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Original Article

Analysis of predictive parameters for extubation in very low birth weight preterm infants

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Key Words
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Mechanical ventilation;
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Background: Mechanical ventilation is the primary treatment for preterm infants with respiratory failure. Prolonged intubation may lead to complications; thus, early extubation is desirable. No standard criteria exist for determining the appropriateness of extubating very-low-birth-weight (VLBW) infants. This study explored the predictors of successful extubation in preterm VLBW infants.
Methods: This retrospective cohort study included 60 preterm VLBW infants who underwent their first extubation in the neonatal intensive care unit in a regional hospital in Hsinchu, Taiwan, between January 2017 and November 2020. Successful extubation was defined as having no requirement of reintubation within 3 days of extubation. Potentially predictive variables, including demographics, prenatal characteristics, and ventilator parameters were compared between a successful extubation group and failed extubation group.
Results: Of the 60 infants, 47 (78.33%) underwent successful extubation. The successful extubation group had higher Apgar scores at 1 (7 vs. 6, $P = 0.02$) and 5 min (9 vs. 7, $P = 0.007$) than those of the failed extubation group. Ventilator inspiratory pressure and mean airway pressure were significantly lower at 24, 16, 8, and 1 h before extubation and upon its completion in the successful extubation group. The areas under a number of the receiver operating characteristic curve curves in this study were moderate, specifically, 0.72, 0.74, and 0.69. Statistical analysis revealed an association between ventilator parameters before 1 h extubation (IP > 17.5cmH_2O, MAP >7.5 cmH_2O, RSS >1.82) and extubation failure (odds ratio 1.73, 2.27, 2.46 and 95% confidence interval:1.16–2.6, 1.26–4.08, 1.06–5.68, respectively).

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Conclusion: Higher Apgar scores at birth, lower ventilator inspiratory pressure, and mean airway pressure 24, 16, 8, and 1 h and 1 h RSS prior to extubation are associated with successful extubation in VLBW preterm infants.

1. Introduction

In the neonatal intensive care unit (NICU), most very-low-birth-weight (VLBM) preterms require mechanical ventilator support because of the immature function and structure of the lung. Mechanical ventilators have been used for supporting respiratory failure and increasing the survival of VLBW preterms since the 1960s. The ventilators support the respiratory system of preterm infants, who have a weak respiratory pump and poor central respiratory drive. However, the mechanical ventilator is associated with potential complications such as sepsis, atelectasis, ventilator-associated pneumonia, ventilator-induced lung injury, and ventilator-induced diaphragm dysfunction in premature infants.[1–3] Therefore, it is important to extubate and remove the ventilators in VLBW preterm infants as early as possible. The best time for elective extubation is crucial and challenging in VLBW preterm infants. Extubation failure and endotracheal tube reintubation of VLBW infants are common in the NICU. Approximately 30%–40% of preterm infants are reintubated within 1 week after extubation. Meanwhile, in VLBW infants it is difficult to compare the extubation strategies because the appropriate observation days which define successful extubation vary: 3, 5 or 7 days.[4,5] Approximately 15%–20% of preterm infants undergo reintubation and ventilatory support in the NICU three or more times before discharge.[5,6] Complications of preterm infants with repeat tracheal intubation include upper airway trauma and poor lung expansion leading to lung injury.[7,8] There are different types of mechanical ventilation in neonatal ventilator care. After assessing the advantages and disadvantages of ventilator mode, it is important to select the adopted weaning mode and strategies in preterm infants. The weaning strategy helps to decrease the length of the weaning process and medical costs, which benefits both patients and hospitals.[9–13] Additionally, it decreases complications of ventilator use in VLBW infants and improves the quality of clinical care. Weaning predictors facilitate the weaning process, resulting in fewer intensive care unit admission days and reduction in the cost of ventilator use. Nevertheless, a universal and standardized protocol to assess VLBW infants for extubation in the NICU is still lacking. This study aimed to analyze the predictive parameters and influencing factors for extubation in VLBW preterm infants.

2. Methods

This retrospective study was conducted at Hsinchu Mackay Memorial Hospital, Taiwan, from January 2017 to November 2021. The study was approved by the Research Ethics Committee of Mackay Memorial Hospital (IRB number: 20MMHIS393e). The inclusion criteria included receiving mechanical ventilation through an endotracheal tube for ≥24 h, and birth weight less than 1500 gm. The exclusion criteria were as follows: death before the first extubation, accidental extubation, and severe congenital cardiopulmonary abnormalities. Successful weaning was defined as being extubated and off-ventilator longer than 72 h without reintubation and mechanical ventilation support. All VLBW preterms use the SLE 5000 Neonatal Ventilator.

To determine the association between subjects' characteristics and weaning success, potential predictive variables, including demographics of VLBW preterm infants, maternal variables, ventilator parameters, and clinical parameters, were compared between the successful extubation group and failed extubation group. The collected demographic information of VLBW preterm infants included gestational age, birth weight, post menstrual age (PMA) at the time of extubation, and Apgar score at 1 and 5 min. The maternal variables included delivery type, PROM, and histologically confirmed chorioamnionitis, colonized with GBS and steroid use. Ventilator parameters included inspiratory pressure, mean airway pressure (MAP), positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO2), duration of mechanical ventilation prior to the first extubation, and respiratory severity score (RSS; RSS = MAP x FiO2) before 24 h, 16 h, 8 h, and 1 h of extubation. Clinical parameters included respiratory rate, heart rate, and oxygen saturation before 24 h, 16 h, 8 h, and 1 h of extubation.

VLBW preterm infants were weaned to extubation according to basic standardized guidelines in line with the medical team workers' assessment of respiratory pattern, resolution of clinical infection source, and the ventilator setting. When the ventilatory mode was set as synchronized intermittent mandatory ventilation (SIMV) or SIMV + pressure support mode, the rate was <20 breaths/min, and Fio2 <0.3, the VLBW preterm infants were extubated and shifted to non-invasive ventilation or nasal CPAP.

2.1. Statistical analysis

Data are presented as standard deviation, frequency distribution, percentage, mean or median, and interquartile range of continuous variables for basic attributes of VLBW preterm infants. The Mann–Whitney U test was used for the analysis. Frequencies were analyzed using the chi-square test. A sample T-test was used for the continuous variables. It is used to analyze whether there are significant differences in the basic attribute data, respiratory parameters, and clinical parameters. For the receiver operating characteristic curve (ROC) analysis, the sensitivity and specificity values were calculated and summarized over all possible clinical cut-off values. The logistic regression was done and Odds ratio of predictive parameters of extubation. A P value < 0.05 was considered statistically significant. Data were organized in Excel and statistical analysis was performed using SPSS 25 software.

3. Results

A total of 100 VLBW preterm infants who were admitted to the Neonatology Department and intubated endotracheally with ventilatory assistance between January 2017 and November 2021 were enrolled. A total of 40 VLBW preterms were excluded from the study for the following reasons: 37 (37%) VLBW preterms expired before the first extubation and three (3%) VLBW preterms had severe congenital heart and lung malformations. Finally, 60 VLBW preterms satisfied the inclusion criteria for the study as shown in Fig. 1. The demographics, prenatal characteristics, and medication use of the VLBW preterms included are described in Table 1. There were 47 VLBW preterms with successful extubation and 13 VLBW preterms with failed extubation; the gestational weeks of preterm infants were between 23 weeks and 32 weeks, and 27.06 ± 1.98 and 26.77 ± 2.92 weeks in the success and failure groups, respectively ($P = 0.297$). Birth weight ranged from 490 g to 1498 g, and the success and failure groups weighed 951 ± 257 and 941 ± 343 g, respectively ($P = 0.7$). The Apgar score for 1 min to assess neonatal health status was 7 vs. 6 ($P = 0.021$), and the Apgar score for 5 min was 9 vs. 7 ($P = 0.007$). The days of ventilator use in the successful and unsuccessful extubation groups were 18.06 ± 22.51 days and 62.77 ± 118 days, respectively ($P = 0.003$) (Table 1).

There were no significant differences in the prenatal characteristics prior to extubation between the two groups. Medications used in the VLBW preterm infants, including surfactant, caffeine, and nitric oxide therapy, showed significant differences: surfactant [64% (30/47) vs. 100% (13/13), respectively ($P = 0.01$)], caffeine [47% (22/47) vs. 100% (13/13), respectively ($P = 0.001$)], and nitric oxide therapy [4% (2/47) vs. 38% (5/13), respectively ($P < 0.001$)].

The analysis of respiratory parameters 1 h before extubation revealed significant differences in inspiratory pressure, mean airway pressure, and respiratory severity score (Table 2). However, we found that the inspiratory pressure and mean airway pressure at 24, 16, 8 and 1 h before extubation were significant. The inspiratory pressure between the success group and failure group were [16.51 vs. 18.23 cmH_2O, respectively ($P = 0.005$)] [16.45 vs. 18.15 cmH_2O, respectively ($P = 0.009$)] [16.45 vs. 18 cmH_2O, respectively ($P = 0.033$)], and [16.38 vs. 18.62 cmH_2O, respectively ($P = 0.014$)] as shown in Fig. 2. The mean airway pressure between the success group and failure group were [7.4 vs. 8.62 cmH_2O, respectively ($P = 0.033$)] [7.26 vs. 8.42 cmH_2O, respectively ($P = 0.016$)] [7.15 vs. 8.31 cmH_2O, respectively ($P = 0.013$)], and [6.96 vs. 8.08 cmH_2O, respectively ($P = 0.007$)].

The predictive respiratory parameters were further analyzed (Fig. 3). The inspiratory pressure cut-off point was 17.5 cmH_2O, and the area under the receiver operator characteristic curve was 0.72 (95% CI: 0.55–0.88, $P = 0.014$), with a sensitivity of 46% and specificity of 89%. The mean airway pressure had a cut-off point of 7.5 cmH_2O and the area under the receiver operator characteristic curve was 0.74 (95% CI: 0.56–0.92, $P = 0$ 0.007), with a sensitivity of 69% and a specificity of 75%. The RSS had a cut-point score of 1.82, and the area under ROC was 0.69 (95% CI: 0.51–0.82, $P = 0.041$), with a sensitivity of 77% and a specificity of 63% (Fig. 3). We undertook further

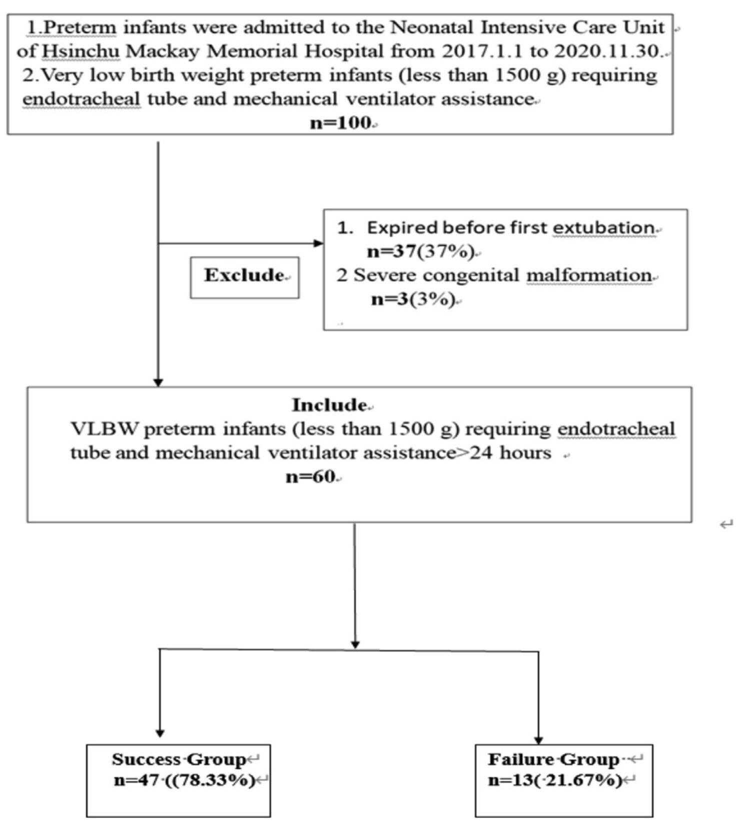

Fig. 1 Flow diagram of patient enrollment.

Table 1 Demographics, prenatal characteristics, and medication use of VLBW preterm infants.

Variable	Success group (n = 47)	Failure group (n = 13)	*P*
Gestational age (week)[a]	27.06 ± 1.98	26.77 ± 2.92	0.297
Birth weight (grams)[a]	951 ± 257	941 ± 343	0.700
Apgar score 1 min[b]	7 (5–8)	6 (3–6.5)	0.021*
Apgar score 5 min[b]	9 (8–9)	7 (6.5–8.5)	0.007**
Ventilator (days)[a]	18.06 ± 22.51	62.77 ± 118	0.003**
PMA at extubation (week)[a]	30.13 ± 2.92	31.85 ± 4.01	0.073
Birth weight at extubation (grams)[a]	1229 ± 561	1341 ± 404	0.114
Cesarean delivery, n (%)	30 (64)	12 (92)	0.047*
PROM, n (%)[b]	22 (47)	10 (77)	0.148
Colonized with GBS,n (%)	3 (6)	3 (23)	0.076
Prenatal steroids, n (%)	44 (85)	13 (100)	0.139
Surfactant, n (%)	30 (64)	13 (100)	0.01*
Caffeine treatment before extubation, n (%)	22 (47)	13 (100)	0.001**
iNO therapy, n (%)	2 (4)	5 (38)	<0.001**

GA = gestational age; PMA = postmenstrual age; PROM = prolonged preterm rupture of membrane; iNO = Inhaled Nitric Oxide.
*$P < 0.05$.
**$P < 0.01$.
[a] Data are presented as mean ± standard deviation.
[b] Data are expressed as median (interquartile range) or n/N (%).

Table 2 Comparison of respiratory-related parameters 1 h before extubation.

Variable	Success group (n = 47)	Failure group (n = 13)	*P*
Inspiratory pressure (cmH_2O)	16 (15–17)	17 (16–21)	0.014
Mean airway pressure (cmH_2O)	7 (6–8)	8 (7–9.5)	0.007
PEEP (cmH_2O)	5 (5–5)	6 (5–6)	0.037
Heart rate (beats/min)	152 (147–158)	154 (148–163)	0.565
FiO_2	0.25 (0.21–0.3)	0.26 (0.22–0.3)	0.348
RSS	1.68 (1.47–2.1)	2.1 (1.67–2.75)	0.041

Data are expressed as median (interquartile range).
PEEP: positive end-expiratory pressure; FiO_2: Fraction of inspired oxygen.
RSS: Respiratory severity score.

statistical analysis of predictive parameters 1 h before extubation with extubation failure through the cut off value for IP, MAP, and RSS. We calculated the odds ratio of extubation failure which revealed an association with ventilator parameters 1 h before extubation (Table 3). Statistical analysis revealed an association between ventilator parameters 1 h before extubation (IP > 17.5cmH2O, MAP >7.5 cmH2O, RSS >1.82) and extubation failure (odds ratio 1.73, 2.27, 2.46 and 95% confidence interval:1.16–2.6, 1.26–4.08,a nd 1.06–5.68, respectively).

4. Discussion

In this study, we found that Apgar score, inspiratory pressure, mean airway pressure, and RSS prior to extubation were significantly different between the extubation success and failure groups. Several studies have assessed whether clinical and respiratory parameters should be used as predictive parameters for extubation in VLBW preterm infants. Some studies have confirmed that Apgar score, gestational age, body weight, duration of ventilation, ventilator parameters, and ventilator mode are associated with successful extubation.[9,13–16]

The Apgar score assessment is more challenging in preterm infants because of immature organs and specificity. The results of our study are consistent with the study of Chawla et al., who found that higher 5-min Apgar scores are associated with extubation success.[16] However, the Apgar score reflects the condition and various underlying diseases of VLBW preterms. Meanwhile, the primary low Apgar score may be related to poor cardiopulmonary function, which leads to extubation difficulty and prolongs mechanical ventilator use.

Previous studies focused on the mean airway pressure associated with successful extubation. Freebairn et al. showed that the mean airway pressure was also affected by other factors such as airway resistance, lung compliance, dead space, and expiratory time.[17] Our study found that the mean airway pressure was dramatically lower in the success group before 24, 16, 8, and 1 h of extubation. RSS is a simple, non-invasive, predictive parameter to effectively assess the indicators of mortality and BPD morbidity in large study centers.[18] Our study results are similar to the outcomes of Mhanna et al.'s study to the effect that cases with failed extubation had higher RSS.[14] RSS, combining both FiO2 and mean airway pressure (which is the byproduct of MAP and FiO2), is a marker of respiratory disease associated with oxygenation index. In the clinical setting, when we use

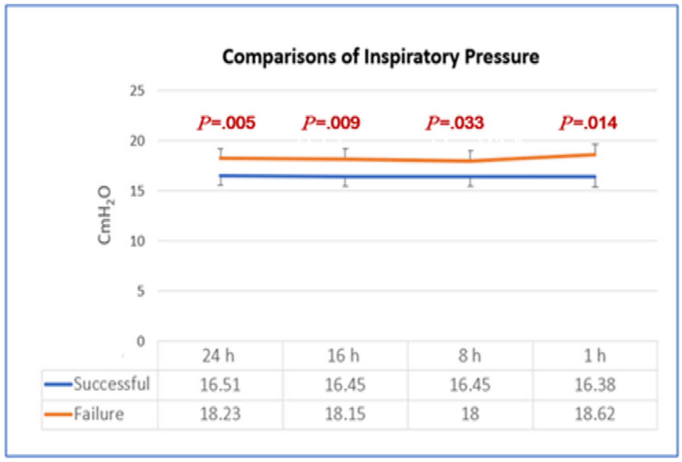

Fig. 2 Analysis of inspiratory pressure between successful and failure groups at 24, 16, 8, and 1 h before extubation.

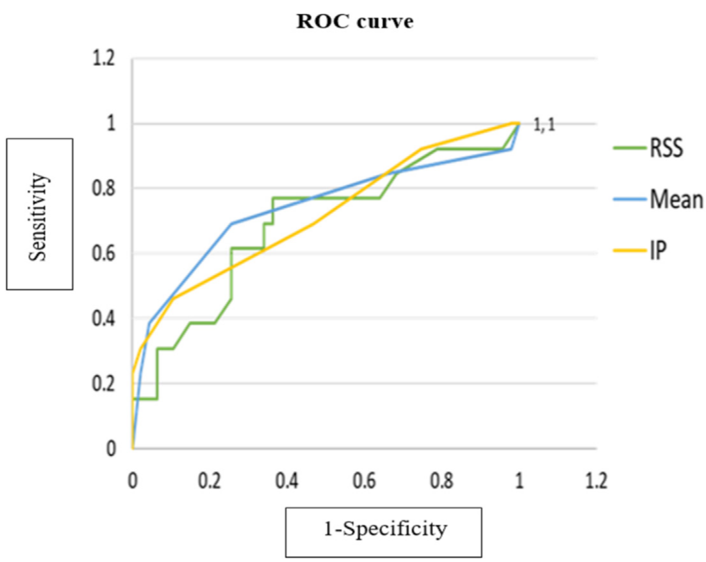

Fig. 3 ROC curve analysis of predictive respiratory parameters 1 h prior to extubation.

adequate mean airway pressure, it may reduce the need for excess oxygen.

The areas under a number of the ROC curves in this study— specifically, 0.72, 0.74, and 0.69 for the inspiratory pressure, mean airway pressure, and the RSS, respectively—moderately reflect the demand of the tidal volume, minute ventilation, and work of breathing in VLBW preterm infants. Vliegenthart RJS et al. found that higher dynamic compliance and minute ventilation prior to extubation were associated with successful extubation.[19] Vento et al. reported that higher spontaneous expiratory minute ventilation prior to extubation could be a useful parameter to predict successful extubation.[20] To our knowledge, it is more difficult to monitor the parameters of tidal volume, minute ventilation, and compliance to predict extubation in intubated preterms. Our study provides the cut-off value of inspiratory pressure, mean airway pressure, and the RSS for clinical application as 17.5 cmH_2O, 7.5 cmH_2O, and 1.82, respectively.

Vliegenthart et al. found that an additional week of invasive ventilator use was associated with a 1.18-fold risk of neurodevelopmental impairment.[19] In our study, the duration of ventilator use in the failed extubation group was about three times that in the success group. Re-intubation will increase the duration of ventilator days and delay extubation in VLBW preterm infants. The

Table 3 Ventilator parameter associated with extubation failure at 1 h prior to extubation.

Parameter	Cut-point	*P*	OR	95% CI
Inspiratory pressure	>17.5 cmH_2O	0.007	1.73	1.16 ~ 2.6
Mean airway pressure	>7.5 cmH_2O	0.006	2.27	1.26 ~ 4.08
Respiratory severity score	>1.82	0.035	2.46	1.06 ~ 5.68

CI = confidence interval; OR = odds ratio.
Data analyzed with logistic regression.

duration of ventilator use is a strong predictor of BPD: an additional week of ventilator use is associated with a 2.7-fold increase in the odds of developing BPD. Approximately 26% of patients on ventilators developed diaphragmatic dysfunction[2,20]; therefore, it is important to determine the optimal timing of extubation and reduce the duration of ventilator use to improve the chance of successful extubation. Several maternal characteristics affect VLBW conditions, including PROM and maternal infections.[21,22] Our study found no difference in PROM and maternal infections in either group. Reports indicate that caffeine reduces apnea, ventilator duration, and oxygen dependence and improves survival in preterm infants.[23,24] In this study, there was a significant difference between the two groups in receiving caffeine medication associated with extubation. The proportion of the success group receiving caffeine drug treatment was 47%. However, caffeine treatment is self-funded, and subject to the influence of economic considerations.

This study has several limitations. First, this was a retrospective review of patients admitted to a single NICU in a regional hospital. Therefore, the results represent only successful extubation and predictive readiness of VLBW preterm infants from a certain region and race. Second, data were recorded during the weaning process; any missing data were obtained later and reanalyzed with the statistical methods. Third, we did not observe long-term outcomes such as BPD, long-term complications of ventilator use, and mortality.

In conclusion, our study demonstrated that respiratory parameters such as inspiratory pressure, mean airway pressure, and RSS influence the success of extubation in VLBW preterm infants. Our findings indicated that lower ventilator inspiratory pressure, mean airway pressure 24, 16, 8, and 1 h, and RSS 1 h prior to extubation have clinical applications for the foundation of an extubation model for VLBW preterm infants in the future.

Declaration of Competing Interest

The authors declare no competing financial interests.

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