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Original Articles

Role of Spontaneous Breathing Trial in Predicting Successful Extubation in Premature Infants

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Summary. Background: The ability of clinicians to predict successful extubation in mechanically ventilated premature neonates is limited. Identifying objective criteria for predicting successful extubation may reduce the incidence of failed extubation and the duration of mechanical ventilation. Objective: To evaluate the validity of objective measures of lung function and spontaneous breathing trial (SBT) in predicting successful extubation among premature neonates with attempted extubations within the first 3 weeks of life. Methods: Respiratory compliance (Crs) along with SBT was performed prior to elective extubations within 3 weeks of age in premature infants $\leq$32 weeks. Extubation was considered successful if patients remained extubated for $>$72 hr. Ventilator settings including mean airway pressure (MAP), set rate, and fraction of inspired oxygen (FiO_2) 24 hr after re-intubation were compared with pre-extubation settings, in patients requiring re-intubation. Results: Thirty-nine of 49 infants (80%) were successfully extubated. Of 41 babies who passed SBT, only 5 infants failed extubation. SBT had 92% sensitivity, 50% specificity, 88% positive predictive, and 63% negative predictive value for successful extubation. Crs was comparable between infants who were successfully extubated and those who were not. Conclusions: A SBT prior to extubation may be a practical objective adjunct in predicting successful extubation in ventilated premature infants. **Pediatr Pulmonol. 2013; 48:443–448.**

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BACKGROUND

Mechanical ventilation is a life-sustaining intervention in premature neonates, with respiratory difficulties. However, prolonged mechanical ventilation and endotracheal intubation may be associated with some life threatening adverse effects, such as plugged endotracheal tube, pneumonia, pneumothorax, and bronchopulmonary dysplasia (BPD).[1,2] Hence, extubation of ventilated infants as early as possible is clinical goal to reduce unwarranted pulmonary morbidities. The decision to extubate premature neonates usually is based on clinical assessment of infant's spontaneous respiratory effort, adequacy of ventilation and oxygenation as judged by blood gas parameters, oxygen saturations, and ventilator settings. Up to 40% of mechanically ventilated infants weighing $<$1,000 g at birth require reintubation following extubation.[3] Failure of extubation has been associated with higher mortality, increased length of hospital stay and more ventilator days in adult and pediatric population.[4,5] Thus, identifying methods for predicting successful extubation attempts may reduce mortality and morbidities associated with ill-timed extubation attempts and improve hospital outcome.

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Adequate brain maturity and lung function are prerequisites for successful transition from mechanical ventilation to spontaneous breathing among premature infants. In the absence of significant apneic episodes, bedside pulmonary function tests may be useful in conjunction with infant's clinical status and blood gas parameters to predict the success of extubation. Data on pulmonary function tests prior to extubation in premature infants are limited and conflicting.[6–8] Most of the studies were conducted in infants with wide ranges of gestational age (GA), birth weight, and postnatal age at extubation and did not account for comorbidities such as patent ductus arteriosus (PDA), pulmonary hemorrhage, severe intracranial hemorrhage, atelectasis, and pneumonia after extubation that may contribute to the failure of extubation. A spontaneous breathing trial (SBT) has been used in adult and pediatric patients for predicting successful extubation[9–11] and was found to be a useful test in one study among premature infants.[12]

In this study, our objectives, were (a) to evaluate the validity of respiratory compliance (Crs) and SBT in predicting successful extubation in premature neonates with planned extubation attempt within the first 3 weeks of life, (b) to identify clinical determinants of successful extubation, (c) to compare ventilator parameters before extubation and 24 hr after re-intubation among infants who fail extubation attempts, and (d) to compare hospital outcomes between infants who fail and those who successfully remain extubated 72 hr later. We hypothesized that Crs and SBT prior to planned extubation within the first 3 weeks of life can independently predict successful extubation >72 hr in preterm infants <32 weeks gestation. We further hypothesized that a failed extubation attempt would be associated with higher ventilator support 24 hr later and worse clinical outcomes at hospital discharge.

MATERIALS AND METHODS

This prospective observational study was approved by the Institutional Review Board at Wayne State University and Detroit Medical Center, Detroit, Michigan. The study was conducted at Hutzel Women's Hospital Neonatal Intensive Care Unit from March 2008 to December 2009. Informed parental consent was obtained for each patient prior to enrollment.

Inclusion Criteria

(1) Infants with GA of 24 to 31 6/7 weeks.
(2) Infants intubated within 24 hr of birth due to respiratory distress and mechanically ventilated for at least 12 hr.
(3) First elective extubation within first 3 weeks of life.

Neonates who were accidentally extubated were excluded from the study. Maternal and infant records were reviewed for baseline characteristics, ventilator parameters prior to extubation attempt and 24 hr after reintubation, as applicable, comorbidities and discharge outcomes. The ventilator management of infants including the need for initial endotracheal intubation, changes in ventilator parameters, decision to extubate, need for re-intubation and the extent of respiratory support following extubation were prerogatives of medical clinical team. Post-extubation respiratory support determined by the clinical team ranged from room air, nasal canula (≤2 L/min), high flow nasal canula (>2 L/min), CPAP (4–6 cmH_2O), or nasal intermittent positive pressure ventilation (NIPPV). Puritan-Bennett Nellcor 840® ventilator, using synchronized intermittent mandatory ventilation with pressure support was used.

In our neonatal intensive care unit (NICU), a strategy of gentle ventilation is pursued and ventilator support is typically reduced for blood capillary pH >7.25 and pCO_2 <55 mmHg. Targets of oxygen saturations are between 88% and 92% and FiO_2 is decreased for oxygen saturations >94%. Extubation is usually attempted when ventilator set rate is between 16 and 20 and FiO_2 <35%. Indications for reintubation are: frequent episodes of apnea and bradycardia (>5 episodes/hr), significant apnea and bradycardia requiring bag and mask ventilation, increased work of breathing (as evidenced by increase in respiratory rate and chest wall retractions) for 5–10 min, hypoxemia (oxygen saturations <85%) with an increase in FiO_2 by >40% of baseline or respiratory acidosis with pH <7.25 and pCO_2 >65 mmHg. The usual policy in our NICU is to escalate the level of support to NIPPV prior to re-intubation. CPAP pressures usually vary from +4 to +6 cmH_2O. We defined failed extubation as need for reintubation within 72 hr of elective extubation.

When a clinical decision was made to extubate an eligible infant on whom parental consent was obtained, the research team was notified. Ventilator settings including peak inspiratory pressure (PIP), mean airway pressure (MAP), fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP), set rate and total minute ventilation (TMV) were noted by the research personnel, who then conducted SBT and measurement of Crs up to 6 hr prior to extubation. Respiratory severity score (RSS) was calculated by multiplying MAP by FiO_2.[13]

Measurement of Respiratory System Compliance

The mode of ventilation was switched to volume control (5 ml/kg tidal volume) with similar FiO_2 on the Puritan-Bennett Nellcor 840® ventilator. All pulmonary

function tests were performed on infants in the quiet or sleep state. Crs was measured using the single breath occlusion technique performed at end inspiration which provokes the Hering–Breuer reflex leading to relaxation of respiratory muscles.[14] Static compliance of the respiratory system can be calculated as the ratio of expired tidal volume and the difference between plateau pressure at end-inspiration and PEEP. The pressure time curve was visually inspected to ensure an adequate airway pressure plateau. An average of three acceptable breaths was recorded. Acceptance criteria for the single-breath occlusion included: (1) stable end expiratory baseline; (2) plateau pressure lasting >100 msec; (3) stable plateau pressure. Rejection criteria included machine-generated signals such as questionable measurements, incomplete exhalation, or plateau not reached.

Spontaneous breathing trial was done after measurement of Crs and before extubation, by switching the mode of ventilation to "Continuous Positive Airway Pressure" without pressure support with endotracheal tube (ETCPAP) for up to 5 min. Due to scarcity of data on SBT among premature infants, the 5-min duration of SBT was arbitrarily chosen a priori. SBT was classified as failed or passed. Failed SBT was defined as any one of the following: significant bradycardia (heart rate <100 bpm for more than 10 sec) or oxygen desaturation (<85% for >15 sec) or significant bradycardia requiring intervention. At this time, minute ventilation was noted, labeled as endotracheal spontaneous minute ventilation (ETSMV) and ratio of ETSMV and TMV was calculated.

If the patient failed the SBT, the study was stopped and infant was placed back on the same ventilator settings as before the SBT. The timing of the extubation was decided by the clinical team who were unaware of the SBT results.

Hospital-based outcomes were compared between infants who failed and those who successfully remained extubated. BPD was defined as need for supplemental oxygen at 36 weeks post-conceptual age.[15] Other examined outcomes included necrotizing enterocolitis (NEC), stage II or more of modified Bell's criteria[16] and PDA diagnosed by echocardiogram, considered hemodynamically significant and requiring medical or surgical treatment. Death/BPD was taken as a composite morbidity, to account for death before 36 weeks post-menstrual age.

Data Analysis

The present study cohort was part of another study that measured respiratory compliance at birth in premature infants with and without antenatal corticosteroid exposure. This was a pilot study and sample size calculations were not performed.

Infants were divided into two groups based upon whether they failed or passed the extubation attempt. Continuous variables were compared using Student's *t*-test or Wilcoxon-signed rank test for non-normally distributed variable. Categorical variables were compared by Chi-squared test. Multivariate logistic regression analysis was used in an exploratory attempt to determine the association between contribution of GA, SBT, weight at extubation, postnatal age and treatment with caffeine and success of extubation. Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL).

RESULTS

Sixty-two infants were eligible for the study and 49 parents consented to their infant's participation. Mean (±SD) birth weight and GA of the participants were 1,077 ± 366 g and 28 ± 2 weeks, respectively. Ninety-two percent of infants were African-Americans, 47% were males, and 31% were born via vaginal delivery. All infants developed respiratory distress syndrome after birth and received surfactant therapy and mechanical

TABLE 1—Clinical Characteristics of Infants

Variable[1]	Success group (n = 39)	Failure group (n = 10)	*P*-value
Gestation (weeks)	29 (2)	27 (1)	0.01
Birth weight (g)	1,116 (393)	925 (172)	0.14
Male	18 (46)	5 (50)	1.0
African-American	36 (92)	9 (90)	1.0
Antenatal steroid	33 (85)	7 (70)	0.36
Surfactant doses	2 (0.9)	2.1 (0.9)	0.7
5-Min Apgar ≤5	6 (15)	1 (10)	0.6
Histologic chorioamnionitis	11 (29)	2 (20)	0.71
Vaginal delivery	12 (31)	3 (30)	1
Weight at extubation (g)	1,127 (340)	890 (194)	0.04
SNAPPE II score	38 (14)	35 (17)	0.60
Age at extubation (days)	4.2 (4.2)	3.7 (2.5)	0.74
Methylxanthine use	12 (32)	5 (50)	0.30

[1]Mean (SD) or n (%).

TABLE 2— Pulmonary Function Tests Prior to Extubation

Variable[1]	Success group (n = 39)	Failure group (n = 10)	*P*-value
Pre-extubation FiO_2	23.5 (2.6)	23.8 (2.4)	0.74
Mean airway pressure (cmH_2O)	5.8 (0.71)	6.2 (0.55)	0.08
pH	7.36 (0.7)	7.3 (0.7)	0.04
pCO_2 (mmHg)	37.5 (7.2)	39.3 (8.9)	0.51
Compliance (ml/cmH_2O/kg)	0.94 (0.33)	0.88 (0.34)	0.59
SMV (L/min)	0.26 (0.11)	0.27 (0.18)	0.86
TMV (L/min)	0.41 (0.13)	0.41 (0.2)	0.94
ETMV (L/min)	0.35 (0.16)	0.24 (0.18)	0.07
ETSMV/TMV	0.81 (0.24)	0.53 (0.29)	<0.01
Passed SBT	36 (92)	5 (50)	<0.01

[1]Mean (SD) or n (%).

ventilation. Mean postnatal age and weight at first extubation attempt were 4 ± 3.9 days and 1,080 ± 330 g, respectively. After elective extubation, 12% of infants were in room air, 23% were on nasal canula with supplemental oxygen and 65% were placed on CPAP or NIPPV. Ten infants (20%) failed extubation and 39 infants (80%) were successfully extubated. Infants who were successfully extubated were more mature and had larger weight at extubation, compared to infants who failed extubation (Table 1). There were no statistically significant differences in birth weight, race, gender, mode of delivery, use of antenatal steroids, age at extubation, use of caffeine therapy between infants who failed and those who were successfully extubated (Table 1). Pulmonary function testing was performed up to 6 hr prior to extubation. Pre-extubation ventilator support and Crs prior to extubation were comparable between infant groups. Infants, who were successfully extubated had higher ETSMV/TMV and were more likely to pass SBT, compared to infants, who failed extubation (Table 2). Eight of 49 infants (16%) failed the SBT, 5 (63%) of whom failed extubation. Near 50% of patients failed SBT around 3–4 min. The reasons for failed SBT was oxygen desaturation in four infants and both bradycardia and desaturation in remaining four. Forty-one infants (84%) passed the SBT with a subsequent extubation failure in 5 (12%) infants. Passing SBT was associated with 92% sensitivity for successful extubation and a positive predictive value of 88%. The specificity of the SBT was 50%, and a negative predictive value of 63%.

The overall extubation failure rate was 20%. The reasons for extubation failure were respiratory acidosis (20%), increased work of breathing (30%), significant apnea and bradycardia (30%), pulmonary hemorrhage (10%), and accidental overdose of morphine (10%). Of the five infants who failed extubation but passed SBT, one had an accidental overdose of morphine, four had a hemodynamically significant PDA, of whom one infant also had pulmonary hemorrhage.

Univariate regression analyses revealed that higher GA and passing SBT were independently associated with successful extubation ($P = 0.01$ and $P < 0.01$, respectively).

Multivariate logistic regression analysis revealed a significant association between passing SBT and success of extubation (Odds ratio 6.6, 95% CI: 1.1–41.9, $P = 0.04$) after adjustment for the effect of GA (Odds ratio 1.3, 95% CI: 0.9–2, $P = 0.15$). The wide confidence interval was possibly due to our limited sample size.

One patient received accidental overdose of morphine. A sub-analysis done after excluding this patient showed a significant association between passing SBT and success of extubation (Odds ratio 7.9, 95% CI: 1.2–52, $P = 0.03$) after adjustment of the effect of GA (Odds ratio 1.4, 95% CI: 0.9–2.2, $P = 0.12$).

TABLE 3— Discharge Outcomes of Patients

Variable[1]	Success group (n = 39)	Failure group (n = 10)	*P*-value
BPD	10 (24)	7 (70)	0.01
NEC ≥ stage 2	9 (23)	2 (20)	1
Death/BPD	10 (24)	7 (70)	0.01
Mortality	1 (2)	0 (0)	1
PDA	13 (33)	8 (80)	0.01
Length of hospital stay (days)	56 (23)	75 (17)	0.02
Days on oxygen	31 (28)	63 (27)	<0.01
Days on ventilator	11 (18)	28 (17)	0.009

[1]Mean (SD) or n (%).

Among infants who failed extubation (n = 10), RSS, FiO_2, and MAP were all higher 24 hr after re-intubation, compared with pre-extubation using Wilcoxon-signed rank test: 2.3 ± 1.2 versus 1.5 ± 0.2, $P = 0.005$, 33.5 ± 12 versus 23.5 ± 2.8, $P = 0.003$ and 7.1 ± 1.1 versus 5.9 ± 0.7, $P = 0.01$, respectively. Table 3 compares outcomes at hospital discharge between infants groups. Infants who failed elective extubation had higher incidence of PDA and BPD, higher length of hospital stay, days on supplemental oxygen and mechanical ventilation, compared to infants who remained extubated. As this study was not powered to look at these secondary outcomes, the results should be interpreted with caution.

DISCUSSION

In a cohort of mechanically ventilated premature infants, we were able to demonstrate that SBT performed up to 6 hr of elective extubation, within the first 3 weeks of life, was able to predict success of extubation with 92% sensitivity and 88% PPV. Respiratory compliance prior to extubation was not helpful in predicting success of extubation. As expected, successfully extubated infants had a higher GA and weighed more at extubation, compared to infants who required re-intubation. Multivariate logistic regression analysis with GA as covariate revealed that passing SBT remained an independent predictor of successful extubation. Infants who passed the SBT were 6.6 times more likely to be successfully extubated, compared to infants who failed the SBT. Finally, rates of BPD, days on oxygen, mechanical ventilation, and hospital stay were significantly increased in infants who failed their first extubation attempts.

Our data on the usefulness of SBT in neonates are comparable to previously reported literature on the SBT in premature infants by Kamlin et al.[12] who found a sensitivity of 97%, and a positive predictive value for extubation success of 93%. In a further prospective audit, the same investigators found that VLBW infants (<1,250 g) were extubated at significantly higher support compared to historic controls.[17] There was no difference in the rate of BPD or proportion of infants who were successfully extubated for 72 hr.[17] We arbitrarily selected 5 min for duration of SBT, because we speculated that a longer duration of SBT (15–120 min)[9,11] as used among children and adults may precipitate atelectasis and increase the work of breathing in premature infants. Low negative predictive value of SBT may be due to increased work of breathing through a small diameter ETT without pressure support, precipitating failure of SBT. In Kamlin's study, SBT was performed for 3 min and most neonates who failed SBT did so in the first 90 sec,[12] compared to 3–4 min in our study. Infants in Kamlin's study were on higher ventilator support prior to elective extubation, compared to those in the current study (ventilator rate of 20–30 breaths/min, MAP of 7.2 mmHg vs. 16 breaths/min and 5.8 mmHg). In addition, in the study by Kamlin, the mode of ventilation was either assist control or SIMV, in contrast to SIMV in all our infants. These differences may explain the difference in the timing of failed SBT in the two studies. Having a shorter time (3 min vs. 5 min) for SBT may miss some patients who would fail the trial after 3 min. Therefore, a 5-min SBT may be a reasonable time period to identify extubation-readiness in the majority of infants, whereas failure of 5-min SBT may suggest reassessment of clinical condition of the patient, prior to extubation.

Previous studies in premature infants have found spontaneous minute ventilation to be a useful predictor of successful extubation.[18,19] Veness-Meeham et al.[6] in a study of 50 premature infants with RDS, found that dynamic lung compliance and minute ventilation were poor predictors of successful extubation. In contrast, Szymankiewicz et al.[7] and Balsan et al.[8] demonstrated that higher lung compliance and low airway resistance measured prior to extubation among very low birth weight infants were predictive of successful extubation. In this study, Crs measurement prior to extubation was not predictive of successful extubation. One possible explanation could be the high use of antenatal steroids and postnatal surfactant therapy which might have improved Crs in our infant population.

Our extubation failure rate of 20% is consistent with previous reported rates of 20–22% in the premature infant population.[12,20] Ventilator parameters 24 hr after re-intubation were significantly higher than pre-extubation parameters among infants who failed extubation. Timing of elective extubation is crucial and needs a balanced approach of avoiding adverse effects of prolonged intubation and potential risks associated with hasty failed extubation in premature neonates.

The need for higher ventilator support after a failed extubation attempt may be due to periods of ineffective spontaneous breathing, associated sub-segmental lung atelectasis, and/or underlying co-morbidity (such as PDA). Higher morbidities at discharge among infants who failed extubation may also be due to younger GA and other inherent differences in baseline characteristics of these infants. Our findings of higher mortality, increased length of hospital stay and number of days on mechanical ventilation among infants who failed extubation is comparable to those reported among adult and older pediatric patients.[4,5]

Our study has the following limitations: a wide range of GA, a convenience sample, small sample size, arbitrary definition of successful extubation (adequate spontaneous breathing for 72 hr) and lack of strict criteria for re-intubation. Practices on methylxanthine therapy

and post-extubation support reflect local policy, since there is paucity of established guidelines and may have modulated our results. The strengths of the study are that it suggests the use of a simple, clinically feasible, bedside approach to predict successful extubation in ventilated premature infants. Moreover, our findings elucidate the co-morbidities that are associated with extubation failure among premature neonates. Our study highlights the increased respiratory support that follows ill-timed extubation attempts and other short-term adverse consequences.

In summary, SBT prior to elective extubation may be used in predicting successful extubation in premature infants. Guidelines for extubation among premature infants are needed in order to reduce unnecessary exposure to adverse effects of mechanical ventilation, while maintaining successful spontaneous breathing efforts.

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