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Decreased Incidence of Bronchopulmonary Dysplasia After Early Management Changes, Including Surfactant and Nasal Continuous Positive Airway Pressure Treatment at Delivery, Lowered Oxygen Saturation Goals, and Early Amino Acid Administration: A Historical Cohort Study

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ABSTRACT

OBJECTIVE. The goal was to investigate the clinical impact of 3 early management practice changes for infants of ≤ 1000 g.

METHODS. We performed an historical cohort study of appropriately sized, preterm infants without congenital anomalies who were born between January 2001 and June 2002 (pre-early management practice change group; $n = 87$) and between July 2004 and December 2005 (post-early management practice change group; $n = 76$).

RESULTS. Only 1 (1%) of 87 infants in the pre-early management practice change group received continuous positive airway pressure treatment in the first 24 hours of life, compared with 61 (80%) of 76 infants in the post-early management practice change group. The proportions of infants who required any synchronized intermittent mandatory ventilation during their hospital stays were 98.8% and 59.5%, respectively. The mean durations of synchronized intermittent mandatory ventilation were 35 days and 15 days, respectively. The combined incidence rates of moderate and severe bronchopulmonary dysplasia at corrected gestational age of 36 weeks were 43% and 24%, respectively. The use of vasopressor support for hypotension in the first 24 hours of life decreased from 39.1% (before early management practice changes) to 19.7% (after practice changes), the cumulative days of oxygen therapy decreased from 77 ± 52 days to 56 ± 47 days, and the proportions of infants discharged with home oxygen therapy decreased from 25.7% to 10.1%; the incidence of patent ductus arteriosus requiring surgical ligation increased from 1% to 10%. There were no differences in rates of death, intraventricular hemorrhage, periventricular leukomalacia, pneumothorax, necrotizing enterocolitis, or retinopathy of prematurity.

CONCLUSIONS. Successful early management of extremely preterm infants with surfactant treatment followed by continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals, and early amino acid supplementation is possible and is associated with reductions in the incidence and severity of bronchopulmonary dysplasia.

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Key Words

continuous positive airway pressure, bronchopulmonary dysplasia, extremely low birth weight neonates, early amino acids, oxygen saturation, prematurity, patent ductus arteriosus

Abbreviations

BPD—bronchopulmonary dysplasia
CPAP—continuous positive airway pressure
EMPC—early management practice change
ELBW—extremely low birth weight
PDA—patent ductus arteriosus
SIMV—synchronized intermittent mandatory ventilation
FiO₂—fraction of inspired oxygen

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MORBIDITY AND DEATH associated with extremely low birth weight (ELBW) neonates are often a result of the interventions used to help them survive. Bronchopulmonary dysplasia (BPD) is a significant example of these morbidities. The cause of BPD is multifactorial, with pathogenesis being linked to immature lung tissue, barotrauma and volutrauma resulting from mechanical ventilation, oxidant injury, and proinflammatory mediators.¹⁻⁵ Patients

classified as having severe BPD, according to the new National Institute of Child Health and Human Development criteria, have a higher risk of death, are at increased risk of life-threatening respiratory infections, may have abnormal pulmonary function testing results into late childhood, and are at increased risk for neurodevelopmental sequelae, compared with infants with mild or no BPD.^{6,7}

ELBW infants are at the highest risk for BPD, and reduction of the incidence and severity of BPD may be possible through reduction of the amount of injury induced by respiratory support interventions. "Gentle ventilation" techniques using nasal continuous positive airway pressure (CPAP) as a primary mode of ventilatory support may reduce barotrauma and volutrauma in ELBW premature neonates and are being used increasingly even for the smallest infants.⁸⁻¹⁰ The potential risks and benefits of CPAP therapy and whether CPAP use among ELBW infants decreases the incidence of BPD have not been fully studied.

In this study, we investigated the pulmonary outcomes before and after introduction of 3 practices in our early management of ELBW neonates. These practices included (1) changing to a respiratory strategy of prophylactic surfactant administration followed by immediate extubation to nasal CPAP treatment in the delivery room, instead of placement on a mechanical ventilator; (2) lowering the goals for oxygen saturation from >95% to 90% to 95% and starting with an initial fraction of inspired oxygen (F_{iO_2}) of 40%, rather than 60%; and (3) starting early amino acid supplementation with 3 gm/kg/dy on the first day of life, as opposed to starting with 1-1.5 gm/kg/dy on the second day of life and gradually increasing to 3 gm/kg/dy over 3-5 days. We tested the hypothesis that initiation of these early management practice changes (EMPCs) would lead to improved pulmonary outcomes for ELBW neonates, including a decrease in the incidence of BPD.

METHODS

Study Design

A retrospective chart review was conducted at the University of Texas Medical Branch in Galveston, after approval by the University of Texas Medical Branch institutional review board. Study inclusion criteria were birth weight of ≤ 1000 g, offer of resuscitation at delivery, and appropriate size for gestational age. Infants born at other hospitals and infants with congenital malformations were excluded. Changes in early management were initiated in the autumn of 2003, and infants born in 18-month periods before and after initiation of the changes were compared. Children born in 2003 and the first half of 2004 were excluded, to ensure that the comparison did not include the transition period after initiation of the new practices. In all, 163 infants met all of the inclusion criteria; their charts were reviewed and all data were entered into a Microsoft Excel (Microsoft, Redmond, WA) spreadsheet. Data collected included demographic features, maternal history, birth history, and final diagnoses, including diagnosis of BPD and other

common morbidities, including necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity. BPD was further classified for each infant on the basis of the National Institute of Child Health and Development criteria; no BPD signifies no oxygen requirement at 28 days of life, mild BPD signifies an oxygen requirement at 28 days but no oxygen requirement at corrected gestational age of 36 weeks, moderate BPD signifies an oxygen requirement of <30% at corrected gestational age of 36 weeks, and severe BPD signifies an oxygen requirement of >30% or the use of positive pressure ventilation at corrected gestational age of 36 weeks. In addition, detailed information regarding the respiratory management of the infants was collected, including oxygen exposure and the number of days of treatment with each respiratory modality. Information on doses of surfactant, use of vasopressors, use of steroids, enteral feedings, growth, days of central line use, and length of stay were also collected. For our statistical analyses, continuous data were analyzed by using Student's *t* test and categorical data were analyzed by using χ^2 analysis. SAS software (SAS Institute, Cary, NC) was used to perform logistic regression analysis and analysis of variance for repeated measures. A *P* value of <.05 was used to indicate significance.

Early Management for Pre-EMPC Cohort

The first cohort of infants (pre-EMPC group) was born between January 2001 and June 2002. The standardized early treatment of ELBW infants in the pre-EMPC group included (1) intubation and surfactant administration in the delivery room, with synchronized intermittent mandatory ventilation (SIMV); (2) initiation of 60% F_{iO_2} , with subsequent adjustments in F_{iO_2} by physician order only; and (3) initial intravenous fluid administration of 10% dextrose at birth, followed by initiation on day of life 2 to 4 of total parenteral nutrition containing 1 g/kg protein per day and advancing by 1 g/kg per day to a maximum of 3 mg/kg per day. Umbilical artery fluid was one fourth normal saline solution with heparin.

Early Management for Post-EMPC Cohort

The second group of infants (post-EMPC group) was born between July 2004 and December 2005. Changes made to the standardized early treatment of ELBW infants in the post-EMPC era included the following. (1) Intubation and prophylactic surfactant administration were followed by immediate initiation of nasal CPAP therapy at 5 cm H_2O in the delivery room. Routine use of this practice began in January 2004. CPAP treatment was delivered through nasal prongs, and flow was generated through a ventilator. (2) Initiation of 40% F_{iO_2} was followed by a standing order for weaning of F_{iO_2} by the bedside nurse to maintain oxygen saturations between 90% and 95%. This practice was initiated with the change to CPAP therapy, but ~4 months elapsed before it was steadily in place. (3) Early parenteral amino acid supplementation was provided with admission intravenous fluids of 10% dextrose with 3% amino acids and calcium gluconate and umbilical artery fluid con-

taining one fourth normal saline solution and 1.5% amino acids with heparin.¹¹ Total parenteral nutrition was initiated on the second day of life with 3 g/kg protein per day, instead of the previous graded advance. This parenteral support started in January 2003 and increased the protein administration in the first 7 days of life from 10 g/kg to 20.5 g/kg.

Aspects of our early management for infants of <1000 g that did not change between the 2 time periods were prophylactic administration of low-dose indomethacin for intraventricular hemorrhage prevention for the first 3 days of life, prophylactic administration of antibiotics (ampicillin and gentamicin), temperature management, skin care, and graded management of blood pressure (normal saline solution bolus and then initiation of dopamine treatment and, if needed, hydrocortisone treatment), with hypotension generally being defined as mean arterial pressures less than the infant's gestational age. Total fluid administration was started at 80 to 100 mL/kg per day and advanced at the discretion of the neonatologist. Total fluid amounts exceeded 130 mL/kg per day only for neonates with large insensible fluid losses, as demonstrated by elevated serum sodium levels (>150 mEq/L). Enteral feedings were generally initiated on the fourth day of life (24 hours after the third dose of indomethacin). Advancement of enteral feedings occurred more rapidly for the post-EMPC cohort, although this did not follow any particular guidelines and was faculty-dependent and neonate-dependent. Management of patent ductus arteriosus (PDA) entailed the use of indomethacin daily for 3 days if the infant was in medically stable condition (without necrotizing enterocolitis or anuria). Indomethacin treatment was repeated if it was initially unsuccessful or if the PDA recurred. Surgical ligation was usually performed after either the second or third attempt at medical closure with indomethacin. This routine and the dosage of indomethacin were unchanged between the cohorts. Vitamin A supplementation was implemented in our unit after completion of this study.

Primary Hypothesis

We predicted that the changes in early clinical practice would decrease the combined incidence of moderate and severe BPD by 50%. With a BPD incidence of 44%,⁶ an α value of .05, a β value of .2, and a σ value of .80, the estimated sample size to observe such a difference was 79 infants per group.

Secondary Outcomes

Other outcomes studied included days of mechanical ventilation, highest F_{iO_2} exposure on days of life 1, 3, 7, 14, and 28 and at corrected gestational age of 36 weeks, need for respiratory support at 36 weeks, number of infants requiring home oxygen therapy at discharge, number of surfactant doses given, number of infants treated with steroids for BPD, and complications such as pneumothorax and pulmonary hemorrhage. We also collected data on the use of intravenous vasopressors within the first 24 hours of life.

TABLE 1 Comparison of Major Demographic Characteristics of Infants in Pre-EMPC and Post-EMPC Cohorts

Demographic Features	Pre-EMPC (n = 87)	Post-EMPC (n = 76)
Gender, %		
Female	49.4	55.3
Male	50.6	44.7
Gestational age, mean \pm SD, wk	25.4 \pm 1.5	25.7 \pm 1.4
Birth weight, mean \pm SD, g		
All subjects ^a	742 \pm 125	788 \pm 120
Survivors	759 \pm 121 (n = 74)	799 \pm 116 (n = 69)
Prenatal care, %	89.7	93.4
Chorioamnionitis, %	14.9	15.8
Pregnancy-induced hypertension, %	25	15
Multiple gestation, %	28.7	25
Delivery, %		
Vaginal	36.8	28.9
Cesarean	63.2	71.1
Prenatal steroid use, %	80.5	89.5
Deaths, n (%)	13 (15)	7 (9)
Race, %		
Non-Hispanic white ^a	37	20
Non-Hispanic black ^a	23	40
Hispanic	39	40

^a $P < .05$.

RESULTS

Subjects

Demographic data are shown in Table 1. The pre-EMPC cohort included 87 infants and the post-EMPC cohort included 76 infants. There were no significant differences in gender, gestational age, prenatal care, prenatal steroid use, maternal chorioamnionitis, pregnancy-induced hypertension, multiple births, delivery method, or deaths. Thirteen infants died in the pre-EMPC group and 7 died in the post-EMPC group ($P = .31$). There was a significant difference in birth weight between the 2 groups ($P = .02$). Infants were excluded from individual outcome measures if they did not survive long enough to attain the diagnosis being measured (eg, BPD). There was not a significant difference in birth weights of survivors. Race also was significantly different between cohorts and was corrected for in our logistic regression analysis.

Interventions

Figure 1 compares the highest F_{iO_2} to which infants were exposed on days of life 1, 3, 7, 14, and 28 and at corrected gestational age of 36 weeks in each cohort. Analysis of variance for repeated measures demonstrated a significant decrease in the post-EMPC group for the highest oxygen exposure on each day of life examined. A repeated-measures analysis of variance demonstrated a group effect (pre-EMPC versus post-EMPC; $P < .01$) and time effect ($P < .01$) on the highest oxygen requirement for any particular day (Fig 1). There was a significant time-group interaction ($P < .01$), with oxygen exposure decreasing with age in both groups.

FIGURE 1

Graph of the highest documented percent oxygen (\pm SD) delivered to infants in both cohorts on days of life 1 through 28 and at 36 weeks' CGA. There is a significant difference between the cohorts in addition to a significant time effect ($P < .05$).

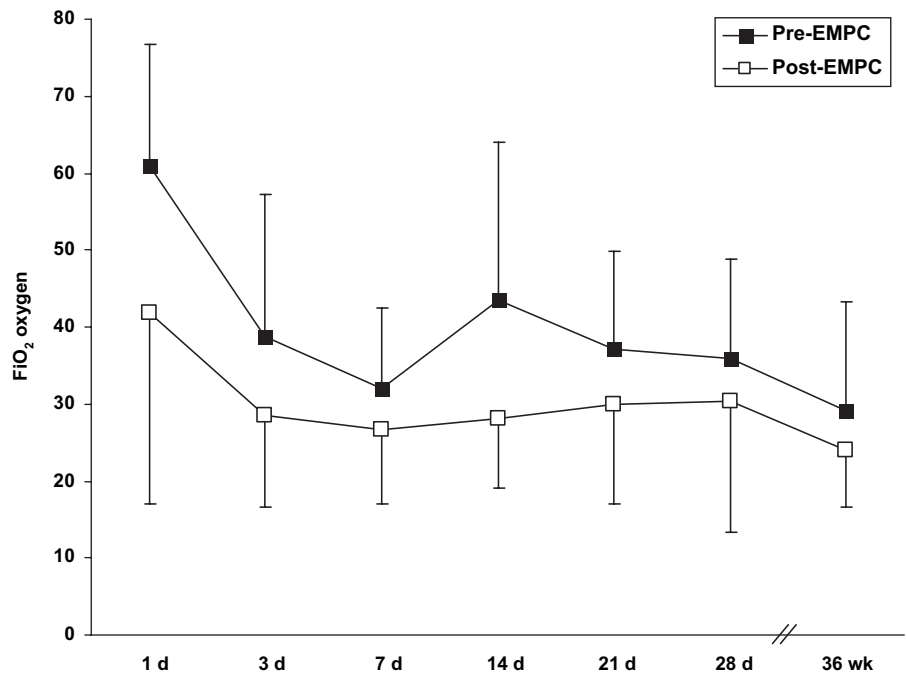


Figure 2 shows the changes in respiratory interventions, measured as total numbers of ventilator and CPAP days, for each group. Over the course of their entire hospital stay, infants in the post-EMPC group spent 15 ± 23 days with SIMV, compared with 35 ± 66 days for the pre-EMPC group ($P < .01$), and 27 ± 18 days with CPAP therapy, compared with 8 ± 10 days for the pre-EMPC cohort ($P < .001$). Only 1 (1%) of 87 infants in the pre-EMPC group received CPAP therapy in the first 24 hours of life, compared with 61 (80%) of 76 infants in the post-EMPC group ($P < .01$). The proportions of infants who required any SIMV during their hospitalizations were 98.8% for the pre-EMPC group and 59.5% for the post-EMPC group ($P < .01$).

The impact of the early amino acids intervention is likely best reflected in the early growth of the neonates. Infants in the pre-EMPC cohort needed 16 ± 5.8 days to

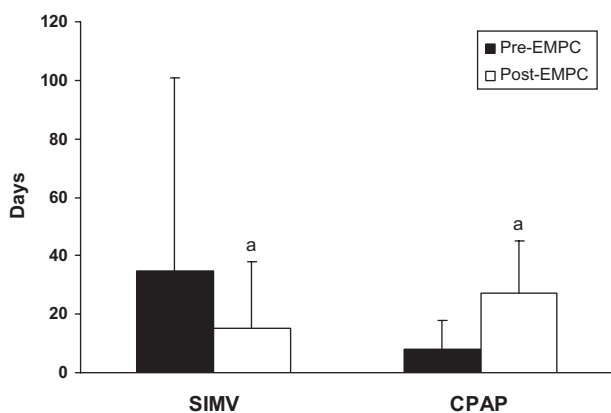


FIGURE 2

Comparison of cumulative days on SIMV and cumulative days on CPAP between the pre-EMPC and post-EMPC cohorts. ^a $P < .01$.

regain birth weight, in comparison with 12 ± 4.5 days for the post-EMPC cohort ($P < .0001$). These data, along with other growth data, are the topic of a separate article.

Outcomes

Infants from both cohorts were classified into BPD categories, that is, no BPD, mild BPD, moderate BPD, or severe BPD (Fig 3). The incidence of severe BPD decreased from 29% (pre-EMPC group) to 11% (post-EMPC group; $P < .01$). The rate of moderate and severe BPD (equivalent to the previous definition of BPD) decreased from 43% (pre-EMPC group) to 24% (post-EMPC group; $P = .02$).

The odds ratios for the development of moderate or severe BPD were determined for individual factors. Co-

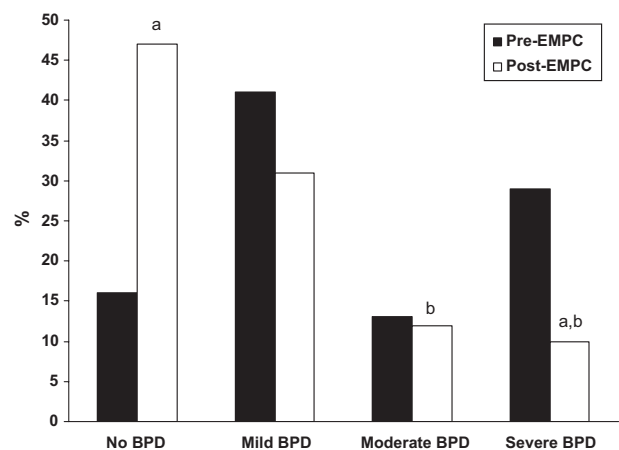


FIGURE 3

Comparison of the incidence of BPD classifications between the pre-EMPC and post-EMPC cohorts. ^a $P < .01$; ^b $P < .03$ for the combined comparison of moderate and severe BPD between cohorts (note: combining moderate and severe BPD is equivalent to the previous definition of BPD).

TABLE 2 Univariate Analysis of Risk of Developing BPD Based on Duration of Maintenance of CPAP Therapy

Maintenance of CPAP Therapy	n (%)		Odds Ratio (95% Confidence Interval)
	Moderate or Severe BPD	No or Mild BPD	
24 h			
Yes	11 (18)	49 (82)	0.65 (0.50–0.82) ^a
No	38 (44)	48 (56)	1.00
48 h			
Yes	9 (17)	45 (83)	0.66 (0.52–0.82) ^a
No	40 (43)	52 (57)	1.00
72 h			
Yes	9 (17)	43 (83)	0.68 (0.55–0.85) ^a
No	40 (43)	54 (57)	1.00
7 d			
Yes	7 (19)	30 (81)	0.81 (0.68–0.96) ^a
No	42 (39)	67 (61)	1.00
14 d			
Yes	3 (13)	20 (87)	0.85 (0.75–0.96) ^a
No	46 (37)	77 (63)	1.00

^a $P < .05$.

hort, birth weight, prenatal steroid use, postnatal steroid use, and race were not significant risk factors for the development of BPD (data not shown). Male gender was a significant risk factor for the development of BPD (odds ratio: 2.63; 95% confidence interval: 1.21–5.68). We also examined the odds ratio for the development of BPD for ELBW infants as a function of their successful continuous maintenance on CPAP therapy. Table 2 shows the absolute numbers and proportions of infants with moderate or severe BPD or with no or mild BPD for each period of continuous maintenance on CPAP therapy. The odds ratios for developing moderate or severe BPD with maintenance on CPAP therapy for the specified period are also presented. There does not seem to be a dose-response effect for a better outcome with initial CPAP exposure for >24 hours after birth. Table 3 shows the odds ratios after adjustment for potential confounders, including cohort, birth weight, gender, race, maternal prenatal steroid use, and postnatal steroid use. Correcting for cohort allowed us to isolate the impact of CPAP therapy duration, because all infants in the post-EMPC cohort received prophylactic surfactant treatment, early amino acid administration, and treatment

TABLE 3 Multivariate Analysis of Risk of Developing Moderate or Severe BPD Based on Duration of Maintenance of CPAP Therapy

Maintenance of CPAP Therapy	Adjusted Odds Ratio (95% Confidence Interval)
24 h	0.23 (0.06–0.91) ^a
48 h	0.22 (0.06–0.80) ^a
72 h	0.30 (0.09–1.05)
7 d	0.77 (0.24–2.50)
14 d	0.46 (0.11–1.95)

The analysis was corrected for the following potential confounders: group, birth weight, gender, race, maternal prenatal steroid exposure, and postnatal steroid exposure.

^a Confidence interval does not include 1.00, using an α value of .05.

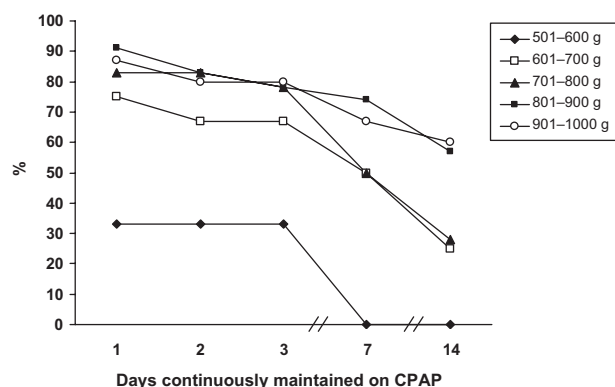


FIGURE 4

Continuous maintenance on CPAP for infants in the post-EMPC cohort stratified according to birth weight. Time to failure of CPAP differed significantly across strata as determined by a log-rank test for survival analysis.

with lowered oxygen saturation goals. Both 24 hours and 48 hours of CPAP therapy remained significantly protective against the development of moderate or severe BPD (adjusted odds ratios of 0.23 for 24 hours and 0.22 for 48 hours). Despite the differences in race (Table 1), race was not identified as a risk factor for BPD.

Figure 4 shows continuous maintenance on CPAP therapy for the post-EMPC neonates, stratified according to birth weight. Infants who experienced failure of CPAP therapy were placed on SIMV and, even if they returned to CPAP therapy within their first 14 days, they were not added back to the CPAP numbers. Time to failure of CPAP therapy differed significantly across strata, as determined with the log-rank test for survival analysis. To assess the utility of offering CPAP therapy to infants of 501 to 600 g (only 33% were treated with CPAP therapy, and only for 72 hours), we compared the BPD outcomes of those few neonates with those of the pre-EMPC cohort. In the pre-EMPC group, 2 of 6 neonates had no or mild BPD and 4 of 6 neonates had moderate or severe BPD. In the post-EMPC group, 4 of 5 neonates had no or mild BPD and 1 of 5 neonates had severe BPD.

Table 4 shows secondary outcome data. Use of intravenously administered vasopressors in the first 24 hours of life decreased significantly for the post-EMPC cohort, compared with the pre-EMPC cohort ($P = .005$). However, more infants in the post-EMPC group required surgical ligation of their PDAs, compared with the pre-EMPC group. Infants in the post-EMPC cohort received significantly fewer doses of surfactant than did those in the pre-EMPC group ($P < .001$) and spent fewer days receiving stimulants (caffeine or aminophylline/theophylline) because of apnea. Fewer infants were treated with steroids for BPD in the post-EMPC cohort than in the pre-EMPC cohort ($P = .002$). Total days of oxygen treatment decreased significantly for the post-EMPC cohort ($P = .05$). Finally, fewer infants required home oxygen therapy at discharge ($P = .016$). There was no difference in the proportions of infants who had pneumothorax, required chest tube placement, or experienced pulmonary hemorrhage.

TABLE 4 Secondary Cardiopulmonary Outcomes for Pre-EMPC and Post-EMPC Cohorts

Additional Cardiopulmonary Outcomes	Pre-EMPC (n = 87)	Post-EMPC (n = 76)	P
Vasopressor support in first 24 h, %	40	20	<.01
Doses of surfactant, %			
1	39	84	<.01
2	47	15	<.01
3	14	1	<.01
Indomethacin for PDA treatment, %	16.7	28	.11
PDA ligation, %	1.1	10	.03
No. of positive sputum cultures per patient, mean \pm SD	0.65 \pm 1.0	0.29 \pm 0.6	.01
Duration of apnea stimulant treatment (survivors), mean \pm SD, d	64 \pm 27	52 \pm 32	.02
Postnatal steroid use, %	37	14	<.01
Cumulative duration of oxygen therapy, mean \pm SD, d	71 \pm 52	56 \pm 47	.05
Home oxygen therapy, %	25.7	10.1	<.01
Pneumothorax, %	3.4	2.6	.78
Length of stay, mean \pm SD, d			
All infants	91.9 \pm 52	90.5 \pm 45	.88
Surviving infants	105 \pm 43	97 \pm 42	.22

Data expressed as proportions were analyzed with the χ^2 test, whereas continuous data were analyzed with Student's *t* test.

DISCUSSION

BPD is a major morbidity for ELBW infants. The pathogenesis of BPD is multifactorial, which suggests that multiple approaches may be necessary to decrease the incidence and severity of BPD. This study found that early management strategies aimed at (1) reducing barotrauma and volutrauma with the use of early CPAP therapy, (2) decreasing oxidant injury by decreasing oxygen saturation goals, and (3) increasing early parenteral amino acid support reduced both the incidence and severity of BPD significantly.

Interest in CPAP therapy has increased since Avery et al¹² suggested that the low incidence of chronic lung disease at Columbia University might be associated with the use of CPAP therapy and permissive hypercapnia. The incidence of BPD in neonates treated with CPAP therapy, compared with historical cohorts, has been reported by multiple groups, with mixed results.^{8-10,13-21} Some studies found significant decreases in the incidence of BPD in very low birth weight infants at 36 weeks and at 28 days with the use of early nasal CPAP therapy,¹³⁻¹⁷ whereas several studies found no significant decrease.^{8-10,18} Elective intubation and prophylactic surfactant treatment before initiation of CPAP therapy were not used in any of those studies. A prospective study by Dani et al¹⁹ showed a decreased need for mechanical ventilation but no difference in rates of chronic lung disease with the use of prophylactic surfactant administration and nasal CPAP therapy in the delivery room for infants of <30 weeks. The study by Dani et al¹⁹ examined the same population and initiated surfactant treatment and CPAP therapy in a way similar to ours. However, their study was powered to identify a difference in total days of mechanical ventilation and thus had too

small a sample size for investigation of the incidence of BPD. Although their total sample size was only 27 in both groups, they did identify a trend toward a decrease in the incidence of BPD. Reininger et al²⁰ showed decreased need for mechanical ventilation but no difference in the rates of chronic lung disease with the use of transient intubation and surfactant administration in a randomized, controlled trial. The larger infants, small sample size, potentially prolonged period before initiation of CPAP therapy and delay in surfactant dosing in the study by Reininger et al²⁰ are significant differences between that study and our study. Although those authors noted a trend toward a decrease in BPD, their study was powered only to identify a difference in total ventilation days. Our additional interventions of amino acid support and decreased oxygen use are other significant differences that might have contributed to the greater impact on BPD that we found. In addition, because we studied only ELBW infants, our initial BPD incidence was significantly higher and thus might have been more affected by the changes in practice. In another study using early surfactant treatment, Verder et al²¹ showed that the use of early surfactant treatment and nasal CPAP therapy reduced the need for mechanical ventilation and improved oxygenation for infants of <30 weeks; however, there was no statistical difference in BPD rates at 36 weeks.

We prophylactically administered surfactant before initiating CPAP therapy, on the basis of data suggesting optimal benefit when surfactant was administered within the first 2 hours of life.^{22,23} Care was taken to minimize barotrauma secondary to intubation and positive pressure ventilation while delivering surfactant. Approximately 51% of our post-EMPC neonates remained on CPAP therapy at 7 days of life. This proportion was significantly greater than the 20% of patients remaining on CPAP therapy in the feasibility trial by Finer et al,²⁴ in which prophylactic surfactant was not administered. Animal studies also showed that preterm lambs needed endogenous surfactant to breathe successfully with CPAP treatment.²⁵ Prophylactic surfactant administration may contribute to the decreased incidence of BPD by reducing atelectasis-induced lung injury or by increasing the duration of continuous CPAP treatment and thus decreasing exposure to barotrauma and volutrauma.

After adjustment for confounders, receiving CPAP therapy continuously for the first 24 to 48 hours decreased dramatically the relative risk of developing BPD, compared with infants not offered CPAP treatment or not maintained successfully on CPAP therapy. With a larger sample size, it is possible that all periods of continuous maintenance on CPAP therapy would protect against BPD. Therefore, offering surfactant administration and CPAP treatment at birth to all ELBW infants (combined with lowered oxygen saturation goals), even for a minimum of 24 hours, may protect against the development of BPD. Failure to maintain continuous CPAP therapy was more common for the smaller neonates and may be related to mechanical challenges and an increased frequency of apnea of prematurity.¹⁶ A

significant number of neonates experienced failure of CPAP therapy after 7 days of life. Clinically, it seemed that an increase in secretions between 9 and 12 days was often related to this failure. A study by Ammari et al²⁶ noted that, although certain variables were associated with CPAP therapy failure, they were not predictive of which infants would experience failure.

Lowering oxygen saturation ranges to 89% to 94% has been studied as a means of reducing oxidant injury to the lungs and retinal vasculature.²⁷ This intervention seems safe, and the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity trial demonstrated that lowered oxygen saturations decreased rates of adverse pulmonary events such as pneumonia and the need for supplemental oxygen. Decreased oxygen toxicity was likely a factor in the decreased incidence of BPD found in our study, corresponding to the findings in a recent study by Deulofeut et al,²⁸ who found a 16% decrease in the BPD rate after oxygen saturation goals in their unit were lowered to 85% to 93%. The lowering of initial F_{iO_2} and subsequent weaning for saturations of 90% to 95% likely contributed to the decrease in cumulative days of oxygen therapy and the decrease in proportions of infants discharged with home oxygen therapy seen in this study; however, healthier lungs resulting from the use of CPAP therapy and improved nutrition may also be key factors.

In addition to mechanical and oxidant injury, inadequate nutritional supplementation has been linked to the development of BPD.^{29–32} Early amino acid supplementation improves dramatically the nitrogen balance of ELBW infants, shifting these patients from the catabolic state that traditional parenteral support induces to a healthier anabolic state.^{33,34} Our change in practice to include early amino acid support also might have contributed to the improvement in pulmonary outcomes seen in this study.

The decreased vasopressor requirements in the first day of life do not seem to be related to changes in the clinical management of hypotension between the 2 time periods. Physiologically, the decrease in mean airway pressure provided by CPAP treatment, compared with SIMV, may enhance pulmonary venous return to the heart and thus cardiac output. Alternatively, a decrease in ventilator-induced release of inflammatory mediators in the neonates treated with CPAP therapy may decrease the hypotension seen in this group.

The increased incidence of PDA requiring therapy is concerning. Early CPAP treatment may alter the cascade of mediators responsible for PDA closure.³⁵ Alternatively, CPAP therapy may decrease pulmonary vascular resistance, thus increasing left-to-right flow through the PDA and impeding its closure. Although an increase in fluid administration could explain both an increased incidence of PDA and a decreased incidence of hypotension, there was no clear shift in the total volume of fluid administered between the 2 cohorts, and there was no change in the approach to the management of PDAs. The decreased postnatal steroid exposure likely reflects a change in the practices of our neonatologists, because of concerns regarding neurodevelopmental outcomes, and

also reflects healthier lungs and less BPD with the use of CPAP therapy.

A significant limitation of this study is the time period between the 2 groups and the potential for practice changes to have taken place over time. The reason for the gap between the cohorts was to ensure that the initial sporadic CPAP treatment attempts in the unit during late 2002 and early 2003 were not included in either group and also to ensure an adequate time for our team to become proficient with all of the changes. Some of the factors minimizing significant changes were the consistent presence of 5 of our 6 neonatologists and our use of admission protocols for neonates of <1000 g.

CONCLUSIONS

Prophylactic surfactant treatment, followed by early management that decreases barotrauma and oxidant injury and provides enhanced nutrition, seems to improve pulmonary outcomes. Discerning the individual roles of the 3 EMPCs could best be addressed with prospective, single-intervention clinical trials; however, the synergistic effects of the 3 EMPCs might have contributed to our findings. Identifying the factors that lead to failure of CPAP therapy and classifying the infants who proceed to develop moderate or severe BPD could greatly aid in determining which infants may benefit from therapies such as inhaled nitric oxide or postnatal steroid treatment.

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Decreased Incidence of Bronchopulmonary Dysplasia After Early Management Changes, Including Surfactant and Nasal Continuous Positive Airway Pressure Treatment at Delivery, Lowered Oxygen Saturation Goals, and Early Amino Acid Administration: A Historical Cohort Study

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