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Original article

Trends in respiratory management and morbidities of very preterm or very low birth weight infants from 2000 to 2013: results from a Portuguese tertiary level Neonatal Intensive Care Unit

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Abstract

Summary: Considerable progress has been made regarding children's morbidity and mortality. Nonetheless, recent developments have been insufficient to meet set targets. This study aims to evaluate trends and outcomes in respiratory management following a 14-year collaboration with the Vermont Oxford Network (VON).

Methods: Data were collected prospectively at a Level III NICU in the North of Portugal and submitted to the VON between 2000 and 2013. The primary outcome was bronchopulmonary dysplasia (BPD). Pneumothorax and respiratory distress syndrome were secondary outcomes.

Results: A total of 323 very low birth weight infants hospitalised in our centre met the inclusion criteria. Significant changes were observed with supplemental oxygen use and endotracheal intubation decreasing, whilst surfactant use rose. Conventional ventilation techniques at any time were used less often. No differences in the rates of BPD were observed.

Conclusion: A review of current practice has led to a more cautious approach, privileging less invasive ventilatory techniques and pondered oxygen supplementation, albeit with no significant improvement in the evaluated respiratory outcomes.

Keywords

Very low birth weight infants, VON network, respiratory morbidity, bronchopulmonary dysplasia, neonatal intensive care, respiratory outcomes.

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Introduction

Considerable progress has been made regarding children's morbidity and mortality. Nonetheless, recent developments have been insufficient to meet set targets [1-3]. Prematurity remains the single most important determinant of neonatal morbidity and mortality [4-7] and is now the second-leading cause of death in children under the age of 5, after pneumonia [2]. An estimated fifteen million children are born preterm every year, of which more than one million die due to related complications [8, 9]. In addition, almost all countries with reliable data display rising rates of preterm birth [8], making this an important public health priority.

Different degrees of prematurity are closely associated with birth weight, an important predictor of infant health. Very low birth weight (VLBW) infants, those born weighing less than 1,500 g, and very preterm (VPT) are an extremely vulnerable group. They account for about 1.5% of live births, yet they have a substantial impact on overall mortality rates, representing more than 50% of infant deaths [10]. Approximately half of these deaths occur in the first few days after delivery and those who survive continue to be at increased risk following hospital discharge. During their initial hospitalization, VLBW infants may experience major morbidities, namely chronic lung disease/bronchopulmonary dysplasia (CLD/BPD), pneumothorax and respiratory distress syndrome (RDS) [11-13]. These adverse outcomes expose infants to additional interventions, causing emotional distress for families, increasing length of stay and risk of rehospitalisation, and an overall rise in healthcare expenditure [14-16]. Moreover, the implications of being born too soon may extend beyond the neonatal period [17-21].

The availability of neonatal intensive care has had a significant impact on infant morbidity and mortality. Higher survival rates have paralleled improvements in neonatal care, such as antenatal corticosteroid therapy, postnatal surfactant administration and ventilation support [22-24]. Furthermore, referral to appropriate care centres has shown to be associated with decreased mortality in VLBW infants [25, 26].

Several international groups have developed multidisciplinary collaborations focused on improving neonatal care. The Vermont Oxford Network (VON) is an organization created in the late 1980s with the goal of improving the quality and safety of medical care for newborn infants and their families [27]. The network sustains a clinical database of VLBW and VPT infants with data submitted by several Neonatal Intensive Care Unit (NICU) groups worldwide, providing quarterly and annual reports for members to compare practices and results in the pursuit of better infant care [28, 29].

This study aims to compare changes over time in the respiratory management and respiratory morbidities among VPT and/or VLBW infants in a Portuguese tertiary level NICU following a 14-year collaboration with the VON.

Methods

Data were collected prospectively from 2000 to 2013, during our centre's subscription to the VON. A predefined protocol was used for data collection and, at submission, all data underwent automated checks for completeness [30].

As exposure variable, we categorized the year of birth into two groups (2000-2006 and 2007-2013) according to the changes performed in local guidelines of respiratory management.

Data on infants with birth weight between 401 g and 1,500 g and/or gestational age between 22 weeks 0 days and 29 weeks 6 days, born at our centre and alive at discharge from NICU, were included for analysis (**Fig. 1**).

We collected data on pregnancy characteristics (prenatal corticosteroids, multiple pregnancy and mode of delivery), infant characteristics (sex, gestational age at birth, birth weight, and Apgar score) and variables recorded during NICU stay (use of oxygen, face mask ventilation, endotracheal tube ventilation, epinephrine, surfactant, conventional ventilation, high-frequency ventilation, nasal continuous positive airway pressure [CPAP], and steroids for BPD). The primary outcome was BPD. Pneumothorax and RDS were secondary outcomes. Definitions for outcomes and other variables recorded are provided by the VON's *Manual of Operations* [30].

Sample characteristics across two time periods (2000-2006 vs. 2007-2013) are presented as counts and proportions for all categorical variables and compared using the Chi-Square or Fisher's exact test, as appropriate. We estimated crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) using logistic regression for the association between two time periods of birth and respiratory management and morbidities. Models were adjusted for sex, gestational age at birth and birth weight. The statistical analysis was performed using STATA®, version 15.1 (StataCorp LP, College Station, Texas, USA). This study was approved by the ethics committee of Centro Hospitalar Universitário de São João, Porto, Portugal.

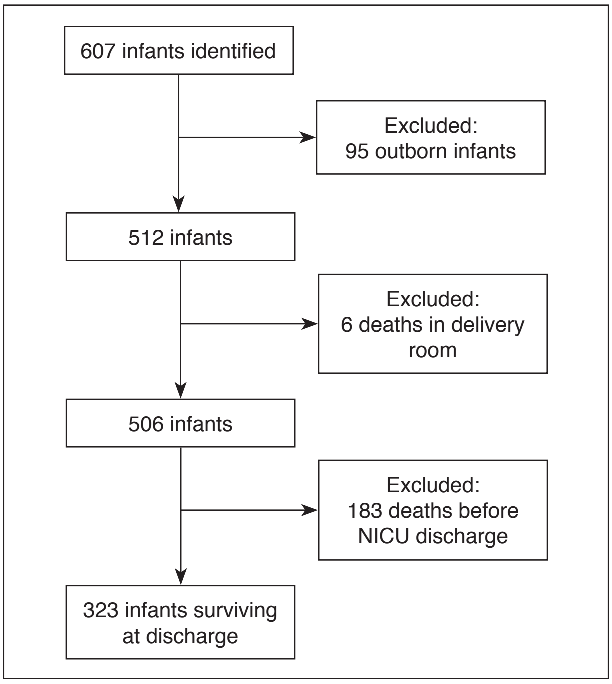

Figure 1. Flowchart for study sample definition.

Results

Tab. 1 summarises pregnancy and infant characteristics of the study population. We included 323 infants, the majority of them were males (162, 50.2%), had a gestational age between 28 and 31 weeks (163, 50.5%) and a birth weight ≥ 1,000 grams (187, 57.9%). Most infants were of single gestations (235, 73.1%), received antenatal steroids (274, 84.8%) and were delivered by caesarean section (226, 70.0%). No significant differences were observed by year of birth group for all the aforementioned variables. There was a significant worsening of Apgar score at 5 minutes ($p = 0.025$), with no significant change for Apgar score at 1 minute.

Initial resuscitation in the delivery room suffered significant changes over time. After adjustments for sex, gestational age at birth and birth weight, infants born between 2007-2013 were significantly less likely to receive oxygen (Adjusted OR = 0.37, 95% CI: 0.21-0.66) and endotracheal intubation (Adjusted OR = 0.32, 95% CI: 0.18-0.56). All infants born between 2000 and 2006 did not receive surfactant in the delivery room. No identifiable trends were noted in the use of epinephrine or facial mask vent.

Regarding respiratory support after initial resuscitation, infants born between 2007-2013 were significantly less likely to receive oxygen (Adjusted OR = 0.42, 95% CI: 0.22-0.81) and conventional ventilation (Adjusted OR = 0.51, 95% CI: 0.28-0.93) at any time during NICU stay. A trend towards higher use of surfactant at any time was observed, although not statistically significant. No identifiable trends were noted in the use of high-frequency ventilation, nasal CPAP and steroids for BPD (**Tab. 2**).

There was no significant difference in the incidence of BPD, pneumothorax and RDS between groups (**Tab. 3**). A trend towards lower odds of BPD and higher odds of pneumothorax was observed in the second time period group (OR = 0.75 [0.40-1.40] and OR = 1.97 [0.63-6.15], respectively), albeit non-significant.

Discussion

BPD is a CLD most commonly seen in preterm infants requiring mechanical ventilation and oxygen therapy. Advances in neonatal care have resulted in improved survival and decreased morbidity, but limited effect has been shown in

Table 1. Comparison of pregnancy and infant characteristics by year of birth group (2000-2006 vs. 2007-2013).

		Total (n = 323) n (%)	2000-2006 (n = 176) n (%)	2007-2013 (n = 147) n (%)	p-value
Sex of the infant	**Female**	161 (49.8)	80 (45.4)	81 (55.1)	0.084
	Male	162 (50.2)	96 (54.6)	66 (44.9)	
Gestational age (weeks)	**22-27**	92 (28.5)	54 (30.7)	38 (25.9)	0.526
	28-31	163 (50.5)	84 (47.7)	79 (53.7)	
	32-36	68 (21.0)	38 (21.6)	30 (20.4)	
Birth weight (grams)	**< 1,000**	136 (42.1)	74 (42.0)	62 (42.2)	0.981
	≥ 1,000	187 (57.9)	102 (58.0)	85 (57.8)	
Multiple gestation	**No**	236 (73.1)	133 (75.6)	103 (70.1)	0.267
	Yes	87 (26.9)	43 (24.4)	44 (29.9)	
Antenatal steroids	**No**	49 (15.2)	26 (14.8)	23 (15.6)	0.827
	Yes	274 (84.8)	150 (85.2)	124 (84.4)	
Mode of delivery	**Caesarean section**	226 (70.0)	122 (69.3)	104 (70.8)	0.780
	Vaginal	97 (30.0)	54 (30.7)	43 (29.2)	
Apgar score at 1 minute	**< 7**	161 (49.8)	89 (50.6)	73 (49.7)	0.871
	≥ 7	162 (50.2)	87 (49.4)	74 (50.3)	
Apgar score at 5 minutes	**< 7**	50 (15.5)	20 (11.4)	30 (20.4)	**0.025**
	≥ 7	273 (84.5)	156 (88.6)	117 (79.6)	

Table 2. Respiratory management by year of birth group (2000-2006 vs. 2007-2013).

		Total (n = 323) n (%)	2000-2006 (n = 176) n (%)	2007-2013 (n = 147) n (%)	p-value	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Initial resuscitation							
Oxygen	**No**	86 (26.6)	34 (19.3)	52 (35.4)	**0.001**	Reference	Reference
	Yes	237 (73.4)	142 (80.7)	95 (64.6)		**0.44 (0.26-0.72)**	**0.37 (0.21-0.66)**
Facial mask ventilation	**No**	189 (58.5)	107 (60.8)	82 (55.8)	0.362	Reference	Reference
	Yes	134 (41.5)	69 (39.2)	65 (44.2)		1.23 (0.79-1.92)	1.28 (0.80-2.02)
Endotracheal tube ventilation	**No**	137 (42.4)	59 (33.5)	78 (53.1)	**< 0.001**	Reference	Reference
	Yes	186 (57.6)	117 (66.5)	69 (46.9)		**0.45 (0.28-0.70)**	**0.32 (0.18-0.56)**
Epinephrine	**No**	314 (97.2)	172 (97.7)	141 (96.6)	0.737	Reference	Reference
	Yes	9 (2.8)	4 (2.3)	5 (3.4)		1.51 (0.40-5.74)	1.65 (0.42-6.53)
Surfactant	**No**	307 (95.0)	176 (100.0)	131 (89.1)	**< 0.001**	Reference	Reference
	Yes	16 (5.0)	0 (0.0)	16 (10.9)		-	-
Respiratory support after initial resuscitation							
Surfactant (any time)	**No**	133 (41.2)	79 (44.9)	54 (36.7)	0.138	Reference	Reference
	Yes	190 (58.8)	97 (55.1)	93 (63.3)		1.40 (0.90-2.20)	1.77 (1.03-3.04)
Oxygen (any time)	**No**	68 (21.0)	28 (15.9)	40 (27.2)	**0.013**	Reference	Reference
	Yes	255 (79.0)	148 (84.1)	107 (72.8)		**0.51 (0.29-0.87)**	**0.42 (0.22-0.81)**
Conventional ventilation (any time)	**No**	100 (31.0)	46 (26.1)	54 (36.7)	**0.040**	Reference	Reference
	Yes	223 (69.0)	130 (73.9)	93 (63.3)		**0.61 (0.38-0.98)**	**0.51 (0.28-0.93)**
High-frequency ventilation (any time)	**No**	303 (93.8)	165 (93.8)	138 (93.9)	0.962	Reference	Reference
	Yes	20 (6.2)	11 (6.2)	9 (6.1)		0.98 (0.39-2.43)	0.97 (0.38-2.52)
Nasal CPAP (any time)	**No**	90 (27.9)	49 (27.8)	41 (27.9)	0.992	Reference	Reference
	Yes	233 (72.1)	127 (72.2)	106 (72.1)		0.99 (0.61-1.62)	0.91 (0.53-1.56)
Steroids for BPD	**No**	301 (93.2)	165 (93.8)	136 (92.5)	0.661	Reference	Reference
	Yes	22 (6.8)	11 (6.2)	11 (7.5)		1.21 (0.51-2.88)	1.47 (0.58-3.72)
Oxygen on day 28	**No**	245 (75.8)	128 (72.7)	117 (79.6)	0.151	Reference	Reference
	Yes	78 (24.2)	48 (27.3)	30 (20.4)		0.68 (0.41-1.15)	0.71 (0.40-1.27)

BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; OR: Odds Ratio.
[a] Adjusted for sex, gestational age and birth weight.

Table 3. Respiratory morbidities by year of birth group (2000-2006 vs. 2007-2013).

		Total (n = 323) n (%)	2000-2006 (n = 176) n (%)	2007-2013 (n = 147) n (%)	p-value	Crude OR (95% CI)	Adjusted [a] OR (95% CI)
BPD	**No**	275 (85.1)	147 (83.5)	128 (87.1)	0.371	Reference	Reference
	Yes	48 (14.9)	29 (16.5)	19 (12.9)		0.75 (0.40-1.40)	0.78 (0.41-1.51)
Pneumothorax	**No**	310 (96.0)	171 (97.2)	139 (94.6)	0.236	Reference	Reference
	Yes	13 (4.0)	5 (2.8)	8 (5.4)		1.97 (0.63-6.15)	2.15 (0.67-6.92)
RDS	**No**	134 (41.5)	74 (42.0)	60 (40.8)	0.823	Reference	Reference
	Yes	189 (58.5)	102 (58.0)	87 (59.2)		1.05 (0.67-1.64)	1.17 (0.69-1.97)

BPD: bronchopulmonary dysplasia; OR: Odds Ratio; RDS: respiratory distress syndrome.
[a] Adjusted for sex, gestational age and birth weight.

reducing BPD [31-35]. Therapeutic options to protect the vulnerable developing lung and to treat lung injury are limited, resulting in ongoing concerns for long-term pulmonary morbidity in preterm infants [36, 37].

In this study, we compared the respiratory management and respiratory morbidities between two groups (2000-2006 and 2007-2013). Both groups were similar in prenatal and neonatal characteristics. Surprisingly, we found a significant difference between the groups' Apgar score at 5 minutes. No other differences were shown in the studied prenatal and neonatal data between the groups. In fact, in the second time period, we have significantly decreased oxygen use and intubation in the delivery room. Therefore, this worsening in the Apgar score is likely related to interrater variability. We believe the evaluation of Apgar score was certainly more accurate in recent years.

Whilst active intervention and invasive approaches have shown to play a fundamental role in the management of BPD, they can also have short- and long-term adverse effects. In this regard, conventional ventilation techniques have been giving place to non-invasive ventilation modalities, such as CPAP and non-invasive positive pressure ventilation (NIPPV) [38].

During the last 14 years, our centre has transitioned from more invasive and aggressive treatment modalities according to the most up-to-date guidelines [39]. Significant changes were observed with supplemental oxygen use and endotracheal intubation decreasing, whilst surfactant use in the delivery room rose. We have challenged the standard of initial use of 100% oxygen and reviewed our practice leading to a significant decrease in oxygen use at resuscitation on day 28 and at any time. This is in keeping with increasing evidence showing that hyperoxia due to oxygen supplementation may result in tissue and organ injury [40-42]. Recent studies [43, 44] have also reported that infants maintained at a higher $PaCO_2$ level required lower inspiratory pressures, mean airway pressure, and ventilator rates. This has implications in ventilation requirements, as Carlo et al. reported: infants randomized to permissive hypercapnia required less ventilation at 36 weeks [45].

Efforts to reduce endotracheal intubation and mechanical ventilation were put into place to promote a shift towards less invasive techniques, as per recent literature [46-49]. The use of mechanical ventilation has significantly reduced between study periods whilst CPAP showed almost no change, attesting that a more conservative and less invasive initial approach has been taken. This reflects recent RCTs showing better oxygenation, respiratory rates and CO_2 levels with bilevel CPAP [50]. Lista et al. also reported that preterm infants with RDS receiving primary support with bilevel CPAP had fewer days of respiratory support and supplemental oxygen [51].

Conventional ventilation techniques at any time were also used less often in our neonatal department.

However, there is controversy in the literature and not all studies point in the same direction. Lemyre et al. have demonstrated that moving to a less invasive respiratory management in preterm neonates improves only short-term outcomes, but has no effect in reducing BPD and mortality[35].

Despite all that is known, a recent survey of neonatal specialists showed that, although there is variability in treatment strategies of premature babies, neonatologists used early CPAP for the management of RDS, considered a $FiO_2 \geq 0.4$ and a MAP $\geq$ 10 cmH_2O as criteria for surfactant therapy, and used caffeine to prevent BPD and steroids in the management of BPD in infants who are difficult to extubate [52].

Over the years, our increasingly cautious approach to lung support, coupled with several improvements in prenatal care, has followed the best available data in the literature.

To the best of our knowledge, this is the first study in Portugal comprising the most recent and comprehensive analysis of respiratory outcomes and ventilatory practices in VLBW infants. The strength of this study relies on its prospective nature; nonetheless, it is limited by the amount of data collected as per VON protocol. Prospective and multicentre studies providing in-depth reports on ventilation modes and newer less invasive strategies are recommended.

Conclusion

A review of current practice has led to a more cautious approach, privileging less invasive ventilatory techniques and pondered oxygen supplementation, albeit with no significant improvement in the evaluated respiratory outcomes.

Declaration of interest

The Authors declare no conflict of interest.

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