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Predictors of extubation failure and reintubation in newborn infants subjected to mechanical ventilation

Fatores preditivos para falha de extubação e reintubação de recém-nascidos submetidos à ventilação pulmonar mecânica

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ABSTRACT

Objective: To identify risk factors for extubation failure and reintubation in newborn infants subjected to mechanical ventilation and to establish whether ventilation parameters and blood gas analysis behave as predictors of those outcomes.

Methods: Prospective study conducted at a neonatal intensive care unit from May to November 2011. A total of 176 infants of both genders subjected to mechanical ventilation were assessed after extubation. Extubation failure was defined as the need to resume mechanical ventilation within less than 72 hours. Reintubation was defined as the need to reintubate the infants any time after the first 72 hours.

Results: Based on the univariate analysis, the variables gestational age <28 weeks, birth weight <1,000g and low Apgar scores were associated with extubation failure and reintubation. Based on the multivariate analysis, the variables length of mechanical ventilation (days), potential of hydrogen (pH) and partial pressure of oxygen (pO_2) remained associated with extubation failure, and the five-minute Apgar score and age at extubation were associated with reintubation.

Conclusion: Low five-minute Apgar scores, age at extubation, length of mechanical ventilation, acid-base disorders and hyperoxia exhibited associations with the investigated outcomes of extubation failure and reintubation.

Keywords: Infant, newborn; Infant; premature; Respiration, artificial; Intubation, intratracheal/adverse effects; Ventilator weaning/adverse effects; Treatment failure

INTRODUCTION

Mechanical ventilation (MV) is a life support procedure that contributes to increasing the survival of premature and full-term infants and is one of the therapeutic resources most widely used in neonatal intensive care units (NICU).[1,2]

Despite its crucial role in reducing the mortality rate, MV is associated with morbidity, risks and complications, prominently including bronchopulmonary dysplasia and periventricular hemorrhage.[3,4]

To minimize such risks and complications, it is recommended to discontinue MV as soon as infants are able to maintain spontaneous breathing and achieve appropriate gas exchange with minimal respiratory effort.[2]

The ideal time for weaning from MV is frequently established based on clinical and laboratory parameters assessed at the time extubation is proposed for consideration. However, such parameters are not very objective, which makes MV discontinuation in NICUs a trial-and-error approach.[2,5]

Based on the damage associated with the inappropriate duration of MV in newborn infants, there is a clear need to establish objective criteria for extubation,

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which would help to avoid undesirable outcomes, such as extubation failure[3,5,6] and reintubation, which bear direct associations with morbidity and mortality.[7,8]

For these reasons, the aims of this study were to identify risk factors for extubation failure and the need for reintubation in newborn infants and to establish whether ventilation parameters and blood gas analysis behave as predictors of extubation failure and the need for reintubation.

METHODS

This work was a prospective study based on the collection of data regarding newborn infants admitted to the NICU of *Hospital Sofia Feldman* (HSF) from May 1, 2011 to November 1, 2011 who were subjected to MV and extubation. The study was approved by the Research Ethics Committee of HSF under opinion CAAE 0014.0.439.308.11 (Certificate of Presentation for Ethical Appraisal/*Certificado de Apresentação para Apreciação Ética - CAAE*), with waivers of informed consent. Newborn infants of both genders born at HSF and subjected to MV and extubation during the data collection period were included in the study, whereas infants referred from other institutions and infants with heart and lung malformations were excluded.

Mechanical ventilation was performed using Inter 3 and Inter 5 (Intermed brand) ventilators. The infants' gestational age (GA) was established by means of ultrasound or calculated based on the date of the mother's last menstrual period (LMP). The infants' weight at birth (BW) was measured using the Filizola BP Baby scale.

Assessment included the occurrence of extubation failure in addition to clinical and treatment-related variables. Extubation was considered successful when the infants were able to remain without invasive ventilatory support for 72 hours; extubation failure was defined as the need for reintubation for any reason within 72 hours after extubation, while reintubation occurred when the infants needed to be reintubated any time after 72 hours without MV. Accidental extubation followed by immediate reintubation and the use of noninvasive ventilatory support were not considered as extubation failure. The time for extubation was determined by the medical staff based on, at minimum, the presence of clinical and hemodynamic stability, regular respiratory drive and the behavioral status of reactivity.

The data were recorded using an HSF standard form by two healthcare professionals. The variables analyzed included the following: date of birth, GA, chronological age, BW, one- and five-minute Apgar scores, gender, antenatal corticosteroids, postnatal corticosteroids, exogenous surfactant, postnatal xanthines, date of extubation, length of MV (days), orotracheal tube (OT) brand, last blood gas test before extubation, ventilation parameters at the time of extubation, extubation failure and reintubation. The samples for blood gas analysis were collected one hour after endotracheal aspiration by arterial puncture and a heparinized syringe. The samples were immediately analyzed using a model Abl5 radiometer (Radiometer Copenhagen).

The data were entered into tables and analyzed using the software Statistical Package for the Social Sciences (SPSS). To achieve 95% reliability with a margin of error of ±7.5%, the sample should comprise at least 161 infants subjected to MV.

Descriptive analysis was performed to identify the main treatment-related characteristics of the participants. The association of the participants and treatment-related variables with extubation failure and reintubation was investigated using a bivariate logistic regression model. Multiple logistic regression was used to assess the multiple relationships between extubation success and failure, need for reintubation or not and the participants' characteristics. The variables included in the multiple logistic regression analysis were the ones that exhibited minimal relationships with the investigated outcome, whose significance level was set to 0.25.

In addition to the logistic regression mode, regression analysis stratified by confounding factors was performed to assess the direct relationship between exposure to MV and outcome (extubation failure/reintubation) in addition to the causal relationship between exposure and outcome.

Based on the logistic regression model, the strength of the association between the participants' characteristics that exerted significant impact on the outcomes was assessed by calculating odds ratios (OR) and corresponding 95% confidence intervals (95%CI). Those data were used to analyze and interpret the final model, for which purpose differences and associations were considered significant when the p-value was ≤0.05.

RESULTS

A total of 433 infants were admitted to the HSF-NICU during the study period. Among them, 224 were subjected to MV, of whom 176 were eligible for this study. The exclusions corresponded to 34 infants who died, 5 who were transferred from another institution and 9 who had not been extubated by the end of the data collection period.

Regarding the risk factors for extubation failure, univariate analysis showed that the infants with lower one-minute Apgar scores exhibited higher odds of failure (p=0.049). The same was true for the infants with lower five-minute Apgar scores (p=0.006). The infants with lower chronological age and shorter length of MV at the time of extubation exhibited a greater propensity for extubation failure.

The bicarbonate concentration exhibited a significant association with increased frequency of extubation failure (p=0.054). The same tendency was exhibited by *base excess* (BE) and potential of hydrogen (pH), as the lower their values, the higher the odds of extubation failure (p=0.020 and p=0.019, respectively). With regard to the ventilation parameters, the higher the mean airway pressure (MAP) was, the higher the odds of extubation failure (p=0.063). These data are shown in table 1.

Table 1 - Demographic and treatment-related characteristics of the study population as predictors of extubation failure, controlled for gestational age and birth weight

Variable	Failure		p value
	Yes N (%)	No N (%)	
Gestational age			0.017
≤28 weeks	3 (12.5)	5 (3.4)	
>28 to ≤32 weeks	8 (33.3)	35 (23.5)	
>32 to ≤36 weeks	3 (12.5)	47 (31.5)	
>36 weeks	10 (41.7)	62 (41.6)	
Weight			0.005
≤1,000g	12 (48.0)	27 (18.0)	
1,000g to ≤1,500g	2 (8.0)	43 (28.7)	
>1,500g to ≤2,000g	3 (12.0)	20 (13.3)	
>2,000g to ≤2,500g	1 (4.0)	21 (14.0)	
>2,500g	7 (28.0)	39 (26.0)	
Female gender	15 (60.0)	74 (49.0)	0.631
Antenatal corticosteroids	11 (57.9)	69 (53.9)	0.475
Surfactant	16 (64.0)	86 (57.0)	0.619
Postnatal corticosteroids	23 (92.0)	144 (95.4)	0.227
Xanthines	9 (36.0)	64 (42.4)	0.551
1-minute Apgar	5.1 (2.9)	6.3 (2.4)	
5-minute Apgar	7.1 (2.7)	8.2 (1.6)	0.006
MV length (days)	5.0 (5.3)	6.1 (7.8)	0.051
OT brand	8.3 (1.4)	8.5 (1.1)	0.346
Age at extubation	6.3 (7.3)	8.0 (9.2)	0.023
FiO_2	26.6 (6.4)	26.1 (8.9)	0.624
PIP	14.8 (0.4)	14.7 (0.7)	0.592
PEEP	4.8 (0.4)	4.7 (0.5)	0.910
TI	0.3 (0.04)	0.3 (0.03)	0.941
RR	28.2 (5.2)	27.5 (5.1)	0.607
MAP	7.4 (0.8)	7.0 (1.0)	0.063
Flow	6.8 (0.8)	6.9 (0.8)	0.661
pH	7.36 (0.08)	7.42 (0.09)	0.019
$PaCO_2$	32.0 (10.1)	31.7 (10.7)	0.987
PO_2	100.4 (76.1)	81.9 (39.5)	0.099
StO_2	90.6 (7.2)	90.2 (10.6)	0.559
Bicarbonate	17.8 (3.3)	19.9 (5.1)	0.054
BE	-5.1 (5.4)	-2.0 (5.4)	0.020

MV - mechanical ventilation; OT - orotracheal tube; FiO_2 - fraction of inspired oxygen; PIP - peak inspiratory pressure; PEEP - positive end-expiratory pressure; TI - inspiration time; RR - respiratory rate; MAP - mean airway pressure; pH - potential of hydrogen; $PaCO_2$ - partial pressure of carbon dioxide; PO_2 - partial pressure of oxygen; StO_2 - oxygen saturation; BE - *base excess*.

The independent variables associated with increased risk of extubation failure identified through multivariate analysis were as follows: pH (p=0.016), PO_2 (p=0.024) and length of MV (p=0.021) (Table 2). In this regard, the higher the pH, the lower the risk of failure, the latter being 99.9% lower for each increase by one pH unit. The same relationship was found for the length of MV, as the risk of failure decreased 16% per day of MV use. An increase of one PO_2 unit was found to increase the risk of failure by 1.2%.

Table 2 - Risk factors for extubation failure, controlled for gestational age and birth weight

Independent variable	Categories	OR	95%CI OR	p value
Constant	-	-	-	0.015
MV length (days)	-	0.843	0.728-0.975	0.021
pH	-	0.001	0.001-0.220	0.016
PO_2	-	1.012	1.002-1.023	0.024

OR - *odds ratio*; 95%CI - 95% confidence interval; MV - mechanical ventilation; pH - potential of hydrogen; PO_2 - partial pressure of oxygen.

With regard to the risk factors for reintubation, GA (p<0.001) and BW (p=0.003) exhibited significant associations with reintubation according to univariate analysis. Table 3 describes the results regarding the impact of clinical and treatment-related characteristics on reintubation. The infants with the lowest values of OT fixation tended to exhibit greater odds of reintubation (p=0.007), as was also the case for the infants with the lowest one- and five-minute Apgar scores (±7.5). However, the one-minute Apgar score was not retained in the model following multivariate analysis. Shorter inspiration time (IT), lower flow and lower PO_2 were most frequently found among the infants who required reintubation (p=0.019). The bicarbonate concentration was higher among the infants who required reintubation (p=0.024).

According to the multivariate analysis, the risk of reintubation was independently and significantly associated with the five-minute Apgar score (p≤0.001) and age at extubation (p≤0.001) (Table 4). The risk of reintubation increased by 37% with each decrease by one unit in the five-minute Apgar score, while it increased 13% with each increase of one unit in the age at extubation.

Table 3 - Demographic and treatment-related characteristics of the study population as predictors of reintubation, controlled for gestational age and birth weight

Variable	Reintubation No N (%)	Reintubation Yes N (%)	p value
Gestational age			<0.001
≤28 weeks	8 (4.6)	11 (17.7)	
>28 to ≤32 weeks	43 (24.9)	28 (45.2)	
>32 to ≤36 weeks	50 (28.9)	10 (16.1)	
>36 weeks	72 (41.6)	13 (21.0)	
Weight			0.003
≤1,000g	39 (22.3)	34 (52.3)	
>1,000g a ≤1,500g	45 (25.7)	14 (21.5)	
>1,500g a ≤2,000g	23 (13.1)	4 (6.2)	
>2,000g a ≤2,500g	22 (12.6)	1 (1.5)	
>2,500g	46 (26.3)	12 (18.5)	
Female gender	89 (50.6)	43 (66.2)	0.186
Antenatal corticosteroids	67 (45.6)	13 (27.1)	0.319
Surfactant	74 (42.0)	15 (23.1)	0.547
Postnatal corticosteroids	167 (94.9)	55 (86.4)	0.138
Xanthines	73 (41.5)	16 (24.6)	0.683
1-minute Apgar	6.1 (2.5)	5.4 (2.7)	
5-minute Apgar	8.0 (1.9)	7.5 (2.3)	0.001
MV length (days)	6.0 (7.5)	7.9 (7.8)	0.458
OT brand	8.5 (1.2)	8.1 (1.2)	0.007
Age at extubation	7.8 (9.0)	26.7 (17.8)	<0.001
FiO_2	26.2 (8.6)	28.9 (9.8)	0.405
PIP	14.7 (0.6)	14.8 (0.7)	0.384
PEEP	4.8 (0.5)	4.8 (0.6)	0.460
TI	0.34 (0.03)	0.33 (0.02)	<0.001
RR	27.6 (5.1)	28.7 (5.2)	0.166
MAP	7.0 (1.0)	7.0 (1.2)	0.869
Flow	6.96 (0.83)	6.85 (0.77)	0.009
PH	7.42 (0.09)	7.40 (0.06)	0.637
$PaCO_2$	31.7 (10.6)	35.2 (9.9)	0.072
PO_2	84.4 (46.1)	67.8 (33.0)	0.019
StO_2	90.2 (10.2)	87.6 (10.0)	0.374
Bicarbonate	19.6 (5.0)	21.4 (5.2)	0.024
BE	-2.4 (5.5)	-1.7 (4.8)	0.590

MV - mechanical ventilation; OT - orotracheal tube; FiO_2 - fraction of inspired oxygen; PIP - peak inspiratory pressure; PEEP - positive end-expiratory pressure; TI - inspiration time; RR - respiratory rate; MAP - mean airway pressure; pH - potential of hydrogen; $PaCO_2$ - partial pressure of carbon dioxide; PO_2 - partial pressure of oxygen; StO_2 - oxygen saturation; BE - *base excess*.

Table 4 - Risk factors for reintubation, controlled for gestational age and birth weight

Independent variable	Categories	OR	95%CI OR	p value
Constant	-	-	-	0.631
5-minute Apgar	-	0.632	0.490-0.815	<0.001
Age at extubation	-	1.137	1.088-1.189	<0.001

OR - *odds ratio*; 95%CI - 95% confidence interval.

DISCUSSION

This study analyzed risk factors that behave as predictors of extubation failure and reintubation, as determining the ideal time to perform extubation in newborn infants is quite difficult and a subject of controversy, where clinical judgment is required to balance the benefits of extubation with the damaging effects of reintubation.[2,6]

The results of this study show that the greater the chronological age, the greater the likelihood of reintubation as a function of the risk of complications, such as bronchopulmonary dysplasia,[4] hospital-acquired infection, airway injury and longer hospital stay.[3,8] Shorter MV length and older chronological age increased the odds of extubation failure. According to Kurachek et al.,[8] both shorter MV length and extubation failure are related to a lack of resolution of the underlying problem that required intubation. For Hermeto et al.,[9] in turn, prematurity is one of the causes of extubation failure, as a function of the immaturity of the muscle and lung systems. Danan et al.[10] hypothesized that in extubated premature infants who are subjected to MV for a shorter time, there is not enough time for maturation of the respiratory system function and alveolar stabilization.

The lowest one- and five-minute Apgar scores exhibited a positive association with extubation failure and the need for reintubation, whereas only the five-minute Apgar score remained associated with the need for reintubation based on multivariate analysis. Similar results were reported by Hermeto et al.,[11] who found that the infants with extubation success exhibited higher scores compared to the cases with extubation failure.

Low pH, BE and bicarbonate are indicators of metabolic acidosis, leading to changes in the cell metabolism, and all three exhibited association with extubation failure. Metabolic acidosis might account for low or normal $PaCO_2$ levels, as a reduction in $PaCO_2$ is a response to metabolic acidosis.[12] High bicarbonate levels were associated with the risk of reintubation; such an increase might be a post-hypercapnic effect because while the $PaCO_2$ might be corrected by adjusting the ventilation parameters, the renal response requires a longer time, and thus, the bicarbonate level remains initially high.[13]

Hyperoxia, i.e., the condition de fined by PO_2>80 mmHg, causes oxidative stress, inflammation and bronchopulmonary dysplasia in premature infants due to the deficiency of the antioxidative system,[14] which depends on maturation and nutritional factors,[10] and thus accounts for the association of hyperoxia with extubation failure.

Although variable GA did not show significant association based on multivariate analysis, it has been described as a risk factor for extubation failure and the need for reintubation, exhibiting an inverse correlation with those outcomes, as the study by Fávero et al.[1] showed. That fact might be related to the anatomical and physiological immaturity of the respiratory system,[15] leading to greater chest and upper airway instability that hinder successful extubation.[11] Similarly, although in contrast to the results of the multivariate analysis in the present study, infants with BW<1,000 g exhibit high morbidity rates, which increase their energy expenditure and nutritional requirements, thus impairing the respiratory function, which is nutrition dependent.[16]

The postnatal use of corticosteroids or xanthines did not exhibit a significant association with extubation failure and the need for reintubation. Other studies found that postnatal corticosteroids improve lung function and reduce the incidence of chronic pulmonary disease in newborns.[17] Similarly, other studies have indicated the effectiveness of xanthines in the prevention of prematurity-related apnea and the reduction of extubation failure through the stimulation of the central nervous system.[18,19]

Some of the limitations of this study derive from the fact that it was conducted at a single center and had an observational nature, and thus, it does not allow for any causal inference but only for the identification of significant associations. Furthermore, the investigator who performed the data collection was not blinded to the infants' outcomes. In addition, the minimum period of time between sample collection for blood gas analysis and extubation was not standardized, which is relevant, as although the samples were collected when the infants were clinically stable, factors such as crying, irritability and instability caused by pain might have interfered with the results. Finally, only survivors were analyzed, which is an intrinsic limitation of the object under study but might also be a source of bias.

CONCLUSION

The variables five-minute Apgar score, MV length, acid-base disorders and hyperoxia exhibited association with the investigated outcomes of extubation failure and reintubation. These data might contribute to decision-making regarding favorable time and conditions for extubation success and non-reintubation in newborn infants.

RESUMO

Objetivo: Identificar os fatores de risco para falha de extubação e reintubação em recém-nascidos submetidos à ventilação pulmonar mecânica, e determinar se parâmetros ventilatórios e dados gasométricos são fatores preditores desses eventos.

Métodos: Estudo prospectivo, realizado no período entre maio a novembro de 2011, em uma unidade de terapia intensiva neonatal. Foram avaliados 176 recém-nascidos de ambos os gêneros, submetidos à ventilação pulmonar mecânica posterior à extubação. Considerou-se falha na extubação se o retorno à ventilação pulmonar mecânica ocorresse antes de 72 horas. A reintubação ocorreu quando, em algum momento após as 72 horas, os recém-nascidos necessitassem de ser reintubados.

Resultados: Na análise univariada, idade gestacional <28 semanas, peso <1.000g e valores baixos de Apgar estiveram associados a falha de extubação e a reintubação. Já na análise multivariada, as variáveis que se mantiveram associadas à falha na extubação foram dias de ventilação mecânica, potencial hidrogeniônico e pressão parcial de oxigênio, e, para a reintubação, foram Apagar no 5º minuto e idade na extubação.

Conclusão: Menores Apgar no 5º minuto, idade na extubação e tempo de ventilação mecânica, além da presença de distúrbios ácido-base e hiperóxia foram variáveis que apresentaram relação com os eventos analisados.

Descritores: Recém-nascido; Prematuro; Respiração artificial; Intubação intratraqueal/efeitos adversos; Desmame do respirador/efeitos adversos; Falha de tratamento

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