Association of Patent Ductus Arteriosus with extubation failure among preterm infants

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Abstract

Backround: Mechanical ventilation is associated with mortality/morbidities in preterm infants. Nearly a third of these infants fail extubation and this may increase morbidities. **Objective:** To evaluate the association of symptomatic patent ductus arteriosus with failure of extubation among preterm infants. **Methods:** This was a retrospective study on preterm infants (birth weight <1,250 grams and gestational age [?]23weeks) born between January 2009 and December 2016, who were mechanically ventilated and extubated within the first 60 days of age. **Results:** 360 infants were evaluated, of these, 26% failed and 74% succeeded the initial extubation attempt. On adjusted analysis, symptomatic ductus was associated with an increased risk of extubation failure. **Conclusion(s):** Presence of symptomatic patent ductus arteriosus was associated with extubation failure. Further investigations are needed to establish whether screening for presence of ductus and treatment of the same, prior to extubation among these infants, improves chances of successful extubation and cardiorespiratory outcomes.

INTRODUCTION

Patent ductus arteriosus (PDA) is a common morbidity in extremely preterm infants. Failure of ductal closure has been associated with many severe morbidities, including broncopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and mortality [1-4], but there is lack of evidence for a cause-and-effect relationship [5]. Practices in PDA management are not consistent among institutions ranging widely from universal prophylactic treatment to selective treatment on the basis of various clinical criteria, to no treatment at all [6].

The majority of extremely preterm infants receive invasive mechanical ventilation (IMV) to maintain oxygenation and ventilation [7] and prolonged IMV has been associated with an increased risk of mortality and neonatal morbidities, including upper airway injury, nosocomial infections and BPD [8-10]. Failed extubation is also independently associated with increased risk of mortality, BPD, severe IVH, longer hospitalization, more days on respiratory support and significant respiratory setback lasting multiple days after re-intubation.[11-15]

There have been reports of an association between presence of PDA and extubation failure in preterm infants [16, 17]. Limitations of these studies include small sample size (9 out of 39 infants [16] and 22 out of 82 infants [17]) with extubation failure, lack of use of Nasal Intermittent Positive Pressure Ventilation (NIPPV) prior to re-intubation [17] and lack of data on the timing of diagnosis of PDA.

The objective of the current study was to evaluate the association between a hemodynamically significant PDA and failure of first elective extubation among extremely low birth weight infants.

METHODS

Study Design:

This was a retrospective, cohort study that included preterm infants born at Hutzel Women's Hospital, Detroit, MI, from January 2009 to December 2016. The study was approved by the Institutional Review Board at Wayne State University.

Study Population:

All infants with a birth weight <1,250 grams, gestational age [?]23weeks, and admitted to the Neonatal Intensive care Unit (NICU) at Hutzel Women's Hospital were screened. Infants were eligible for the study if they a) received MV with an endotracheal tube, and b) had a first elective extubation attempt within 60 days of age. The decision for initial endotracheal intubation, weaning of respiratory support, extubation, post-extubation respiratory management and need for reintubation were at the discretion of the clinical team.

Definitions:

Gestational age was estimated based on best obstetric estimate using early ultrasound, last menstrual period or Ballard examination [20] in that order. Acute chorioamnionitis was based on placental pathology. The primary outcome was successful extubation, defined as survival for minimum of five days on either no or non-invasive respiratory support. Extubation failure was defined as need for re-intubation within 5 days of extubation. Hemodynamically significant PDA was defined by Echocardiogram findings suggestive of a moderate to large PDA in an infant with low diastolic blood pressure, wide pulse pressure, hypotension, renal insufficiency, or signs of pulmonary edema (tachypnea, increased respiratory support and oxygen requirements), either before or within five days of elective extubation. Echocardiograms in our center were generally ordered for symptomatic patients as assessed by the primary clinical team.

Ventilation index (VI) was used as an objective measure of adequacy of ventilation in response to the respiratory support provided. VI was calculated as the product of the set rate, partial pressure of carbon dioxide in arterial or capillary blood (pCO_2) and the difference between peak inspiratory and positive end expiratory pressure divided by 1000[18]. We calculated the highest respiratory severity score (RSS) in the first 6 hours of age, as an objective marker of oxygenation in relation to mean airway pressure received by the patient. RSS was calculated as the product of the mean airway pressure (MAP) and fraction of inspired oxygen (FiO_2) [19].

Statistical Analysis:

Perinatal and peri-extubation characteristics were compared between those who failed the first extubation attempt and those who were successful. Categorical variables between the two groups were compared using chi-squared or Fisher's exact tests, and continuous variables were analyzed using Wilcoxon rank sum tests. Logistic regression analysis was performed to determine associations between perinatal and peri-extubation characteristics, including PDA, with success of extubation. Variables in the logistic regression analysis were selected based on a backward selection method (all covariates were initially included, and then nonsignificant covariates were removed if the P value was >0.2). Statistical analysis was conducted using Stata version 16.1 (StataCorp, College Station, TX).

RESULTS

During the study period, a total of 702 infants with birth weight < 1,250 grams and gestational age [?]22 weeks were admitted to the NICU. Infants who died prior to an extubation attempt or had an unplanned extubation prior to their first elective extubation attempt were excluded from the analysis. One infant with missing outcome of successful extubation was excluded and twelve patients were excluded from the analysis as they were part of another study on extubation readiness—Automated Prediction of Extubation Readiness (clinicaltrials.gov NCT01909947). After excluding the infants as listed above, a total of 360 infants were

included in the study who received MV via an endotracheal tube and had an elective extubation attempt within the first 60 days of age. Among them, 268 (74%) were successful and 92 (26%) failed extubation.

Factors associated with successful extubation

Infants who failed extubation had a higher incidence of hemodynamically significant PDA at extubatio. These infants were also noted to have a lower gestational age, lower birth weight, higher RSS in first 6 hours of age, and higher incidence of histological chorioamnionitis. These infants also had a lower post-menstrual age, lower weight at extubation, higher receipt of nasal CPAP or non-invasive positive pressure ventilation (NIPPV) as post extubation respiratory support, lower pre-extubation pH, and higher pre-extubation Fio_2 **(Table 1)** .

On logistic regression analysis successful extubation was significantly associated with absence of hemodynamically significant PDA (Odds Ratio 0.32, 95% Confidence Interval 0.17-0.61) after adjusting for gestational age, age at extubation, sex, pH at extubation, Fio_2 at extubation and highest RSS in first 6 hours of age.

DISCUSSION:

In the current study, we noted a significant association between the presence of a hemodynamically significant PDA and extubation failure, which is in concurrence with previous studies [16, 17] that have reported a similar association.

We speculate that PDA may contribute to extubation failure due to pulmonary edema, leading to increased work of breathing. The PDA may become more hemodynamically significant after reduction of mean airway pressure applied to the lungs after extubation.

It is not known if proactively evaluating for PDA prior to extubation and its treatment would be associated with an improved likelihood of successful extubation. The data from the current study are hypothesis generating and may serve as a basis for future prospective observational and randomized controlled trials to evaluate the role of treatment for PDA prior to extubation to improve the cardiorespiratory outcomes of these infants.

There is no consensus on the definition of extubation success for premature infants. We defined extubation success as need for re intubation within five days of extubation as a significant proportion (25%) of infants might fail extubation beyond 48-72 hours of extubation. [13]

Current study had some limitations. As this was an observational study, we cannot establish a cause-and-effect relationship between presence of PDA and extubation failure. Endotracheal intubation, extubation and reintubation, were at the discretion of the primary clinical team. Strengths of the current study include inclusion of all eligible infants using well defined criteria with no selection bias. All infants were born in a single center that reduced the variability in clinical practice.

CONCLUSION

Among a recent cohort of extremely low birth weight infants, presence of hemodynamically significant PDA was significantly associated with failure of first elective extubation. Further investigations are needed to establish whether proactive screening for presence of PDA and treatment of the same prior to extubation, improves the chances of successful extubation and neonatal outcomes.

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Table 1: Clinical characteristics of patients with and without successful extubation

Variable[a]	**Successful (n=268)**	**Failure (n=92)**	**p-value**
Hemodynamically significant PDA: peri-extubation	67 (25%)	46 (50%)	<0.001
GA (wks)	27 (25-28)	26 (24-27)	<0.001
Birth Weight (gms)	920 (770-1090)	795 (690-914)	<0.001
Highest RSS in first 6 hours	3.60 (2.50-4.95)	3.80 (2.58-6.15)	0.045
Gender: Male	129 (48%)	47 (51%)	0.63
Histologic chorioamnionitis	124/253 (49%)	53/84 (63%)	0.03
Complete ANS Course	168/266 (63%)	59/91 (65%)	0.77
Vaginal delivery	84 (31%)	28 (30%)	0.87
Age at extubation (days)	3 (2-10)	4 (2-10)	0.21
PMA at extubation (wks)	28 (27-29)	27 (26-28)	<0.001
Weight at extubation (gms)	960 (800-1090)	815 (695-980)	<0.001
Post extubation respiratory support (NIPPV/NCPAP vs others[b])	186 (69%)	73 (80%)	0.047
Caffeine use prior to extubation	222 (83%)	83 (90%)	0.09
Pre-extubation VI	5.88 (4.34-7.74)	5.56 (4.43-8.00)	0.83
Pre-extubation Fio_2	23 (21-28)	25 (21-30)	0.001
Pre-extubation pH	7.36 (7.30-7.41)	7.34 (7.29-7.37)	0.004

PDA, patent ductus arteriosus, GA gestational age, RSS respiratory severity score, ANS antenatal steroids, PMA post menstrual age, NCPAP nasal continuous positive airway pressure, NIPPV nasal intermittent positive pressure ventilation, VI ventilation index, Fio2 fraction of inspired oxygen.

[a] Data are given as median (interquartile range) or n/N (%)

[b] Others include high-flow nasal cannula, nasal cannula, and room air