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Continuous Positive Airway Pressure versus Mechanical Ventilation on the First Day of Life in Very Low-Birth-Weight Infants

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Abstract

Objective—The objective of this study was to determine differences in the incidence of bronchopulmonary dysplasia (BPD) or death in very low-birth-weight (VLBW) infants managed successfully on continuous positive airway pressure (CPAP) versus mechanical ventilation on the first day of life (DOL).

Study Design—This is a retrospective analysis of the Alere neonatal database for infants born between January 2009 and December 2014, weighing 1,500 g. Baseline demographics, clinical characteristics, and outcomes were compared between the two groups. Multivariate regression analysis was performed to control the variables that differ in bivariate analysis.

Results—In this study, 4,629 infants (birth weight $1,034 \pm 290$ g, gestational age 28.1 ± 2.5 weeks) met the inclusion criteria. The successful use of early CPAP was associated with a significant reduction in BPD or death ($p < 0.001$), as well as days to room air, decreased oxygen use at discharge, lower risk for severe intraventricular hemorrhage, and patent ductus arteriosus requiring surgical ligation ($p < 0.001$ for all outcomes).

Conclusion—Successful use of early CPAP on the first DOL in VLBW infants is associated with a reduced risk of BPD or death.

Keywords

continuous positive airway pressure; prematurity; bronchopulmonary dysplasia; very low birth weight

Bronchopulmonary dysplasia (BPD), characterized by early lung injury in premature neonates, is the most common cause of chronic lung disease during infancy. Pathologically,

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Conflict of Interest

The authors report no conflict of interest including no competing financial interests in relation the work described.

there is uniform airway inflation and smooth muscle hypertrophy with absence of epithelial metaplasia and alveolar hypoplasia. Clinically, the disease leads to significant long-term morbidities in affected infants.^{1–3} Infants with BPD have higher rates of rehospitalization in the first year of life, impairment in lung function into late adolescence, persistent respiratory symptoms into early adulthood, and an increase in neurodevelopmental adverse outcomes.^{1,2} Mechanical ventilation-induced lung injury contributes to the development of BPD in premature infants with respiratory distress syndrome (RDS).^{3,4} Avoiding mechanical ventilation and using noninvasive respiratory support may reduce lung injury and therefore prevent BPD. Three randomized clinical trials (RCTs) comparing initial therapy with nasal continuous positive airway pressure (CPAP) versus intubation and mechanical ventilation showed no difference in the primary outcome of BPD or death between the two groups, although there were trends toward improved outcomes in the CPAP groups of these studies.^{5–7} In addition, these trials have demonstrated that nasal CPAP is a safe and effective alternative to intubation and mechanical ventilation in premature infants with RDS. After these RCTs, use of CPAP is likely to be increased as a mode of initial respiratory support in preterm infants with RDS. Recent guidelines also suggest developing protocols directed at avoidance of mechanical ventilation and instead using noninvasive support when possible.^{8,9} The objective of the current study was to determine differences in the incidence of BPD or death in very low-birth-weight (VLBW) infants managed successfully with CPAP versus mechanical ventilation on the first day of life (DOL) after widespread use of CPAP as an initial therapy for RDS. We hypothesized that the successful use of CPAP on the first DOL compared with mechanical ventilation would be associated with the reduction in BPD or death in VLBW infants. In addition, we wanted to evaluate the impact of successful use of early CPAP on other neonatal morbidities associated with prematurity.

Materials and Methods

Study Population

This study is a retrospective data analysis from the Alere neonatal database for infants weighing $\geq 1,500$ g admitted to the neonatal intensive care unit (NICU) between January 2009 and December 2014 and managed with CPAP or mechanical ventilation on the first DOL. Alere's NICU database comprises standardized clinical, sociodemographic, and cost-related information pertaining to neonates admitted to the NICU in more than 700 hospitals nationwide. All infants included in the study were admitted to the NICU, level II and level III, in both community and academic settings. Daily clinical, sociodemographic, and cost-related information was abstracted concurrent with each hospitalization three to four times per week by experienced neonatal nurses. The Institutional Review Board at Thomas Jefferson University Hospital approved this study. The baseline demographics, clinical characteristics, and the respiratory and neonatal outcomes were compared between the infants who were on CPAP or mechanical ventilation on the first DOL.

Infants were coded for the highest respiratory support modality used in the unit on the first DOL. Infants in the CPAP group included those managed with CPAP only on the first DOL without mechanical ventilation (early CPAP success). Infants in the ventilation group included those intubated at the outset without prior CPAP, as well as those initially on CPAP

who were subsequently intubated and mechanical ventilated during the first DOL (early CPAP failure). BPD was defined as oxygen requirement at 36 weeks postmenstrual age. Prespecified secondary outcomes were patent ductus arteriosus (PDA) requiring surgical ligation, modified Bell stage 2 or higher necrotizing enterocolitis (NEC), severe intraventricular hemorrhage (IVH) defined as grade 3 or 4, retinopathy of prematurity (ROP) stage 3, pneumothorax, days of room air, use of postnatal steroids, discharge home on oxygen, and length of hospital stay (LOS). We considered high volume centers to be those contributing > 25 infants during the study period, and low volume centers to be those contributing ≤ 25 infants during the study period.

Statistical Analysis

Statistical analysis was performed using the Sigma plot version 13 (Systat Software, Inc., Point Richmond, CA) and the SPSS version 22 (IBM Corporation, Armonk, NY). The two groups were compared by Student *t*-tests, Mann–Whitney *U*-tests, or chi-squared tests as appropriate. Clinical and demographic characteristics that were found to be significantly different between the two groups in bivariate analyses were then used in multivariable regression models. Linear and logistic regression models were used and adjusted for gestational age (GA), birth weight (BW), centers, 5-minute Apgar score, surfactant use, late onset sepsis, and use of inotropes. The difference was considered significant for $p < 0.05$.

Results

Characteristics of the Study Subjects

There were 6,563 infants born during the study period with BW ≥ 1,500 g, of which 4,629 were managed with mechanical ventilation or CPAP on the first DOL and were included in the analysis (BW $1,034 \pm 290$ g, GA 28.1 ± 2.5 weeks). Of these, 2,750 required mechanical ventilation on the first DOL and 1,879 required CPAP without mechanical ventilation on the first DOL. A total of 32% of infants (595 out of 1,879), who were initially on CPAP (DOL 1), were later ventilated during the hospitalization. Moreover, 70% of infants (1,933 out of 2,750) who were ventilated on the first DOL subsequently received CPAP. Demographics and baseline clinical characteristics of both the mechanical ventilation and CPAP groups are summarized in Table 1. The two groups differed in BW, GA, 5-minute Apgar score, surfactant use, late-onset sepsis rate, inotrope use, total ventilator days, and proportion born at high volume centers.

There were 744 contributing centers and the range of infants per center was 1 to 191. High volume centers ($n = 58$) contributed 2,090 infants, of which 904 were in the CPAP group (43%) and 1,186 were in the mechanical ventilation group (57%). Low volume centers ($n = 686$) contributed 2,539 infants, of which 975 were in the CPAP group (38%) and 1,564 were in the mechanical ventilation group (62%).

Primary and Other Respiratory Outcomes

There was an increase in successful early CPAP use over time, from 27% (301/1107) on the first DOL in 2009 to 38% (286 of 752) in 2014 ($p = 0.001$). Similarly, the use of mechanical ventilation decreased from 49% (538/1107) on the first DOL in 2009 to 26% (197/752) in

2014 ($p = 0.001$). After adjusting for confounding variables, the successful use of CPAP on the first DOL was associated with a significant reduction in BPD or death in VLBW infants (adjusted odds ratio [aOR], 0.615; 95% confidence interval [CI], 0.496–0.764; $p < 0.001$) (Table 2). The mortality was lower (aOR, 0.417; 95% CI, 0.275–0.633; $p < 0.001$), as well as BPD (aOR, 0.692; 95% CI, 0.567–0.843; $p < 0.001$) in the CPAP group (Table 3). Similarly, infants in the CPAP group had decreased rate of oxygen use at discharge (aOR, 0.626; 95% CI, 0.496–0.790; $p < 0.001$) and decreased number of days to room air ($p < 0.001$). However, the length of hospitalization, pneumothorax, and the use of postnatal steroids were similar between the two groups.

Secondary Outcomes

Adjusted odds for developing severe IVH (aOR, 0.286; 95% CI, 0.165–0.497; $p < 0.001$) and PDA requiring ligation (aOR, 0.590; 95% CI, 0.441–0.788; $p < 0.001$) were lower with the successful use of CPAP on the first DOL (Table 3). Adjusted odds for developing NEC or ROP were similar between the two groups.

Subgroup Analysis

For infants 23 to 25 weeks' gestation, the odds of developing BPD or death were similar between the two groups (Table 4). The successful use of CPAP on the first DOL was associated with a lower risk of severe IVH and PDA ligation in this subgroup. For infants 26 to 28 weeks' gestation, use of CPAP on the first DOL was associated with a lower risk of BPD or death as well reduced risk for developing severe IVH. For infants 29 to 31 weeks' gestation, the CPAP group had lower adjusted odds of BPD or death, PDA requiring ligation.

Discussion

Despite improvement in neonatal care, BPD remains a significant problem in VLBW infants.^{1,10} The lung injury from mechanical ventilation plays an important role in the pathogenesis of BPD.^{3,4} However, previous studies have failed to demonstrate that using CPAP and avoiding mechanical ventilation is beneficial in preventing BPD.^{5–7} By using a large cohort of VLBW infants from an era with high CPAP use as an initial respiratory support, we found that using CPAP successfully on the first DOL is associated with a reduction in BPD or death in VLBW infants. The VLBW infants successfully managed with CPAP on the first DOL also had a lower risk of severe IVH, PDA requiring surgical ligation, shorter time to room air, and were less likely to be discharged home on oxygen.

In the past, VLBW infants with RDS were managed with intubation, surfactant therapy, and mechanical ventilation. In some units, the most premature infants may be intubated immediately after delivery regardless of fetal condition. Previous studies analyzing the link between early intubation and mechanical ventilation have shown mixed results. Avery et al demonstrated that units using less intubation and mechanical ventilation had lower rates of BPD, and Van Marter et al found a link between early intubation and increased risk of BPD.^{11,12} Gagliardi et al, however, demonstrated that early intubation and brief mechanical ventilation do not increase BPD risk and that prolonged mechanical ventilation may be a stronger predictor of BPD.¹³

Several observational studies and RCTs have shown that it is safe and feasible to provide nasal CPAP starting in the delivery room, even in extremely preterm infants.^{5-7, 14-16} The COIN (CPAP or Intubation at Birth) trial randomized 610 infants (25–28 weeks' gestation) to CPAP or intubation and ventilation 5 minutes after birth.⁵ They found that early nasal CPAP did not reduce the rate of death or BPD compared with the intubation and ventilation group. The Vermont Oxford Network (VON) study group enrolled 648 infants (26–29 weeks' gestation) in an RCT and also found no difference in the primary outcome of BPD or death in neonates initially managed with CPAP (either nasal CPAP or prophylactic surfactant with rapid extubation to CPAP) and those treated with prophylactic surfactant followed by a period of mechanical ventilation.⁶ The SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trial was the largest RCT (1,316 infants born between 24 and 27 weeks' gestation) comparing outcomes in infants randomized to mechanical ventilation or CPAP at birth.⁷ The primary outcome of BPD or death was similar in the two groups. However, infants managed on CPAP were less frequently treated with postnatal corticosteroids and required fewer days of mechanical ventilation. The data from these clinical trials have shown that the use of CPAP as an initial respiratory support in VLBW is safe and feasible. After these RCTs and recent guidelines on RDS management, the use of CPAP as an initial mode of respiratory support for the management of VLBW with RDS is increased.⁹ In our cohort, more than one-third of VLBW infant were managed successfully with CPAP on the first DOL. Our study, using a large sample size, indicates that the risk of BPD or death is lower with the successful use of CPAP on the first DOL in VLBW infants. The number of infants analyzed in the current study (4,629) was almost twice the combined total of 2,574 infants from the three previously discussed RCTs. A recent meta-analysis using all RCTs comparing CPAP and mechanical ventilation also showed benefit for the combined outcome of death or BPD for infants treated with CPAP.¹⁷ Due to the requirement of prenatal consent, three RCTs enrolled only about one-third of the eligible infants, preselecting more stable pregnancies with lower incidence of mortality and morbidities.

In a recent policy statement, the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn recommended that using CPAP immediately after birth may be considered as an alternative to routine intubation and surfactant therapy.¹⁸ In the statement, the AAP concluded that preterm infants treated with early CPAP are not at increased risk for adverse outcomes if treatment with surfactant is delayed or not given. In our study, only 35% of infants in the CPAP group received surfactant compared with 77% in the mechanical ventilation group. Even with the lower use of surfactant, infants in the CPAP group had better respiratory outcomes. These data corroborate the AAP's recommendation of using CPAP without surfactant use or delayed surfactant use if infants require intubation. Only 32% of the infants who were managed on CPAP on the first DOL eventually required mechanical ventilation in our cohort.

The successful use of CPAP on the first DOL was not only associated with reduction in primary outcome of BPD or death, it was also associated with decrease in other morbidities. The VLBW infants managed successfully on CPAP on the first DOL had a lower risk of severe IVH and PDA requiring surgical ligation. We speculate that less fluctuation in PaCO₂ and blood pressure with the use of nasal CPAP may have contributed to the reduction in the risk of severe IVH. The management of PDA in preterm infants has drastically changed over

the last few years.^{19,20} Clinicians may be less inclined to surgically ligate a PDA if an infant is on CPAP. We also found that VLBW infants managed successfully with CPAP on the first DOL required fewer days of mechanical ventilation, weaned to room air more quickly, and were less frequently discharged home on oxygen. The SUPPORT trial also reported fewer days of mechanical ventilation and less frequent use of postnatal steroids in the infants in the CPAP group.⁷

The VON trial included infants born between 26 and 29 weeks' gestation while the COIN trial enrolled infants born between 25 and 28 weeks' gestation.^{5,6} Only the SUPPORT trial included infants born at 24 weeks' gestation (24–27 weeks).⁷ Our analysis also included infants born at 23 weeks' gestation. In subgroup analysis, for infants born between 23 and 25 weeks' gestation, there was no significant difference in the primary outcome of BPD or death between the two groups. In this subgroup, there were a limited number of infants who were managed successfully with CPAP on the first DOL, although those that were had a lower risk of developing severe IVH and PDA requiring surgical ligation. Subgroups of infants born between 26 and 28 weeks' gestation and 29 and 31 weeks' gestation had a lower risk of developing BPD or death with the successful use of CPAP on the first DOL.

The major strength of the current study is the large sample size. The results from this study should be broadly generalizable as the analysis included infants from more than 700 NICUs across the nation in both academic and community settings. We also included infants born at 23 and 24 weeks' gestation. We recognize some important limitations of this study. This is a retrospective study, and although the data were collected prospectively by experienced health care professionals, limitations of data collection are apparent. For instance, details about delivery room resuscitation, number and timing of prenatal steroid doses, and whether an infant was outborn and transferred in were not available from the database. Infants in the ventilation group may have been intubated for mechanical ventilation at the outset, or may have initially required CPAP with subsequent mechanical ventilation (early CPAP failure). The use of prenatal steroids is low in our cohort. Not all eligible infants in the study sites were enrolled as only infants with health plans managed by Alere are included in the database. It is possible that the population served by Alere has more limited prenatal care given the lower use of antenatal steroids. However, there was no significant difference in the use of prenatal steroids between the two groups in our study population. The infants were not randomized and, therefore, infants in the CPAP group may have had less severe lung disease. The groups differed in a few baseline demographics and clinical features. The analysis was performed to adjust for confounding variables, but the possibility of differences in outcomes due to the variation in baseline clinical characteristics still exists. Our data suggest only an association between primary and secondary outcomes with the use of CPAP and mechanical ventilation on the first DOL; a causal relationship cannot be established.

In conclusion, our findings suggest that successful use of CPAP on the first DOL is associated with lower risk of BPD or death in VLBW infants. In addition, the successful use of CPAP on the first DOL may reduce the risk of severe IVH, PDA requiring surgical ligation, days on mechanical ventilation, number of infants discharged home on oxygen, and days to room air in VLBW infants. Our data support the recent AAP recommendation of

using CPAP for the management of RDS as an alternative to routine intubation and surfactant therapy in VLBW infants.

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Table 1Demographics and baseline clinical characteristics of the study population (mean $\pm$ SD)

	Ventilated day 1 (2,750)	CPAP day 1 (1,879)
GA (wk)	27.2 $\pm$ 2.4	29.4 $\pm$ 2.1 ^a
BW (g)	940 $\pm$ 248	1,171 $\pm$ 233 ^a
Male sex (%)	1,469 (53)	942 (50)
Caucasian race (%)	975 (35.4)	694 (37.0)
Prenatal steroids (%)	1,316 (48)	948 (50)
5-minute Apgar 5 (%)	520 (21)	69 (4) ^a
Ventilated any time (%)	2,750 (100)	595 (32) ^a
Surfactant (%)	2,117 (77)	658 (35) ^a
Dose of surfactant (median, range)	1 (1–4)	1 (1–4)
Early-onset sepsis (%)	19 (0.69)	12 (0.64)
Late-onset sepsis (%)	808 (29.4)	196 (10.4) ^a
Required inotrope (%)	922 (33.5)	126 (6.7) ^a
Ventilation days	25.4 $\pm$ 32.7	3.5 $\pm$ 11.4 ^a
High volume centers (%)	1,186 (43.1)	904 (48.1) ^a

Abbreviations: BW, birth weight; CPAP, continuous positive airway pressure; GA, gestational age; SD, standard deviation.

^a
 $p < 0.05$.

Table 2

Primary and respiratory outcomes in infants ventilated versus CPAP on day 1

	Ventilated day 1 (2,750)	CPAP day 1 (1,879)
BPD or death (%)	1,509 (54.8) ^{a,b}	445 (23.7)
Death (%)	370 (13.4) ^{a,b}	54 (2.9)
BPD (%)	1,175 (42.7) ^{a,b}	402 (21.4)
Days to room air	56.5 ± 37.9 ^{a,b}	29.3 ± 29.2
Pneumothorax (%)	112 (4.1) ^b	26 (1.4)
Use of postnatal steroids (%)	384 (14) ^b	69 (3.7)
Home on oxygen (%)	579 (21) ^{a,b}	185 (9.8)
Length of hospitalization (d)	77.1 ± 43.5 ^b	56.9.0 ± 27.5

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure.

^a $p < 0.05$ on multivariate regression analysis after adjusting for BW, GA, 5-minute Apgar, surfactant use, centers, late-onset sepsis, and use of inotropes.^b $p < 0.05$ on bivariate analysis.

Table 3

Neonatal outcomes in infants ventilated versus CPAP on day 1 (adjusted for BW, CA, 5-minute Apgar, surfactant use, centers, late-onset sepsis, and use of inotropes)

	OR (95% CI)	<i>p</i>-Value
BPD or death	0.615 (0.496–0.764)	< 0.001
Death	0.417 (0.275–0.633)	< 0.001
BPD	0.692 (0.567–0.843)	< 0.001
Severe IVH	0.286 (0.165–0.497)	< 0.001
PDA requiring surgical ligation	0.590 (0.441–0.788)	< 0.001
NEC	1.237 (0.818–1.869)	0.3
ROP age 3	1.194 (0.746–1.911)	0.5

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; CPAP, continuous positive airway pressure; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

Table 4

Subgroup analysis of infants ventilated versus CPAP on day 1

CA (wk)	CPAP day 1	Ventilated day 1	OR (95% CI)
23–25	n = 107	n = 899	
BPD or death (%)	71 (67.0)	719 (80.0)	0.610 (0.342–1.089)
Severe IVH (%) ^a	10 (9.4)	174 (19.3)	0.294 (0.103–0.840)
LOS (d)	91 ± 40	93 ± 54	
PDA ligation (%) ^a	51 (15.1)	251 (27.9)	0.437 (0.200–0.954)
26–28	n = 580	n = 1,155	
BPD or death (%) ^a	189 (32.6)	580 (50.3)	0.751 (0.577–0.976)
Severe IVH (%) ^a	14 (2.4)	101 (8.7)	0.281 (0.135–0.586)
LOS (d)	73 ± 25	79 ± 35	
PDA ligation (%)	48 (8.3)	166 (14.4)	0.767 (0.506–1.162)
29–31	984	618	
BPD or death (%) ^a	156 (15.8)	187 (30.2)	0.499 (0.367–0.680)
Severe IVH (%)	7 (0.7)	14 (2)	0.739 (0.252–2.171)
LOS (d)	50 ± 19	55 ± 22	
PDA ligation (%) ^a	25 (2.5)	54 (8.7)	0.425 (0.239–0.753)

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; CPAP, continuous positive airway pressure; GA, gestational age; IVH, intraventricular hemorrhage; LOS, length of stay; OR, odds ratio; PDA, patent ductus arteriosus.

^a $p < 0.05$ on multivariate regression analysis after adjusting for BW, CA, 5-minute Apgar, surfactant use, centers, late-onset sepsis, and use of inotropes.