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E sob a Coorientação de:
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Early CPAP versus Surfactant in very low birth weight babies

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Abstract

For many years endotracheal intubation and mechanical ventilation have been the standard 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 tradition ventilation technics. 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. Afterwards, a subgroup analysis of newborns with gestational age between 28 and 31 weeks was 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

Introduction

Approach to the 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 one hand, numerous studies have shown that mechanical ventilation associated with surfactant administration lead to a reduction in many complications of premature birth (among others, it leads to a decrease in death rates and in 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 it might be associated with higher rates of bronchopulmonary dysplasia (BDP) [5,6]).

There are a great number of both observational and clinical trial studies whose data supports that early nasal continuous positive airway pressure (NCPAP) is associated with lower rates of mechanical ventilation without 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 or endotracheal intubation with mechanical ventilation.

Material and Methods

The authors performed a retrospective study comparing a strategy of early NCPAP use with 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 was recorded. The inclusion criteria were birth weight less than 1500g 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 stratified into two different subgroups, one treated with early NCPAP and another with endotracheal intubation and mechanical ventilation. After global analysis, a subgroup analysis was performed and newborns with gestational age between 28 and 31 weeks were selected since their demographic characteristics were similar. This new group was also stratified into two subgroups, one of those treated with early NCPAP and another treated with endotracheal intubation and mechanical ventilation.

The data that was collected from NICU's data base 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, eclampsia, pre-eclampsia, gemelar 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 neonatologist. 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 by Intubation-Surfactant-Extubation (INSURE) or by endotracheal intubation followed by mechanical ventilation in the newborns treated with early NCPAP and through the endotracheal tube in the newborns treated with early endotracheal intubation [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 was 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 latest for expected values less than 5. A multivariate analysis by logistic regression or multiple linear regression (categorical or continuous variables, respectively) was performed. P value less than 0.05 was considered statistically significant.

Results

From 2007 to 2012, 156 infants with less than 1500g 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. After preliminary evaluation, we found that the two defined groups had too many differences to be compared without obvious bias (there were significant statistical differences in gestational age ($p=<0.0001$), birth weight ($p=<0.0001$), Apgar score at 5th minute ($p=<0.0001$) and C-section delivery ($p=0.043$)). So, it was decided to select a more balanced group for further analysis and all newborns with less than 1500g and between 28 and 31 gestational weeks were selected. A total of 57 newborn fulfilled the inclusion criteria and 29 (50.9%) infants were treated with NCPAP and 28 (49.1%) underwent intubation and mechanical ventilation (Figure 1).

In the group of newborns between 28 and 31 gestational weeks, Apgar score at 5th min was less than 7 in 16 (57.1%) in endotracheal intubation group and higher than 8 in 26 (89.7%) in 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 comparing to intubation (table 2).

There were no significant differences in secondary outcomes in both groups, NCPAP and intubation group, excepting the prevalence of HMD which was 51.7% in the NCPAP group vs 89.3% in intubation group (p=0.033) and the need of surfactant which was 55.2% in the NCPAP group vs 89.3% in intubation group (p=0.021). The secondary outcomes are summarized in table 3.

In the early NCPAP group we found that one-third (32%) of the newborns needed endotracheal intubation at some point of their stay in the NICU.

Discussion

The prevalence of the primary outcomes (death and BPD) was higher in the intubation group in both analysis, but when adjusted for gestational age, birth weight and Apgar score (low birth weight, gestational age and Apgar score are widely known to be associated with higher rates of morbidity and mortality [13]) we found that there was no statistically significant differences. These results are similar to other studies on the role of NCPAP in the prevention of mortality and morbidity in preterm infants [14]. Despite this, the chance for death was higher in NCPAP group in both analyses (only when adjusted for gestational age, birth weight and Apgar score) and the chance for BPD was higher in intubation group in both analysis but 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 widening of antenatal steroid and the improvement of ventilation technics the incidence of BPD has not decreased [5,15]. 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 have not found any 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 only included infants from 28 to 31 weeks there was statistical 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 study. Since this was a retrospective study there was no intervention of the study coordinators in the choice of ventilation technic. This choice was entirely dependent on the neonatologist that assisted the birth and this may result in differences in the way similar newborns are treated. This difference can also be explained by differences in preterm steroid use. Prenatal steroids are known to reduce the risk of HMD and, although there is no statistical significant difference between both groups (when adjusted for birth weight, gestational age and Apgar score). 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 group, 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

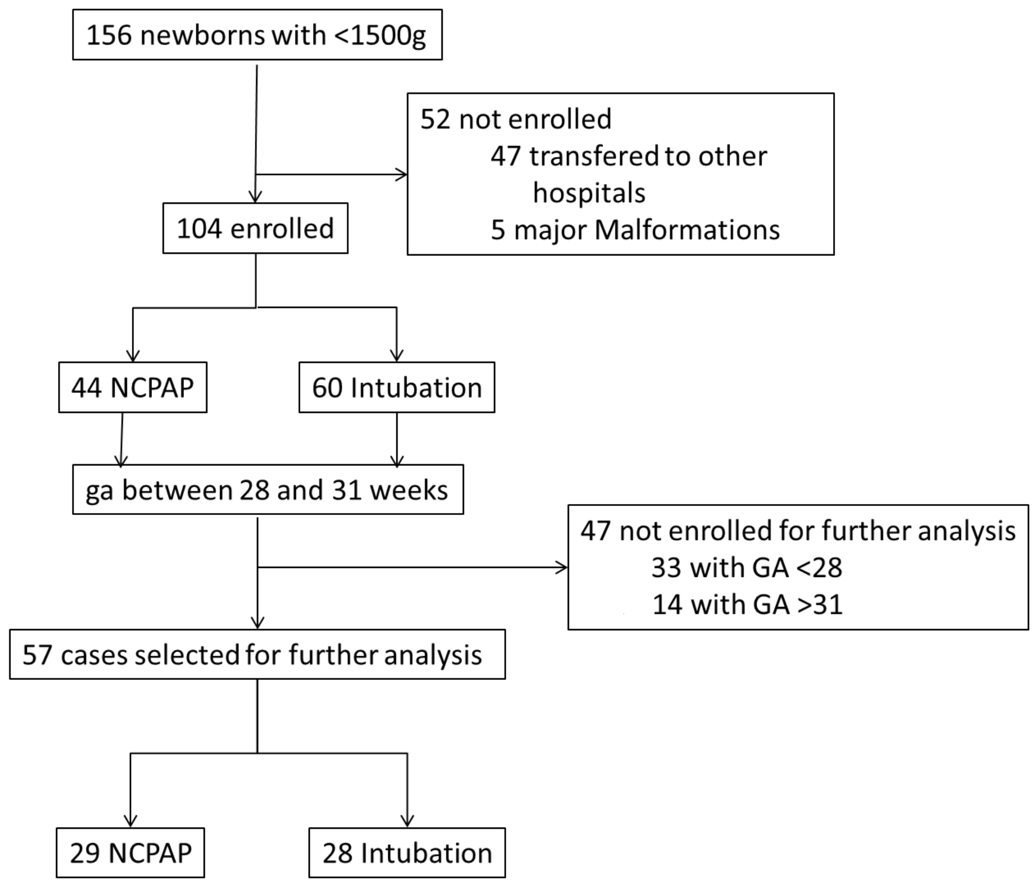
The results presented by this study supports the use of NCPAP in the early approach of most very low birth weight newborns as demonstrated by previous studies. In fact when we adjusted the variables for birth weight, gestational age and Apgar score there are no statistical differences in the prevalence of death and BPD. There were no other differences in the incidence of other predictable outcomes with the exception of HMD and the need for surfactant that was more frequent in the intubation group. Previous studies about the role of NCPAP in newborns have also shown this decrease in the incidence of these variables.

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

References

1. Flor-de-Lima F, Rocha G, Guimaraes H. Impact of changes in perinatal care on neonatal respiratory outcome and survival of preterm newborns: an overview of 15 years. Critical care research and practice. 2012;2012:643246
2. Ruegger C, Hegglin M, Adams M, Bucher HU. Population based trends in mortality, morbidity and treatment for very preterm- and very low birth weight infants over 12 years. BMC pediatrics. 2012;12:17.
3. Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? Pediatrics. 1999 May;103(5 Pt 1):961-7.
4. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane database of systematic reviews (Online). 2000 (2):CD000511
5. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001 Jun;163(7):1723-9.
6. Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr. 1989 Jul;115(1):115-20
7. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. The New England journal of medicine. 2008 Feb 14;358(7):700-8.
8. De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. Journal of paediatrics and child health. 2001 Apr;37(2):161-7.
9. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. The New England journal of medicine. 1994 Oct 20;331(16):1051-5.
10. Dunn MS, Reilly MC. Approaches to the initial respiratory management of preterm neonates. Paediatr Respir Rev. 2003 Mar;4(1):2-8.
11. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). Acta paediatrica. 2010 Jul;99(7):978-92.
12. Jobe AH, Ikegami M. Prevention of bronchopulmonary dysplasia. Current opinion in pediatrics. 2001 Apr;13(2):124-9.
13. Lee BH, Stoll BJ, McDonald SA, Higgins RD. Adverse neonatal outcomes associated with antenatal dexamethasone versus antenatal betamethasone. Pediatrics. 2006 May;117(5):1503-10
14. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. The New England journal of medicine. 2010 May 27;362(21):1970-9
15. Jobe AH. The new bronchopulmonary dysplasia. Current opinion in pediatrics. 2011 Apr;23(2):167-72.

Figure 1. Enrollment method



GA: gestational age ; NCPAP: nasal continuous positive airway pressure

Table 1. Demographic and clinical characteristics

	CPAP (n=44)	Intubation (n=60)	p	CPAP 28-31wk (n=29)	Intubation 28-31wk (n=28)	p
Gestational age (wk), mean ± SD	30.3±2	27.1±2	**<0.0001***	29.4±1	28.9±1	0.108*
Birth weight (g), median (min-max)	1140 (550-1486)	860 (360-1450)	**<0.0001**¥	1092 (550-1486)	1120 (440-1450)	`0.943¥
Male Sex, n (%)	14 (33.3)	23 (39)	0.561§	9 (33.3)	10 (37)	0.776 §
C-section, n (%)	34 (72.3)	35 (58.3)	**0.043**§	20 (69)	21 (75)	0.612§
Multiple pregnancy, n (%)	13 (29.6)	23 (38.3)	0.352§	10 (34.5)	10 (35.7)	0.922 §
Apgar score 5th min, n (%)						
0-7	3 (6.8)	38 (63.3)	**<0.0001§**	3 (10.3)	16 (57.1)	**<0.0001§**
8-10	41 (93.2)	22 (36.7)		26 (89.7)	12 (42.9)	

* Independent t test, ¥ Mann-Whitney U test, § Chi-squared test

Table 2. Death and BPD adjusted for gestational age and birth weight

Outcome	All Infants with <1500g					All infants with <1500g and 28-31 gestational weeks				
	CPAP (n=44)	Intubation (n=60)	p	OR*	P*	CPAP (n=29)	Intubation (n=28)	p	OR*	p*
Death, n (%)	2 (4.5)	20 (33.3)	**<0.001**§	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; § Chi-squared test; OR: odds ratio; *Adjusted for gestational age, birth weight and Apgar score; n.s.: non-significant

Table 3. Prenatal risk factors and major postnatal morbidity causes in newborns with 28-31 weeks

	CPAP (n=29)	**Intubation (n=28)**	**P***
Antenatal steroids, n (%)	26 (92.9)	18 (69.2)	0.071
Maternal infection, n (%)	6 (20.7)	5 (17.9)	0.901
Maternal diabetes, n (%)	0	1 (3.6)	0.998
Maternal hypertension, n (%)	1 (3.4)	1 (3.6)	0.369
Eclampsia, n (%)	0	0	-
Pre-Eclampsia, n (%)	6 (20.7)	4 (14.3)	0.627
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
Surfactant, n (%)	16 (55.2)	25 (89.3)	**0.021**
Respiratory support, 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; *p adjusted for gestational age, birth weight and Apgar score

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- **book**: Cowan CP, Cowan PA. When partners become parents: the big life change for couples. New York: Basic Books, 1992.

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