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

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 (pO₂) 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).

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

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.

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.

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,
which would help to avoid undesirable outcomes, such as extubation failure\(^{2,3,5,6}\) 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 xanthises, 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     | No      |
|                       | N (%)   | N (%)   |
| Gestational age       |         |         |
| ≤28 weeks             | 3 (12.5)| 5 (3.4) |
| >28 to ≤32 weeks      | 8 (33.3)| 35 (23.5)| 0.017
| >32 to ≤36 weeks      | 3 (12.5)| 47 (31.5)|
| >36 weeks             | 10 (41.7)| 62 (41.6)|
| Weight                |         |         |
| ≤1,000 g              | 12 (48.0)| 27 (18.0)|
| 1,000 g to ≤1,500 g   | 2 (8.0) | 43 (28.7)|
| >1,500 g to ≤2,000 g  | 3 (12.0)| 20 (13.3)|
| >2,000 g to ≤2,500 g  | 1 (4.0) | 21 (14.0)|
| >2,500 g              | 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) | 0.006
| 5-minute Apgar        | 7.1 (2.7) | 8.2 (1.6) | 0.001
| 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
| FiO₂                  | 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) | 0.083
| Flow                  | 6.8 (0.8) | 6.9 (0.8) | 0.661
| pH                    | 7.36 (0.08) | 7.42 (0.09) | 0.019
| PaCO₂                 | 32.0 (10.1) | 31.7 (10.7) | 0.987
| PO₂                   | 100.4 (76.1) | 81.9 (39.5) | 0.099
| SO₂                   | 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; FiO₂ - 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; PaCO₂ - partial pressure of carbon dioxide; PO₂ - partial pressure of oxygen; SO₂ - 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), PO₂ (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 PO₂ 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   |
| PO₂                  | -          | 1.012 | 1.002-1.023 | 0.024   |

OR - odds ratio; 95%CI - 95% confidence interval; MV - mechanical ventilation; pH - potential of hydrogen; PO₂ - 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 PO₂ 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                        | No Reintubation | Yes Reintubation | p value |
|---------------------------------|-----------------|------------------|---------|
| Gestational age                 |                 |                  |         |
| ≤28 weeks                       | 8 (4.6)         | 11 (17.7)        | <0.001  |
| >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                          |                 |                  |         |
| ≤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 (21.1)        | 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  |
| FiO₂                            | 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   |
| PaCO₂                           | 31.7 (10.6)     | 35.2 (9.9)       | 0.072   |
| P O₂                            | 84.4 (46.1)     | 67.8 (33.0)      | 0.019   |
| S O₂                            | 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; FiO₂ - 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; PaCO₂ - partial pressure of carbon dioxide; PO₂ - partial pressure of oxygen; S O₂ - 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 exhaled 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.,\(^1\) 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 PaCO₂ levels, as a reduction in PaCO₂ 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 PaCO₂ 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 defined by PO₂ >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,\(^16\) 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.
REVISTAS

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 preatorres 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 Apagar no 5º minuto, idade na extubação e tempo de ventilação mecânica, além da presença de distúrbios ácido-base e hiperoxia 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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