Markers of Successful Extubation in Extremely Preterm Infants, and Morbidity After Failed Extubation

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Objectives To identify variables associated with successful elective extubation, and to determine neonatal morbidities associated with extubation failure in extremely preterm neonates.

Study design This study was a secondary analysis of the National Institute of Child Health and Human Development Neonatal Research Network's Surfactant, Positive Pressure, and Oxygenation Randomized Trial that included extremely preterm infants born at $24^{0/7}$ to $27^{6/7}$ weeks' gestation. Patients were randomized either to a permissive ventilatory strategy (continuous positive airway pressure group) or intubation followed by early surfactant (surfactant group). There were prespecified intubation and extubation criteria. Extubation failure was defined as reintubation within 5 days of extubation.

Results Of 1316 infants in the trial, 1071 were eligible; 926 infants had data available on extubation status; 538 were successful and 388 failed extubation. The rate of successful extubation was 50% (188/374) in the continuous positive airway pressure group and 63% (350/552) in the surfactant group. Successful extubation was associated with higher 5-minute Apgar score, and pH prior to extubation, lower peak fraction of inspired oxygen within the first 24 hours of age and prior to extubation, lower partial pressure of carbon dioxide prior to extubation, and non-small for gestational age status after adjustment for the randomization group assignment. Infants who failed extubation had higher adjusted rates of mortality (OR 2.89), bronchopulmonary dysplasia (OR 3.06), and death/ bronchopulmonary dysplasia (OR 3.27).

Conclusions Higher 5-minute Apgar score, and pH prior to extubation, lower peak fraction of inspired oxygen within first 24 hours of age, lower partial pressure of carbon dioxide and fraction of inspired oxygen prior to extubation, and nonsmall for gestational age status were associated with successful extubation. Failed extubation was associated with significantly higher likelihood of mortality and morbidities. *(J Pediatr 2017;189:113-9).*

Trial registration ClinicalTrials.gov: NCT00233324.

See editorial, p 17

Mechanical ventilation support is needed for most extremely preterm (EPT) infants (gestational age [GA] <28 weeks] to maintain adequate oxygenation and ventilation.[1] The coexistence of lung immaturity, weak respiratory drive, excessively compliant chest wall, and surfactant deficiency often contribute to dependency on mechanical ventilation during the first days or weeks after birth. Prolonged mechanical ventilation is associated with high mortality and morbidities including ventilator-associated pneumonia, pneumothorax, and bronchopulmonary dysplasia (BPD).[1-3] Each additional week of mechanical ventilation is associated with an increase in the risk of neurodevelopmental impairment.[1]

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
EPT	Extremely preterm
FiO_2	Fraction of inspired oxygen
GA	Gestational age
ICH	Intracranial hemorrhage
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
P_{CO2}	Partial pressure of carbon dioxide
PMA	Postmenstrual age
SGA	Small for gestational age
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Reduction in the need and duration of invasive mechanical ventilation may potentially improve outcome of preterm infants. This goal may be achieved by the use of noninvasive respiratory support and, among intubated infants, by reducing the duration of mechanical ventilation by successful extubation as early as possible. Large randomized controlled trials have demonstrated that the outcome of neonates supported initially with noninvasive support (such as continuous positive airway pressure [CPAP]) is comparable with those intubated and given early endotracheal surfactant.[4,5] Weaning from the ventilator in preterm neonates is quite variable and inconsistent among centers and clinicians who have limited ability to predict extubation readiness.[6] The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network's (NRN) randomized controlled Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) provided specific extubation and reintubation criteria for the 2 randomization groups of permissive ventilation (CPAP group) or ventilation and early surfactant (surfactant group). The variables established for the SUPPORT trial were targeted to minimize ventilation time for the CPAP group, and allow for more time intubated for the surfactant group. At present, there is a paucity of data on the incidence of failed elective extubation and its association with the clinical outcome of preterm infants. Rates of extubation failure may be as high as 40%-50% among extremely preterm infants in some centers.[7-9] The incidence of extubation failure varies significantly in studies because of lack of uniform definitions and criteria for extubation and reintubation.

Extubation failure has been independently associated with increased mortality, longer hospitalization, and more days on oxygen and ventilatory support.[10-12] It is critical, therefore, to attempt extubation early and at a time when successful extubation is likely. Identifying factors associated with successful extubation may help reduce the duration of mechanical ventilation, improve outcomes, as well as help in designing future research studies to improve the outcomes of ventilated preterm infants.

We used a cohort of EPT infants enrolled in the SUPPORT randomized controlled trial of permissive ventilation strategy (CPAP) vs endotracheal intubation followed by surfactant (surfactant) to identify clinical variables that were associated with a successful first elective extubation and to evaluate mortality and short-term morbidities associated with extubation failure after elective extubation. The primary hypothesis was that perinatal and peri-extubation characteristics are associated with successful extubation among EPT infants. The secondary hypothesis was that failed extubation would be associated with higher mortality and neonatal morbidities among these infants.

Methods

This was a secondary analysis of pre-existing data from the SUPPORT trial conducted at the participating sites of NICHD NRN (ClinicalTrials.gov: NCT00233324). Institutional review board approval and parental consent was obtained for the main SUPPORT trial. Patients were eligible for the SUPPORT trial if they were (1) $24^{0/7}$ to $27^{6/7}$ weeks by best obstetric estimate; (2) born without known malformations; and (3) if a decision had been made to provide full resuscitation for them after written informed consent had been obtained from a parent. Enrolled subjects were randomized before delivery to either noninvasive respiratory support and a permissive ventilatory strategy (CPAP group) or intubation followed by early surfactant (surfactant group). Infants were also randomized to different oxygen saturation targets (85%-89% and 91%-95%). For the current study, all infants enrolled in the SUPPORT trial who were endotracheally intubated within the first 24 hours of postnatal age were included. Infants who died before an extubation attempt, had accidental extubation, or were transferred/discharged home prior to an elective extubation attempt were excluded.

Detailed data were collected for baseline characteristics (GA, birth weight, sex, race, hypertensive disorders of pregnancy, acute chorioamnionitis, prolonged rupture of membrane [>18 hours], mode of delivery, multiple births, antenatal steroids administration, resuscitation in the delivery room), and respiratory support on day 1. Successful extubation was defined as survival without the need for respiratory support with an endotracheal tube for more than 5 days. Peri-extubation characteristics were collected, including age at extubation, ventilator support (fraction of inspired oxygen [FiO_2], pH, and partial pressure of carbon dioxide [P_{CO2}] prior to extubation), and postextubation respiratory support. An electronically altered pulse oximeter (Masimo Radical Pulse Oximeter; Masimo, Radical, Yorba, California), which had a maximum variation of 3%, was used in SUPPORT trial until 36 weeks' postmenstrual age (PMA) for both lower (85%-89%) and higher (91%-95%) target saturation groups.

Criteria for intubation, extubation, and reintubation were different in the 2 study groups during the first 2 weeks of age. Infants in the CPAP group could be intubated if they met any of the following criteria: FiO_2 >0.50 required to maintain oxygen saturation at or above 88% using the study electronically altered pulse oximeter, P_{CO2} >65 mm Hg, or hemodynamic instability. Intubation could also be performed at any time for repetitive apnea requiring positive pressure ventilation, clinical shock, sepsis, and/or the need for surgery. Extubation of an infant in the CPAP group was to be attempted within 24 hours after the infant met all of the following criteria: a P_{CO2} below 65 mm Hg with a pH higher than 7.20; an oxygen saturation at or above 88% using the altered study pulse oximeter with an FiO_2 less than or equal to 0.50; a mean airway pressure of less than 10 cm H_2O; a ventilator rate of less than or equal to 20 breaths per minute; an amplitude of less than twice the mean airway pressure if high-frequency oscillatory ventilation was being used; hemodynamic stability; and the absence of clinically significant patent ductus arteriosus. Criteria for reintubation were the same as those for initial intubation.

All patients in the surfactant group were to be intubated in the delivery room and receive surfactant within 1 hour of birth. The infants were to be extubated within 24 hours after meeting