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Original article

Respiratory support strategy in 499 preterm newborns with gestational age ≤ 32 weeks

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Abstract

Objectives: To evaluate the respiratory support strategy and its association with morbidity and mortality in preterm infants with Gestational Age (GA) ≤ 32 weeks, admitted between 2000 and 2008.

Methods: Chart data from newborns with GA ≤ 32 weeks admitted to a tertiary Neonatal Intensive Care Unit between 2000-2008, were reviewed retrospectively. Newborns were divided into two groups according to the year of birth: Group 1 (2000-2004) and Group 2 (2005-2008). Each group of newborns was subdivided in subgroups according to their GA: 23-28 gestational weeks and 29-32 gestational weeks. Each group was compared in terms of ventilation and surfactant strategy, morbility and mortality. The statistical analysis was carried out with SPSS 21.0.

Results: We included 499 newborns, 224 in Group 1 and 275 in Group 2. The mean GA, sex and birth weight were similar in both groups. The comparison of the two groups showed a statistically significant difference in the rate of invasive ventilation and surfactant strategy. The mortality before discharge rate was 17.4% for Group 1 and 13.5% for Group 2.

The comparison of the subgroups, revealed a statistically higher incidence of INSURE strategy and noninvasive ventilation in newborns born after 2004, with reduction of the mortality rate in newborns with GA comprised between 29-32 weeks and reduction of pneumothorax, severe chronic lung disease and intraventricular hemorrhage in newborns with GA comprised between 23-28 weeks.

Conclusion: There was a tendency towards non-invasive strategy and INSURE administration of surfactant over the years. Mortality and major morbidity decreased along with these changes in the therapeutic approach of the respiratory distress syndrome in preterm newborns.

Keywords

Prematurity, invasive ventilation, noninvasive ventilation, surfactant therapy, morbidity, mortality, INSURE strategy.

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Introduction

In the past decades great advances were made in the care of preterm newborns, leading to an increased number of survivors. These new strategies include the widespread use of antenatal corticosteroids, the introduction of surfactant therapy and new strategies of NonInvasive Ventilation (NIV), like nasal Continuous Positive Airway Pressure (nCPAP) [1] and nasal ventilation.

Contrary to expectations, new mechanical ventilation strategies like High Frequency (HFV) or Volume Target Ventilation (VTV), have not shown to reduce the incidence of Chronic Lung Disease (CLD) [2].

Invasive Ventilation (IV) has been implicated as a strong risk factor for CLD [3, 4]. Studies performed in animals have demonstrated that barotrauma and volutrauma during IV contribute to lung damage [4-6] as well as lung damage occurs after only a few breaths of IV with ventilator settings similar to those used for premature infants with Respiratory Distress Syndrome (RDS) [7]. These observations suggest that interventions that decrease the need for IV may prevent CLD.

Verder et al. [8, 9] and Reininger et al. [10] demonstrated a reduction in the need for IV in infants with established RDS of moderate severity using intratracheal surfactant as a rescue therapy for a wide range of times after birth (up to 72 hours).

In the last decade we have seen a tendency towards less aggressive strategies, which intend to prevent CLD. These strategies include optimizing the use of oxygen, using less IV and the increasing use of the INSURE strategy (INtubate – SURfactant – Extubate) if possible [11-16].

Several randomized controlled studies have demonstrated that the use of prophylactic surfactant in combination with NIV reduced the need for invasive ventilatory support, with decreased co-morbidity and mortality [16].

Our strategy evolved accordingly to these new data. The authors studied the results in terms of mortality and major morbidity, associated with that change in ventilation strategy.

Material and methods

Chart data of infants with a with Gestational Age (GA) ≤ 32 weeks admitted in the period 2000-2008 in the Neonatal Intensive Care Unit (NICU) of a tertiary referral hospital (Hospital de Santa Maria in Lisbon, Portugal) were reviewed retrospectively.

On average, about 50,000 newborns are born annually in this area with an annual rate of 1% of Very Low Birth Weight (VLBW) infants.

Between 2000 and 2008, there were 26,737 deliveries in our Hospital and a total of 727 newborns (673 inborn and 54 outborn) with a GA ≤ 32 weeks were admitted at our NICU. The small number of outborn Extremely Low Birth Weight (ELBW) newborns admitted is explained by the high rate of "in utero transport".

Antenatal steroids are routinely administered to mothers in labor before 34 weeks of gestation.

Since 2005, we have established in our Unit a protocol for surfactant administration (**Tab. 1**). The timing of surfactant administration is defined according to GA, risk of Hyaline Membrane Disease (HMD) and signs of RDS.

Preterm newborns that require resuscitation are intubated and surfactant is administered

Table 1. NICU protocol of surfactant administration and ventilatory strategy since 2005.

Gestational age	GA < 30	GA ≥ 30 < 32	GA ≥ 30 < 32	GA ≥ 32
Risk of HMD	-	**High risk***	**Low risk****	-
Surfactant strategy	Prophylactic 200 mg/kg	Prophylactic 200 mg/kg	Early treatment if RDS 200 mg/kg	Treatment if RDS 200 mg/kg
Ventilatory strategy	IV/NIV	Prophylactic NIV	Early NIV	Early NIV if RDS

*High risk of HMD: no antenatal corticosteroids, diabetic mother, twins.
**Low risk of HMD: antenatal corticosteroids, mother with hypertension, labour, prolonged membrane rupture, small for dates (SGA).

in the labor ward. According to the evolution, they are invasively ventilated or are extubated to nCPAP. Those that don't need resuscitation initiate nCPAP and receive surfactant according to the protocol.

nCPAP is started with airflow of 6-8 L/minute and a mean pressure of 4-6 cm H_2O. Pressure and FiO_2 are adjusted according to the presence of sternal and intercostal, subcostal recession or transcutaneous oxygen saturation levels, which are kept between 86% and 93%. If surfactant is indicated, the child is orally intubated, surfactant is administered as a bolus through the sideport of the endotracheal tube which is immediately removed, and nCPAP is started or continued.

Newborns on nCPAP are intubated and invasively ventilated if they met any of the following criteria: a fraction of inspired oxygen (FiO_2) greater than 0.50 required to maintain an indicated saturation of peripheral oxygen (SpO_2) at or above 88% for 1 hour; a partial pressure of arterial carbon dioxide ($PaCO_2$) greater than 65 mm Hg, documented by a single measurement of blood gases within 1 hour before intubation; or hemodynamic instability, defined as a blood pressure that was low for GA, poor perfusion, or both, requiring volume or pressure support for a period of 4 hours or more.

Extubation is attempted within 24 hours after the infant met all of the following criteria: a $PaCO_2$ below 65 mm Hg with a pH higher than 7.20, an SpO_2 above 88% with an FiO_2 below 0.50, a mean airway pressure of less than 10 cm of water, a ventilator rate of less than 20 breaths per minute, hemodynamic stability, and the absence of clinically significant patent ductus arteriosus.

NIV devices used were nCPAP and SiPAP both using brand Infant Flow®.

The ventilators used were VIP Bird gold®, VIP Bird sterling® and Sensormedics 3100®.

The surfactant used was the alpha poractant (CUROSURF®) 100-200 mg/kg/dose.

The prophylactic therapy with surfactant and INSURE strategy are made in the delivery room or in the NICU during the first hour of life.

Data were collected retrospectively from clinical charts. We excluded newborns who died in the first 24 hours of life, the outborns, and those with major malformations or serious congenital diseases.

The newborns were divided in two groups according to the year of birth: Group 1 (2000-2004) and Group 2 (2005-2008). Each of these groups was subdivided in two subgroups according to GA: 23-28 weeks and 29-32 weeks.

Each group and subgroup was characterized in terms of gender, GA, birth weight, antenatal corticosteroids, surfactant therapy, INSURE strategy, duration and mode of ventilation, mortality, and morbidity (pneumothorax, sepsis, IntraVentricular Hemorrhage [IVH], PeriVentricular Leukomalacia [PVL] and CLD).

We used the definition of Papile et al. to classify the IVH [17].

The presence of a pneumothorax was confirmed by chest-x-ray.

PVL was classified according to De Vries et al. [18].

We used the definition of Shennan [19] for the diagnosis of CLD (need for supplemental oxygen at 28 days of life) and the definition of Bancalari [20] to classify the CLD as mild, moderate or severe depending on the need of oxygen at 36 weeks post-menstrual age: mild CLD (air); moderate CLD (22-29% FiO_2); severe CLD ($FiO_2 \geq 30\%$)

Statistical analysis was performed with SPSS 21.0.

The clinical characteristics of the newborns were described by data given as mean values, SD, or rate and percentage. The analysis of association was done for qualitative variables using Fisher's exact test for 2 by 2 tables when at least one expected frequency was less than 5 and Pearson Chi-Square in the other cases. For scale variables assuming a normal distribution we used T-test for independent samples. Test results were considered statistically significant when $p < 0.05$.

Results

We included 499 from the total of 727 newborns with GA ≤ 32 weeks admitted to the NICU from 2000 to 2008.

The newborns included in the study were divided into two groups: 224 infants in Group 1 (2000-2004) and 275 infants in Group 2 (2005-2008). The mean GA, sex and birth weight were similar in the two groups (**Tab. 2**). The antenatal corticosteroids, caesarean section, twins and amnionitis rates were also similar in both groups.

57.1% of infants in Group 1 and 45.8% of infants in Group 2 underwent therapy with natural surfactant ($p < 0.05$). 17.4% of newborns included in Group 1 and 16% in Group 2 received repeated surfactant doses ($p > 0.05$) (**Tab. 3**).

Regarding ventilation strategy, 24% of infants in Group 1 and 44.4% of infants in Group 2 were only noninvasively ventilated ($p < 0.05$). INSURE strategy was performed in 13% of infants in

Table 2. Characteristics of the two groups.

Characteristics	Group 1 (N = 224)	Group 2 (N = 275)	P
Male (%)	53.3	58.2	0.288[a]
Birthweight, mean, SD (grams)	1,140 ± 350	1,184 ± 403	0.242[b]
Gestational age, mean, SD (weeks)	28.5 ± 2.4	28.6 ± 2.5	0.699[b]
Antenatal corticosteroids (%)	64.3	72.4	0.053[a]
Chorioamnionitis (%)	20.6	17.6	0.39[a]
Caesarean section (%)	73.7	70.5	0.441[a]
Twins (%)	42	34.2	0.074[a]
Early onset sepsis (%)	13.9	15.3	0.667[a]
Late onset sepsis (%)	9.5	12.8	0.240[a]

[a]Pearson Chi-Square; [b]T-test.

Table 3. Comparison of natural surfactant therapy and ventilatory strategy between Group 1 and 2.

	GA 23-28 weeks			GA 29-32 weeks			Overall GA 23-32 weeks		
	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P
Surfactant (%)	88.4	86.2	0.683[a]	43.2	27.1	0.002[a]	57.1	45.8	0.012[a]
Surfactant ≥ 2 (%)	49.3	37.9	0.155[a]	3.2	5.9	0.251[a]	17.4	16	0.674[a]
Invasive ventilation (%)	92.8	89.7	0.501[a]	51	28.7	< 0.001[a]	63.8	48	0.001[a]
INSURE (%)	1.4	12.6	< 0.001[a]	18.1	44.7	< 0.001[a]	13	45.8	0.000[a]
Noninvasive ventilation (%)	4.3	27.6	< 0.001[a]	32.9	69.4	< 0.001[a]	24	44.4	0.000[a]

[a]Pearson Chi-Square.

Group 1 and in 45.8% of infants in Group 2, and these differences were statistically significant. 63.8% of infants in Group 1 and 48% of infants in Group 2 required IV ($p < 0.05$). Of those, 14% and 12% respectively, needed rescue HFV. There was no statistically significant difference in the mean duration days of IV (**Fig. 1**). We verified a median of 4 days of IV in Group 1 (minimum 1; maximum 76) and of 3 days in Group 2 (minimum 1; maximum 115).

The mortality before discharge was 17.4% for Group 1 and 13.5% for Group 2 (not significative). Regarding the rate of major complications (**Tab. 4**), we found a clinically significant difference between the two groups of survivors in the prevalence rates of severe CLD (4.9% in Group 1 and 2.6% in Group 2) and IVH grade 4 (7.6% in Group 1 and 4.6% in Group 2). In newborns who died, Group 1 showed significant higher incidence of pneumothorax.

Tab. 5 resumes the subdivision of Group 1 and 2 according to GA (23-28 weeks; 29-32 weeks). The comparison of each group according to GA showed that there were no statistically significant differences in terms of GA, birth conditions or septic intercurrences between the respective subgroups. Newborns included in Group 2 had a significantly higher birth weight than newborns

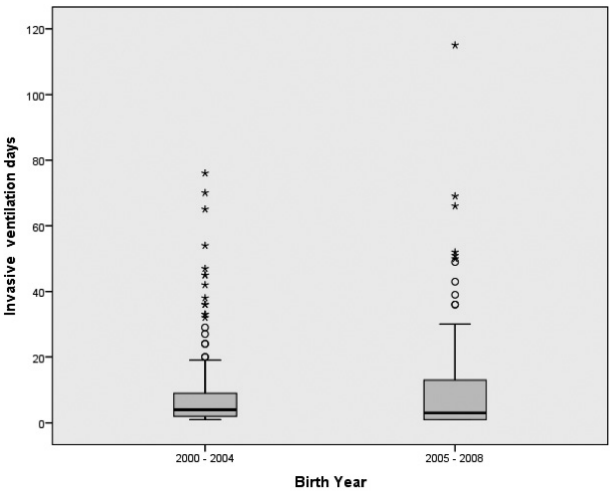

Figure 1. Duration of invasive ventilation days in the two groups.

Table 4. Comparison of major morbidity between both groups in terms of survivors and dead newborns.

	Survivors			Dead		
	Group 1	Group 2	P	Group 1	Group 2	P
Pneumothorax (%)	3.8	2.9	0.799[a]	28.2	10.8	0.057[a]
CLD (%)	24.9	26	0.143[a]	3	11.8	0.218[a]
Serious CLD (%)	4.9	2.6	0.205[a]	0	6.3	0.147[a]
Hydrocephalus (%)	2.2	1.3	0.704[b]	10.3	0	0.117[b]
PVL (%)	3.8	4.2	0.828[a]	5.1	5.7	0.911[a]
IVH grade 4 (%)	7.6	4.6	0.203[a]	59	45.9	0.256[a]

[a]Pearson Chi-Square; [b]Fisher's exact test.

Table 5. Comparison of Groups 1 and 2 according to gestational age.

	GA 23-28 weeks			GA 29-32 weeks		
	Group 1 (n = 69)	Group 2 (n = 87)	P	Group 1 (n = 155)	Group 2 (n = 188)	P
Birthweight, mean, SD (grams)	808 ± 214	789 ± 206	0.58[b]	1,289 ± 293	1,368 ± 335	0.023[b]
Gestational age, mean, SD (weeks)	25.5 ± 1.2	25.4 ± 1.2	0.691[b]	29.9 ± 1.3	30.1 ± 1.4	0.145[b]
Antenatal corticosteroids (%)	60.9	71.3	0.171[a]	65.8	72.9	0.157[a]
Chorioamnionitis (%)	35.3	35.6	0.965[a]	14.2	8.6	0.106[a]
Caesarean sections (%)	65.2	63.2	0.796[a]	77.4	73.9	0.455[a]
Twins (%)	39.1	36.8	0.764[a]	43.2	33	0.051[a]
Early onset sepsis (%)	13.2	24.1	0.088[a]	14.2	11.2	0.4[a]
Late onset sepsis (%)	19.4	28.2	0.208[a]	5.2	5.9	0.781[a]

[a]Pearson Chi-Square; [b]T-test.

included in Group 1. The comparison of natural surfactant therapy and of the ventilatory strategy between the subgroups is shown in **Tab. 3**.

In newborns with GA comprised between 29-32 weeks the mortality before discharge was significantly lower in Group 2 (**Tab. 6**).

In survivors with GA between 23-28 weeks there was a clinically significant higher prevalence of pneumothorax, serious CLD and IVH grade 4 in Group 1 (**Tab. 6**).

Discussion

We have chosen the year 2004 as the cut off between the two groups because in that year we started a new protocol of ventilation and surfactant strategies in the NICU.

The two groups analyzed were comparable in terms of gender, birth weight, GA, caesarean section, amnionitis, antenatal corticosteroids and septic episodes.

Along the nine years, there has been a progressive increase in NIV strategy over IV. More newborns were treated with INSURE strategy, and less newborns have needed surfactant therapy. These data confirm that there was a significant change in the therapeutic strategy after 2004. The increased utilization of the INSURE strategy, combined with the more widespread utilization of nCPAP, may have contributed to reduce the utilization of therapeutic surfactant.

There has also been a trend towards reduction in both mortality and major morbidity rates, which were already very low. Pneumothorax had significant different rates between the newborns who survived and the ones who died. The comparison between the 2 groups of newborns who died revealed a much lower rate of pneumothorax in newborns of Group 2. This fact leads us to consider that pneumothorax may have been a cause of death of newborns included in Group 1, reduced in Group 2 with the alteration of the ventilatory strategy. Carlo Dani et al. [21] also concluded that the INSURE strategy reduces pneumothorax.

The division of the newborns according to GA showed that there were significant changes

Table 6. Mortality and major morbidity in survivors according to gestational age.

	GA 23-28 weeks			GA 29-32 weeks		
	Group 1	Group 2	P	Group 1	Group 2	P
Mortality (%)	36.2	34.5	0.82[a]	9	3.7	0.041[a]
Pneumothorax (%)	9.1	1.8	0.092[a]	2.2	3.3	0.542[a]
CLD (%)	31.5	46	0.262[a]	61.4	71.9	0.544[a]
Serious CLD (%)	13.6	10.5	0.085[b]	2.1	0	0.759[b]
Hydrocephalus (%)	6.8	3.5	0.651[b]	0.7	0.6	1[b]
PVL (%)	9.1	12.3	0.752[b]	2.1	1.7	1[b]
IVH grade 4 (%)	25	7	0.022[a]	2.1	3.9	0.372[a]

[a]Pearson Chi-Square; [b]Fisher's exact test.

in both subgroups (GA > 28 weeks and GA ≤ 28 weeks, respectively), with more newborns being noninvasively ventilated and treated with INSURE strategy over the years. With these changes there was a reduction in mortality rate of the newborns included in subgroup with GA > 28 weeks, and reduction in major morbidity of newborns with GA ≤ 28 weeks.

These results are according to literature [11-16]. Stevens et al. [22] also confirmed these data, concluding that infants with RDS treated with early surfactant replacement therapy and nCPAP are less likely to need mechanical ventilation, less likely to develop severe CLD than are infants treated with nCPAP and later surfactant therapy.

The SUPPORT study group [23, 24] concluded that a less aggressive ventilatory strategy does not increase the mortality rate in premature newborns with GA < 28 weeks, what is concordant with our results.

A significant limitation of this study is that it was a retrospective study of a single center, with a small number of newborns distributed in each subgroup, what sometimes led to clinically significant, but not statistically significant differences between each subgroup. There might have been differences in the treatment of these newborns, such as fluid intake, nutritional support or strategy within IV that could interfere with the results. The length of hospitalization and the cause of death were not evaluated.

The prevalence of Retinopathy Of Prematurity (ROP), a prevalent sequel of prematurity, was not evaluated because before 2004 its screening was not systematic in the NICU.

Nevertheless it seems reasonable to admit that the use of INSURE strategy, with very early surfactant administration combined with initial NIV, contributed as major determinants for the reduction of morbidity and mortality over the years.

Conclusions

Given the statistically significant differences found in both groups, this study points to the benefits of a less aggressive ventilatory strategy and prophylactic surfactant replacement. These can have contributed to the decrease in the mortality and serious complications like pneumothorax, severe CPD and IVH grade 4.

The utilization of surfactant accordingly to the NICU protocol followed by early management that decreases barotrauma and oxidant injury improved preterm outcomes.

Index of acronyms and abbreviations

CLD: Chronic Lung Disease
ELBW: Extremely Low Birth Weight
GA: Gestational Age
HFV: High Frequency Ventilation
HMD: Hyaline Membrane Disease
INSURE: INtubate – SURfactant – Extubate
IV: Invasive Ventilation
IVH: IntraVentricular Hemorrhage
NICU: Neonatal Intensive Care Unit
NIV: NonInvasive Ventilation
PVL: Periventricular Leukomalacia
RDS: Respiratory Distress Syndrome
ROP: Retinopathy Of Prematurity
SGA: Small for Gestational Age
VTV: Volume Target Ventilation
VLBW: Very Low Birth Weight

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Declaration of interest

The Authors declare that there is no conflict of interest.

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