CLINICAL SCIENCE

Initial respiratory management in preterm infants and bronchopulmonary dysplasia

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BACKGROUND: Ventilator injury has been implicated in the pathogenesis of bronchopulmonary dysplasia. Avoiding invasive ventilation could reduce lung injury, and early respiratory management may affect pulmonary outcomes.

OBJECTIVE: To analyze the effect of initial respiratory support on survival without bronchopulmonary dysplasia at a gestational age of 36 weeks.

DESIGN/METHODS: A prospective 3-year observational study. Preterm infants of <32 weeks gestational age were classified into 4 groups according to the support needed during the first 2 hours of life: room air, nasal continuous positive airway pressure, intubation/surfactant/extubation and prolonged mechanical ventilation (defined as needing mechanical ventilation for more than 2 hours).

RESULTS: Of the 329 eligible patients, a total of 49% did not need intubation, and 68.4% did not require prolonged mechanical ventilation. At a gestational age of 26 weeks, there was a significant correlation between survival without bronchopulmonary dysplasia and initial respiratory support. Preterm infants requiring mechanical ventilation showed a higher risk of death and bronchopulmonary dysplasia. After controlling for gestational age, antenatal corticosteroid use, maternal preeclampsia and chorioamnionitis, the survival rate without bronchopulmonary dysplasia remained significantly lower in the mechanically ventilated group.

CONCLUSIONS: In our population, the need for more than 2 hours of mechanical ventilation predicted the development of bronchopulmonary dysplasia in preterm infants with a gestational age >26 weeks (sensitivity = 89.5% and specificity = 67%). The need for prolonged mechanical ventilation could be an early marker for the development of bronchopulmonary dysplasia. This finding could help identify a target population with a high risk of chronic lung disease. Future research is needed to determine other strategies to prevent bronchopulmonary dysplasia in this high-risk group of patients.

KEYWORDS: Bronchopulmonary Dysplasia; Preterm; Nasal CPAP; Surfactant; Initial; Respiratory Support.

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) affects thousands of preterm infants each year. The use of antenatal corticosteroids, postnatal surfactant therapy and modern intensive care has modified BPD into a less-severe disease that is characterized by arrested lung development.[1] The key factors in BPD's pathogenesis are extreme lung immaturity, antenatal and postnatal inflammation, and the effects of oxygen and mechanical ventilation.[2-4]

Because ventilator-induced lung injury is a major contributing factor to BPD,[5] early respiratory management in preterm infants may affect pulmonary outcomes. The use of positive end-expiratory pressure (PEEP) at delivery[6-8] and early postnatal nasal continuous positive airway pressure (nCPAP) may be beneficial in reducing the need for intubation and mechanical ventilation and in preventing chronic lung disease (CLD).[9-12] It has been suggested that avoiding ventilator-induced injury may be an effective way to reduce the incidence of BPD.[13] Retrospective data suggest that preterm infants supported by nCPAP from delivery have shorter hospital stays and less surfactant use and that these infants are less likely to develop CLD (although not significantly so). However, randomized clinical trials have demonstrated no effect of prophylactic CPAP in reducing the incidence of BPD.[14,15]

Since September 2003, our regular practice for the respiratory support of preterm infants below 32 weeks of gestational age (GA) has been modified to prevent tracheal intubation by giving prophylactic CPAP in the delivery room to all spontaneously breathing infants. Those infants requiring surfactant treatment are extubated to nCPAP as

soon as possible (ideally, with less than two hours of mechanical ventilation). We performed a prospective, observational study of all inborn admissions with a GA of less than 32 weeks from January 2004 to December 2006. We analyzed the risk of BPD and/or mortality according to the initial respiratory support needed.

DESIGN

A prospective, observational study conducted in the Neonatology Service of the Hospital General Universitario Gregorio Marañón from January 2004 to December 2006.

Patients

All preterm infants of <32 weeks GA and free from major congenital abnormalities were eligible for this study.

Methods

All preterm infants of <32 weeks GA who had spontaneous respiratory effort in the delivery room were given noninvasive continuous airway pressure support through a Neopuff infant resuscitator (Fisher & Paykel Healthcare Corporation Limited, Auckland, New Zealand). The Neopuff delivers oxygen from a blender at concentrations ranging from 21% to 100%. The patients' T-pieces were connected to neonatal masks. The peak inspiratory pressure (PIP) (<20 cm H_2O) and PEEP (5 cm H_2O) were preset by the neonatologist before delivery and checked using the integrated manometer. A valve on the T-piece provided PEEP. The PIP and PEEP levels were constant and were maintained automatically for every breath.

The infants were categorized into 1 of 4 groups, based on the respiratory support needed during the first 2 hours of life to maintain the following targets in capillary blood samples: an oxygen saturation of 88% to 92%, a pH >7.25, and a PCO_2 <60 mm Hg. No active intervention or randomization was undertaken by the attending physicians; the infants were classified solely on the basis of their respiratory situation. Outcomes in the first 72 hours of life were used to determine the success or failure of the respiratory support.

The following respiratory support categories were used: the infants in Group 1 received prophylactic CPAP but not supplemental oxygen in the delivery room and did not develop respiratory distress syndrome; the infants in Group 2 received nasal CPAP (nCPAP) with a FiO_2<30% due to low oxygen saturation and an increased respiratory effort after the prophylactic CPAP in the delivery room; the infants in Group 3 received endotracheal intubation to administer 100 mg/kg of exogenous surfactant (Survanta, Abbott Laboratories,) and were extubated successfully to nCPAP within the first two hours of mechanical ventilation (intubation, surfactant, and extubation, or INSURE); and the infants in Group 4 could not be extubated within the first 2 hours of mechanical ventilation and could not be administered surfactant therapy due to high FiO_2 requirements (>30%). The two-hour period was arbitrarily chosen by the investigators. INSURE failure has been defined in the literature as inability to extubate after 1 hour of surfactant administration.[16,17]

A low threshold for administering surfactant was used. Surfactant was given to any infant receiving nCPAP at a pressure >5 cm H_20 who needed an FiO_2 >30% to achieve a target oxygen saturation between 88% and 92%. If the FiO_2 requirements remained >30%, a second dose of surfactant was given six hours after the first. Extubation was attempted when there was an adequate spontaneous respiratory effort, hemodynamic stability and an oxygen saturation from 88% to 92% with an FiO_2 <30%. A loading dose of intravenous theophylline, followed by oral caffeine, was administered to all the infants on admission to the NICU.

The data collected included patient demographics, antenatal corticosteroid use (two 12 mg intramuscular injections of betamethasone given 24 hours apart), preeclampsia (development of new-onset hypertension with proteinuria after 20 weeks gestation), chorioamnionitis (defined as the presence of fever with one or more of the following: maternal leukocytosis >15.000/mm^3, uterine tenderness, fetal tachycardia, and foul-smelling amniotic fluid)[18], surfactant therapy, survival without BPD at 36 weeks gestational age (as determined by the last menstrual period),[19,20] the presence of an air leak (pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema), a Papile' Grade 3 or above intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) requiring surgery, a patent ductus arteriosus (PDA) requiring surgical closure, Stage 3 or greater retinopathy of prematurity (ROP) (using the International Classification of ROP) and mortality.

Ethical committee approval was obtained for the publication of the results.

Outcome Measures

The primary outcome was survival without BPD at 36 weeks and its relation with the initial ventilatory support. We also analyzed whether the need for prolonged (>2 hours) mechanical ventilation after surfactant administration could predict the development of BPD in preterm infants.

The results were analyzed by the following gestational age groups: <26 weeks, 26-28 weeks, and >28 weeks.

Statistical Analysis

SPSS 15.0 was used for the data analysis. The categorical data were analyzed using a chi-square or Fisher's exact test (where appropriate), and continuous variables were analyzed using an ANOVA model or a median test. A multivariate regression model was used to adjust for the differences between the groups in GA, gender, antenatal corticosteroid administration, maternal preeclampsia and chorioamnionitis.

RESULTS

A total of 343 preterm infants of less than 32 weeks GA were delivered during the study period. Of these, 14 were excluded because of major congenital abnormalities, leaving 329 eligible participants. The mean GA was 28.6 weeks (range, 23.0-31.6 weeks), and the mean birth weight was 1.201 g (range, 430-2.100 g). The demographics of the study population by the respiratory-support groups are shown in Table 1.

In the nCPAP group, 18.7% of infants needed intubation and exogenous surfactant due to an FiO_2 requirement >30%. In the INSURE group, 18.3% required reintubation within the first 72 hours of life. Almost half of the preterm infants (49%) did not require intubation (Groups 1 and 2),

Table 1 - The characteristics of the study population by the initial airway-management modality. The results are expressed as the mean (SD).

	All N = 329	Group 1 N = 67 (20.4%)	Group 2 N = 94 (28.6%)	Group 3 N = 64 (19.5%)	Group 4 N = 104 (31.6%)	p
Birth weight, g	1201 (376.8)	1565 (324.7)	1340 (272.2)	1298 (342.9)	1060 (353.8)	0.21
GA, weeks	28.6 (2.1)	30.2 (1.0)	29.4 (1.6)	28.5 (1.9)	26.9 (2.1)	0.00*
Gender, % male	54.4	50.7	51.1	60.9	55.7	0.58
Cord pH	7.29 (0.1)	7.34 (0.07)	7.28 (0.11)	7.31 (0.07)	7.26 (0.14)	0.21
Antenatal corticosteroids, %	62.3	71.6	68.1	62.5	51.0	0.02*
Chorioamnionitis, %	16.7	9.4	9.8	12.1	35.5	0.00*

and 68.4% did not require mechanical ventilation for more than two hours (Groups 1, 2 and 3). The mean age for the first dose of surfactant was 2 hours (Standard Deviation (SD), 1.2 hours). A second dose of surfactant was administered to 35% of the mechanically ventilated infants.

The distribution by GA of the infants into the different respiratory-support groups is shown in Figure 1. The success rates of nCPAP and INSURE (50% for both) were significantly higher for those preterm infants of >26 weeks GA.

The overall BPD-free survival (SF-BPD) rate at 36 weeks GA was 72%: 12.5% for infants less than 25 weeks GA, 56.5% for those of 26 to 28 weeks GA, and 93.4% for those of more than 28 weeks GA (Figure 2).

There was a statistically significant difference in BPD-free survival between the respiratory-support groups. The infants in Group 1 had an SF-BPD rate of 100%. The SF-BPD rate was 88.3% in the nCPAP group, it was 76.6% in the INSURE group, and it was 36.5% in the mechanical-ventilation group ($p<0.01$) (Figure 3). The nCPAP group and the INSURE group did not have a statistically significant difference in SF-BPD.

Table 2 shows the logistic-regression analyses of the individual effects of GA, antenatal corticosteroid treatment, maternal preeclampsia and chorioamnionitis on the SF-BPD rate in both the nCPAP and INSURE groups. In a multivariate model combining gestational age, antenatal corticosteroid treatment, maternal preeclampsia and chorioamnionitis, the SF-BPD rates in both the nCPAP and INSURE groups were significantly higher than in the prolonged-mechanical-ventilation group. The odds ratio (OR) was 3.7 ($p = 0.03$, 95% confidence interval (CI) = 1.5-8.8) for Group 2 and was 2.3 ($p = 0.05$, 95% CI = 1.0-5.5) for Group 3. Regardless of the type of respiratory support, GA was a protective factor, with an OR of 1.89 ($p<0.01$, 95% CI = 1.56-2.29). Preeclampsia was associated with an increased likelihood of developing BPD, with an OR of 2.54 ($p = 0.03$, 95% CI = 1.08-5.97). Neither the antenatal administration of corticosteroids nor maternal chorioamnionitis modified the unadjusted OR, however.

An ROC curve was used to establish a GA threshold at which the need for mechanical ventilation would be the best predictor for later BPD. The need for prolonged mechanical ventilation after a GA of 26 weeks predicted the development of BPD with a sensitivity of 89.5% and a specificity of 67% (Figure 4).

Table 3 shows the adverse outcomes. Significantly higher rates of air leaks (interstitial emphysema or pneumothorax), PDA, IVH, ROP and mortality were associated with the need for prolonged mechanical ventilation. There were no significant differences in the rates of air leaks between the nCPAP and INSURE groups. A logistic-regression analysis that excluded Group 1 and controlled for GA revealed no statistically significant difference in mortality between the INSURE and nCPAP groups ($p = 0.28$). When compared to the nCPAP group, the odds ratio for mortality in Group 4 was 4.6 ($p = 0.02$, 95% CI = 1.23-17.2).

DISCUSSION

The best respiratory-therapy approach for preterm infants in the delivery room remains a controversial issue. Due to mechanical ventilation increasing the risk of BPD, most neonatologists have focused on avoiding the use of mechanical ventilation as much as possible.[13,21] The use of nCPAP to prevent respiratory distress syndrome and the need for intubation and exogenous surfactant administration are generally accepted.[22] Because nCPAP can be used successfully in many preterm infants to avoid the need for invasive mechanical ventilation and prevent lung injury, we modified our clinical approach to respiratory support

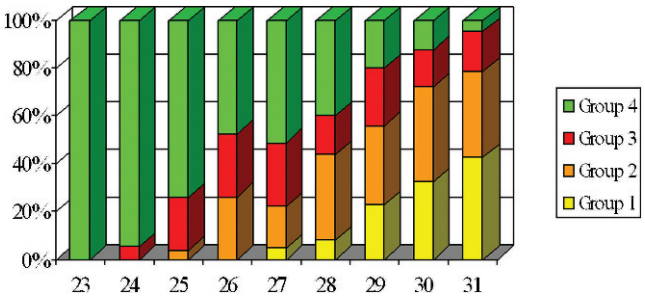

Figure 1 - Respiratory support by GA (weeks).

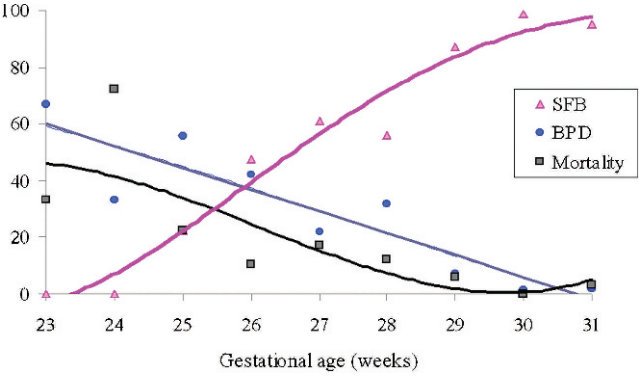

Figure 2 - Survival free of BPD (%) by GA.

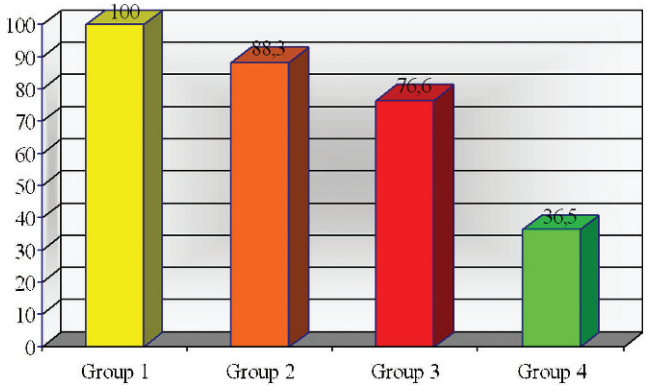

Figure 3 - Survival free of BPD (%) by respiratory care groups.

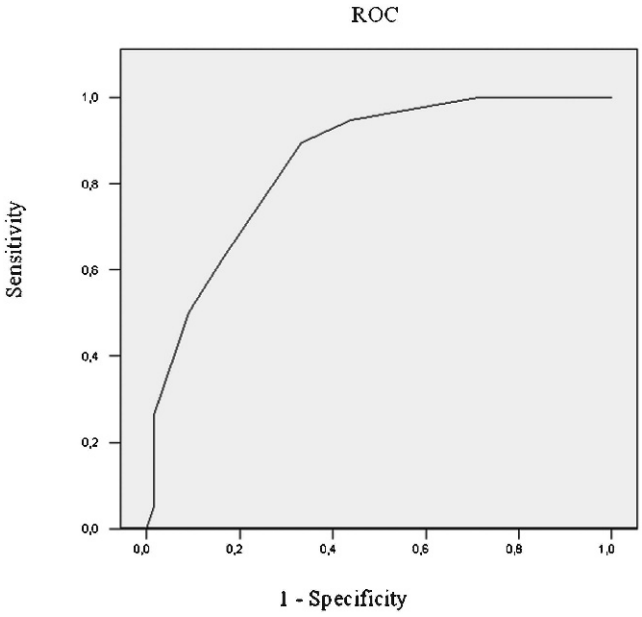

Figure 4 - ROC curve. The need for prolonged mechanical ventilation after a GA of 26 weeks was a good predictor for later development of BDP (Sensitivity 89.5%, Specificity 67%).

during the first few hours of life for preterm infants younger than<32 weeks GA. Prophylactic CPAP starting at delivery was used in an attempt to open the infant's lungs by spontaneous respiratory effort. In our study, 49% of the preterm infants of <32 weeks gestational age did not need intubation or mechanical ventilation, and 68.4% did not require prolonged mechanical ventilation (>2 hours). These data corroborate those of previous studies that have suggested that it is possible to initiate nCPAP for even the most immature neonates.[15,23,24] However, there is still a need for invasive mechanical ventilation in some infants, particularly in the younger GA groups.[25] In our study, we showed that more than 95% of the infants younger than 25 weeks GA required invasive mechanical ventilation, and the success rates for nCPAP and INSURE increased when the GA was greater than 26 weeks.

We found a statistically significant difference in survival without BPD at 36 weeks related to the initial respiratory support needed. The preterm infants requiring mechanical ventilation for more than two hours had a higher risk of death and BPD than those successfully treated with room air, nCPAP or INSURE. To minimize heterogeneity and avoid confounding factors, a multivariate-regression model was used to adjust for the differences between the groups. With the obvious limitations of a descriptive study, we found that the SF-BPD rate remained significantly lower in the mechanically ventilated group than in the other groups after controlling for differences in GA, antenatal corticosteroids, maternal preeclampsia and chorioamnionitis. Because our study was non-interventional and because the preterm infants were allocated to the groups based on the severity of their respiratory failure, the nCPAP group was composed of infants who were not severely ill. This factor may have been one of the reasons for the significantly lower risk of developing BPD. A randomized, controlled intervention trial showed no benefit of nCPAP over invasive mechanical ventilation in decreasing the rate of BPD.[24] Because the patients with severe respiratory distress were in the prolonged-mechanical-ventilation group, we found a higher incidence of pneumothorax among these patients than in the nCPAP group. Moreover, the INSURE-group infants were less likely to develop pneumothorax (1.6%) than the nCPAP group (4.3%). Both the nCPAP and INSURE groups had lower short-term morbidity. The CPAP pressure applied, the FiO_2 chosen for the intubation and the use surfactant are still matters of controversy.[26] In our study, an nCPAP of 5 cm of H_2O and an $nFiO_2$ >30% were used as the criteria for intubation and surfactant therapy, and this choice may have modified the findings. The best approach is yet to be

Table 2 - The results of logistic-regression analyses assessing the individual effects of GA, antenatal corticosteroid treatment, maternal pre-eclampsia and chorioamnionitis on the SF-BPD rate in the nCPAP and INSURE groups. The SF-BPD rate in both these groups was significantly higher than in the prolonged-mechanical-ventilation group.

		OR	95% CI	p
Unadjusted	CPAP	13.1	6.2 – 27.6	<0.01
	INSURE	5.7	2.8 – 11.4	<0.01
Adjusted for antenatal corticosteroids	CPAP	12.6	5.9 – 26.5	<0.01
	INSURE	5.5	2.7 – 11.2	<0.01
Adjusted for chorioamnionitis	CPAP	9.0	4.2 – 19.5	<0.01
	INSURE	3.9	1.8 – 8.2	<0.01
Adjusted for GA	CPAP	4.5	1.9 – 10.6	<0.01
	INSURE	3.3	1.5 – 7.4	0.04
Adjusted for GA, antenatal corticosteroids and chorioamnionitis	**CPAP**	**3.7**	**1.5 – 8.8**	**0.03**
	INSURE	**2.3**	**1.0 – 5.5**	**0.05**

Table 3 - The incidence of adverse outcomes in the different airway-management groups. The need for prolonged mechanical ventilation was associated with significantly higher rates of interstitial emphysema or pneumothorax, PDA, IVH, ROP and mortality.

	Air Leak	PDA	IVH III-IV	ROP >2	NEC	Mortality
Group 1	1 (1.5%)	0 (0%)	1 (1.5%)	0 (0%)	2 (3%)	0 (0%)
Group 2	4 (4.3%)	4 (4.3%)	3 (3.2%)	1 (1.1%)	6 (6.4%)	3 (3.2%)
Group 3	1 (1.6%)	3 (4.7%)	5 (7.8%)	1 (1.6%)	2 (3.1%)	6 (9.4%)
Group 4	20 (19.2%)	20 (19.2%)	20 (19.2%)	9 (8.7%)	11 (10.6%)	29 (27.9%)
	$p<0.01$	$p<0.01$	$p<0.01$	$p=0.03$	$p=0.14$	$p<0.01$

determined and may be different in different gestational age groups.

Our objective was not to compare respiratory strategies but to analyze the severity of respiratory failure within the first hours of life, with the aim of avoiding unnecessary intubation. It seems that the need for mechanical ventilation after the administration of exogenous surfactant may define the risk for BPD.

Our study was not designed to analyze the relationship between preeclampsia and BPD, but our data are consistent with other existing reports showing a positive association between those two pathologies.[27,28] Maternal preeclampsia may impair fetal pulmonary development, thereby increasing the risk of neonatal respiratory distress.

In conclusion, the need for prolonged mechanical ventilation (more than 2 hours) may be an early marker for the development of BPD in preterm infants of more than 26 weeks GA. This association may help to identify a target population with a high risk of BPD. Future research is needed to find strategies to prevent BPD in this high-risk group of patients.

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