower neurodevelopmental sequelae in school-age children who had been VLBW infants managed with respiratory strategy that minimizes ventilatory intervention.[15,17-22] Although many retrospective studies attest to the effectiveness of bubble nasal CPAP in the management of RDS in preterm infants,[6,17-19,23-28] no published randomized prospective controlled trial compares the use of CPAP with other management strategies applied at birth.

At the Children's Hospital of New York, bubble nasal CPAP delivered with Hudson® prongs (Hudson Respiratory Care Inc., Temecula, Calf) is the initial ventilatory support modality for all spontaneously breathing infants regardless of PMA or birth weight. In our study, 76% of spontaneously breathing VLBW infants (birth weight ≤1250 g) were managed successfully with nasal CPAP. Even at the lowest PMA (23-26 weeks), CPAP was successful in about half of the infants.

Few studies have examined factors that might predict CPAP failure in VLBW infants. In a study from Malaysia of infants with moderate or severe RDS, septicemia and pneumothorax during CPAP therapy were found to be significantly associated with failure of CPAP in preterm infants <37 weeks.[29] More than half of infants in this study were on bubble nasal CPAP using Hudson® nasal prongs. In our study, we chose to examine data that could be collected as close as possible to the time of birth to attempt to predict failure and design alternative management strategies that could usefully be applied early in the course of the disease. We found that the factors associated with early CPAP failure were those related to the small birth size (birth weight ≤750 g), immaturity (PMA <26 weeks), severity of RDS (as indicated by A-a DO_2 >180 mmHg and severe RDS on the initial chest x-ray) and need for PPV at delivery. These factors essentially define a "small, sick baby" who may be somewhat depressed at birth. Although each of these factors was strongly associated with early CPAP failure, none had a positive predictive value above 55%; all were relatively poor predictors of failure even in the lowest birth weight and gestation age ranges included in the study. Part of the difficulty with predicting CPAP failure may involve the difficulty in predicting severity of RDS at birth. The median failure time was 16 hours of age; perhaps if we had chosen a slightly later time (but one still early enough to give rescue surfactant effectively), for example, at 4 to 6 hours of age, to collect our data, the PPV of associated factors might have been higher. The higher morbidity/mortality among CPAP failures could reflect either the overall poor health condition of the infant that is associated with adverse sequelae or the stress of a CPAP trial that predisposes to poor outcomes.

Several small studies have demonstrated improved respiratory outcomes when surfactant administration has been followed by extubation to CPAP at birth,[30-32] and even when surfactant has been administered at a median age of 18 hours.[23] None of the infants in our study who succeeded on CPAP received surfactant; among those who failed CPAP, surfactant was given only after CPAP failure and treatment with mechanical ventilation, and only then if the oxygen requirement stabilized at FIO_2 ≥0.60. The fact that only half of our inborn infants in the ventilator-started and CPAP failure groups received surfactant is at variance with generally accepted practice. Our practice of giving a trial of CPAP to all spontaneously breathing VLBW infants with respiratory distress regardless of their birth weight and length of gestation limited the use of early surfactant to those infants who received endotracheal intubation and mechanical ventilation at birth. However, two thirds of infants with severe RDS by x-ray received surfactant, and three quarters of the surfactant given was administered to this group. Although we found that surfactant receipt was not associated with any reduction in the rates of mortality or complications in the groups of infants who either failed CPAP or were initially ventilated, our observational study was not designed or powered to examine outcomes related to surfactant receipt. Nor is it possible to compare our surfactant-related outcomes with those of infants at other institutions who received different patterns of surfactant administration and ventilatory management.[30,33] Whether or not infants at risk for early CPAP failure are better off being treated initially with mechanical ventilation and surfactant is a question that only a prospective, randomized controlled trial can settle. Such a trial might be performed in a group that has about equal odds of CPAP success and failure, that is, in infants with a birth weight ≤750 g or PMA <26 weeks in our study.

It may be useful to discuss briefly the kind of questions that have been addressed by our study that a controlled trial will not need to answer. Given that essentially every infant who could have been possibly started on CPAP received this modality, our observational, retrospective study is adequate to examine the circumstances and outcomes of early CPAP failure. Our study also defines the "outer limits" of complication rates in the CPAP failure group. That is, if infants who failed CPAP fared worse in any important outcome category than the group of very small, very sick babies who required PPV/endotracheal intubation in the delivery room and subsequent mechanical ventilation, then it might be wrong to use CPAP in any infant with a reasonable chance of failure. We found that mortality and complication rates were significantly lower among those failing CPAP than among infants who were ventilator-started, controlling for gestation and initial severity of RDS, but worse than for infants who succeeded on CPAP. This is modest but essential reassurance.

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