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Original article

Early nCPAP versus intubation in very low birth weight infants

Pedro Neves Tavares[1], Filipa Flor-de-Lima[1,2], Henrique Soares[1,2], Hercília Guimarães[1,2]

[1]Faculty of Medicine, Porto University, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
[2]Neonatal Intensive Care Unit, Pediatric Integrated Hospital, São João Hospital, Alameda Professor Hernâni Monteiro, 4202-451 Porto, Portugal

Abstract

For many years endotracheal intubation and mechanical ventilation have been the standard of care for very low birth weight infants but, in the last decade, nasal continuous positive airway pressure (nCPAP) has been described in many studies as an option for the treatment of preterm infants with respiratory distress syndrome. In fact, recent studies have shown that early nCPAP is not associated with higher rates of morbidity and mortality and does not imply more days of ventilation support when compared to traditional ventilation techniques. The authors conducted a study to compare the outcomes (in terms of mortality, morbidity and need for medical support) of very low birth weight infants treated with nCPAP or endotracheal intubation and mechanical ventilation. One hundred and four newborns were enrolled in this study, 44 (42.3%) were treated with nCPAP and 60 (57.7%) with endotracheal intubation followed by mechanical ventilation. A subgroup analysis of newborns with gestational age between 28 and 31 weeks was also performed. It included 57 newborns with similar demographic characteristics, 29 (50.9%) treated with nCPAP and 28 (49.1%) with endotracheal intubation followed by mechanical ventilation. No statistically significant differences were found in the frequency of death or bronchopulmonary dysplasia. Statistically significant differences were found in the prevalence of hyaline membrane disease ($p = 0.033$) and surfactant administration ($p = 0.021$) with lower rates in the nCPAP group. No other differences were found in the prevalence of other morbidities or in the need for medical support after birth. These results suggests that nCPAP might be chosen as primary ventilatory support choice in very low birth weight preterm, when there are no contraindications to its use.

Keywords

Newborn, premature, continuous positive airway pressure, intubation, surfactant, hyaline membrane disease.

Corresponding author

Pedro Neves Tavares, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal; telephone number: +351 22 551 3600; fax number: +351 22 551 3601; email: pedronevestavares@gmail.com.

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Introduction

Approach to very low birth weight infants (VLBW), in both delivery room and Neonatal Intensive Care Unit (NICU), has been changing in the last decade and those changes have led to an improvement in the morbidity and mortality rates in most centers [1, 2].

Assisted ventilation and surfactant have been the standard treatment for VLBW infants [3]. On the one hand, numerous studies have shown that mechanical ventilation associated with surfactant administration leads to a reduction in many complications of premature birth (among others, it leads to a decrease in death rates and the incidence of both bronchopulmonary dysplasia and air leaks) [4]. On the other hand, it has been hypothesized that long term ventilation is associated with lung damage and might be associated with higher rates of bronchopulmonary dysplasia (BDP) [5, 6].

There are many observational and clinical trial studies whose data support that early nasal continuous positive airway pressure (nCPAP) is associated with lower rates of mechanical ventilation with no increase in morbidity and mortality [7-10]. In fact, nCPAP helps the achievement of functional residual capacity and the stabilization of the airways and thoracic cage [11, 12].

The aim of our study is to compare the outcomes (morbidity and mortality) of VLBW infants treated with nCPAP with those treated with endotracheal intubation and mechanical ventilation.

Material and methods

The authors performed a retrospective study comparing a strategy of early nCPAP use with that of endotracheal intubation, both started in the delivery room.

Data from all newborns born in our center, a level III NICU, from 30 June 2007 to 30 June 2012 were recorded. The inclusion criteria were birth weight less than 1,500 g and the need for ventilation at birth. Infants with major malformations and those transferred to other units before the completion of 30 days after birth were excluded from this study.

The newborns included in the study were divided into two different subgroups, one treated with early nCPAP and another with endotracheal intubation and mechanical ventilation. Another group that contained all newborns with gestational ages between 28 and 31 weeks was also analyzed. Both groups were stratified into two subgroups, one of those treated with early nCPAP and another treated with endotracheal intubation and mechanical ventilation.

The data that were collected from the NICU database included information about individual characteristics of the mother and prenatal period that are known prenatal risk factors for neonatal morbidity (maternal infection, diabetes mellitus, hypertension, pre-eclampsia, twin pregnancy, delivery method and treatment with steroids during pregnancy), and demographic characteristics of the newborn that may be associated with postnatal prognosis (gestational age, birth weight, gender and Apgar score).

Antenatal steroid regimen was performed with betamethasone (divided into two doses of 12 mg each) in pregnancies with predictable preterm labor. The decision between early nCPAP and early endotracheal intubation was made in the delivery room by the attending neonatologist according to the NICU perinatal ventilatory support protocol. The diagnosis of bronchopulmonary dysplasia (BPD) was defined by the need of any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen and the characteristic chest radiograph [5]. Exogenous surfactant was administered through an endotracheal tube using an INtubation-SURfactant-Extubation (INSURE) in the newborns treated with early nCPAP [9]. Neonatal sepsis was defined by the detection of any microorganism (bacteria or fungus) in the blood stream with positive blood culture.

The primary outcome of this study was the prevalence of death and BPD. Secondary outcomes included the major causes of postnatal morbidity (pneumothorax, intraventricular hemorrhage [IVH], hyaline membrane disease [HMD], retinopathy of prematurity [ROP], patent ductus

arteriosus [PDA], sepsis, necrotizing enterocolitis [NEC] and acute renal failure [ARF]) and the need for support or medical care after birth (number of days that the newborn requires catheter support, ventilation support, oxygen treatment, number of days with total parenteral nutrition and the number of days until full enteral feeding).

This retrospective study was approved by our institutional ethics committee. Data collection and statistical analysis were performed with *IBM SPSS Statistics v.20*®. Continuous variables were characterized by mean (± standard deviation) and median (medium-maximum) if they had symmetric or asymmetric distribution respectively, and categorical variables by absolute and relative frequencies. To compare continuous variables we used parametric (independent t test) or non-parametric (Mann-Whitney U test) tests if they had symmetric or asymmetric distribution respectively, and Chi-Squared or Fisher's exact test to compare categorical variables, the latter for expected values less than 5. A multivariate analysis by logistic regression or multiple linear regression (categorical or continuous variables, respectively) was performed. A p value less than 0.05 was considered statistically significant.

Results

From 2007 to 2012, 156 infants lighter than 1,500 g were born in our center. Fifty-two (33.3%) newborns were not eligible for this study (47 were transferred to other NICUs and 5 presented major malformations at birth). A total of 104 (66.7%) newborns were enrolled in this study, 44 (42.3%) treated with nCPAP and 60 (57.7%) with endotracheal intubation and mechanical ventilation. The analysis of the demographic characteristics of the newborns showed statistically significant differences in gestational age ($p \leq 0.0001$), birth weight ($p \leq 0.0001$), Apgar score at 5th minute ($p \leq 0.0001$), C-section delivery ($p = 0.043$) and antenatal corticosteroid use ($p = 0.042$). The second group that was evaluated included all newborns of less than 1,500 g and between 28 and 31 gestational weeks. It was composed of 57 newborns, 29 (50.9%) treated with nCPAP and 28 (49.1%) treated with intubation and mechanical ventilation (**Figure 1**).

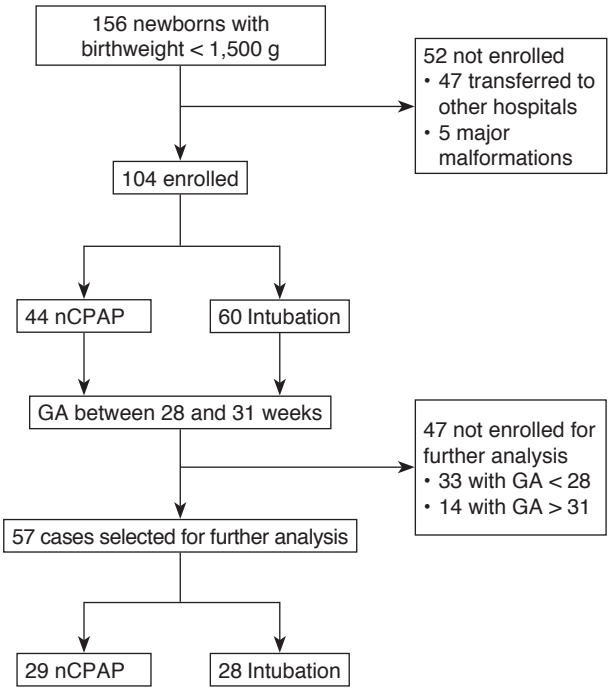
In the group of newborns between 28 and 31 gestational weeks, the Apgar score at the 5th min was less than 7 in 16 (57.1%) in the endotracheal intubation group and higher than 8 in 26 (89.7%) in the nCPAP group ($p < 0.0001$). The other demographic and clinical characteristics are summarized in **Table 1**.

The prevalence of death was 33.3% vs 4.5% (intubation vs nCPAP, $p = 0.001$.) in the global analysis and 10.7% vs 3.5% (intubation vs nCPAP, p = n.s.) in the group of gestational age 28-31 weeks; the prevalence of BPD was 25% vs 13.6% (intubation vs nCPAP, p = n.s.) in the global analysis and 14.3% vs 13.8% (intubation vs nCPAP, p = n.s.) in the group of gestational age 28-31 wk.

The odds of death in nCPAP group was OR = 2.05 and OR = 3.08 (global and subgroup analysis respectively, p = n.s.) and the chance of BPD occurrence in nCPAP group was OR = 0.77 and OR = 0.61 (global and subgroup analysis respectively, p = n.s.) when compared to intubation (**Table 2**).

There were no significant differences in secondary outcomes in the two, nCPAP and intubation groups, excepting the prevalence of HMD which was 51.7% in the nCPAP group vs 89.3% in the intubation group ($p = 0.033$) and the need of surfactant which was 55.2% in the former group vs 89.3% in the latter group ($p = 0.021$). The secondary outcomes are summarized in **Table 3**.

In the early nCPAP group we found that 14 infants (32%) of the newborns needed endotracheal intubation during their stay in the NICU.



GA: gestational age; nCPAP: nasal continuous positive airway pressure.

Figure 1. Enrollment method.

Table 1. Demographic and clinical characteristics.

	nCPAP (n = 44)	Intubation (n = 60)	p	nCPAP 28-31 wk (n = 29)	Intubation 28-31 wk (n = 28)	p
Antenatal steroids, n (%)	39 (90.7)	43 (74.1)	**0.042**[a]	26 (92.9)	18 (69.2)	**0.037**[a]
Maternal infection, n (%)	7 (15.9)	13 (22)	0.437[b]	6 (20.7)	5 (17.9)	0.786[b]
Maternal diabetes, n (%)	0	1 (1.7)	0.999[a]	0	1 (3.6)	0.491[a]
Maternal hypertension, n (%)	1 (2.3)	4 (6.8)	0.390[a]	1 (3.4)	1 (3.6)	0.998[a]
Pre-Eclampsia, n (%)	10 (22.7)	7 (11.9)	0.142[b]	6 (20.7)	4 (14.3)	0.730[a]
Gestational age (wk), mean ± SD	30.3 ± 2	27.1 ± 2	**< 0.0001**[c]	29.4 ± 1	28.9 ± 1	0.108[c]
Birth weight (g), median (min-max)	1,140 (550-1,486)	860 (360-1,450)	**< 0.0001**[d]	1,092 (550-1,486)	1,120 (440-1,450)	0.943[d]
Male Sex, n (%)	14 (33.3)	23 (39)	0.561[b]	9 (33.3)	10 (37)	0.776[b]
C-section, n (%)	34 (72.3)	35 (58.3)	**0.043**[b]	20 (69)	21 (75)	0.612[b]
Multiple pregnancy, n (%)	13 (29.6)	23 (38.3)	0.352[b]	10 (34.5)	10 (35.7)	0.922[b]
Apgar score 5th min, n (%) **0-7** **8-10**	 3 (6.8) 41 (93.2)	 38 (63.3) 22 (36.7)	**< 0.0001**[b]	 3 (10.3) 26 (89.7)	 16 (57.1) 12 (42.9)	**< 0.0001**[b]

[a] Fisher's exact test, [b]Chi-squared test, [c]Independent t test, [d]Mann-Whitney U test.

Table 2. Statistical analysis of the primary outcomes.

Outcome	All Infants with birthweight < 1,500 g					All infants with birthweight < 1,500 g and 28-31 gestational weeks				
	nCPAP (n = 44)	Intubation (n = 60)	p	OR[b]	p[b]	nCPAP (n = 29)	Intubation (n = 28)	p	OR[b]	p[b]
Death, n (%)	2 (4.5)	20 (33.3)	< 0.001[a]	2.05	n.s.	1 (3.5)	3 (10.7)	n.s.	3.08	n.s.
BPD, n (%)	6 (13.6)	15 (25)	n.s.	0.77	n.s.	4 (13.8)	4 (14.3)	n.s.	0.61	n.s.

BPD: Bronchopulmonary dysplasia; [a]Chi-squared test; OR: odds ratio (nCPAP vs intubation); [b]Adjusted for gestational age, birth weight and Apgar score by logistic regression; n.s.: non-significant.

Table 3. Major postnatal mortality and management in newborns with 28-31 weeks.

	nCPAP (n = 29)	Intubation (n = 28)	p[a]
ROP, n (%)	18 (69.2)	17 (70.8)	0.896
ARF, n (%)	1 (3.4)	0	0.998
IVH, n (%)	1 (3.4)	3 (11.5)	0.854
Sepsis, n (%)	17 (58.6)	13 (46.4)	0.305
Early onset sepsis, n (%)	2 (6.9)	0	0.998
HMD, n (%)	15 (51.7)	25 (89.3)	**0.033**
Pneumothorax, n (%)	1 (3.4)	1 (3.6)	0.718
PDA, n (%)	7 (24.1)	8 (32)	0.762
NEC, n (%)	1 (3.4)	2 (7.1)	0.987
Shock, n (%)	2 (6.9)	2 (7.1)	0.971
Exogenous Surfactant, n (%)	16 (55.2)	25 (89.3)	**0.021**
Ventilation (both invasive and noninvasive), median days (min-max)	38 (2-70)	35 (1-71)	0.921
Oxygen therapy, median days (min-max)	2 (0-65)	2 (0-60)	0.380
TPN, median days (min-max)	21 (6-53)	20 (0-53)	0.963
Days until full enteral feeding, median (min-max)	23 (8-54)	21 (0-56)	0.914
Catheterization, median days (min-max)	16 (0-38)	17 (1-50)	0.658

ROP: retinopathy of prematurity; ARF: acute renal failure; IVH; intraventricular hemorrhage; HMD: hyaline membrane disease; PDA: patent ductus arteriosus; TPN: total parenteral nutrition; NEC: necrotizing enterocolitis; [a]p adjusted for gestational age, birth weight and Apgar score.

Discussion

Our data showed no statistical significant differences in the primary outcomes (death and BPD) of the VLBW infants treated with nCPAP or intubation followed by mechanical ventilation when adjusted for gestational age, birth weight and APGAR score.

When we look at the adjusted OR for death in both analyzed groups we observed an increase in the OR for death in the nCPAP group but the difference is not statistically significant. These results are not similar to other studies on the role of nCPAP in the prevention of mortality and morbidity in preterm infants [14]. Despite this, the odds for BPD show that nCPAP might have a protective role in the development of BPD but these results are not statistically significant in either group. BDP is one of the major causes of morbidity and mortality in preterm infants and has been associated with genetic background, lung tissue immaturity, mechanical ventilation and oxygen exposure. In fact, despite the increase in the use of antenatal steroids and the improvement of ventilation techniques the incidence of BPD has not decreased [5, 15]. We hypothesized that these results are associated with the nature of this study. Since this is a retrospective study with the intention to treat analysis and the demographic analysis show statistical differences in the APGAR score ($p \leq 0.0001$), the intubation group may include a more fragile group of newborns, a fact that may lead to these differences. Nonetheless, when adjusted for gestational age, birth weight and APGAR score, the results show that the OR for death and BPD are non-significant. Since it is widely accepted that endotracheal intubation is associated with lung inflammation and injury [5], these results suggest that a non-invasive approach with early nCPAP should be used to avoid mechanical ventilation with endotracheal intubation without the need for more days with ventilation treatment.

Referring to the secondary outcomes, our analysis found no statistically significant differences between the nCPAP and the intubation groups, with the sole exceptions of HMD and surfactant treatment. HMD is a major cause of respiratory distress in preterm newborns and the standard treatment is the administration of exogenous surfactant [4]. In the study group that included infants from 28 to 31 weeks only, there were statistically significant differences between the prevalence of HMD and surfactant treatment in both groups (nCPAP and intubation). This difference might be explained by the nature of this retrospective study with the intention to treat analysis. This decision on what ventilator would be used was made by the attending neonatologist according to the NICU perinatal ventilatory support protocol but, nonetheless some asymmetries might exist. Another explanation for this difference might lie in the differences found with the use of preterm steroids. Prenatal steroids are known to reduce the risk of HMD and, although there is no statistically significant difference between the two groups (when adjusted for birth weight, gestational age and Apgar score), 92.9% of the infants in the nCPAP group received prenatal corticosteroids while only 69.2% in the intubation group received these. Another thing that should be considered in this study is that since the rate of HMD was higher in the mechanical ventilation with endotracheal intubation, we must consider the fact that the newborns in that group might be more prone to higher rates of morbidity than those in the nCPAP group. Although this is true, we found no other statistically significant differences between the two groups, and that shows that this difference is not a major impairment to the validity of the results.

Conclusion

Our data support the use of nCPAP in the early approach of most very low birth weight newborns as demonstrated by previous studies. In fact, when we adjusted the variables for birth weight, gestational age and Apgar score there were no statistical differences in the prevalence of death and BPD. There were no other differences in the incidence of other secondary outcomes with the exception of HMD and the need for surfactant which was more frequent in the intubation group probably because of asymmetries found in the studied populations that could not be assessed by the statistical adjustment techniques used.

We conclude that nCPAP may be a selected technique in the support of very low birth weight newborns with respiratory distress syndrome.

Declaration of interest

The Authors declare that there is no conflict of interest.

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