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ORIGINAL ARTICLE

Mortality among infants with evolving bronchopulmonary dysplasia increases with major surgery and with pulmonary hypertension

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OBJECTIVE: To assess whether mortality in patients with evolving bronchopulmonary dysplasia (BPD, defined as ⩾28 days of oxygen exposure with lung disease) is independently associated with pulmonary arterial hypertension (PAH) and surgery.
STUDY DESIGN: Single institution retrospective birth cohort of preterm infants with gestational age (GA) $23^{0/7}$ to $36^{6/7}$ weeks, and evolving BPD delivered between 2001 and 2014. Surgery was classified as minor or major using published criteria. Mortality was analyzed by stepwise logistic regression analysis.
RESULTS: Among 577 patients with evolving BPD, 33 (6%) died prior to discharge. Mortality decreased with GA (adjusted odds ratio (aOR): 0.69; 95% confidence interval (CI): 0.55, 0.87), birth weight *Z*-score (aOR: 0.69, 95% CI: 0.47, 0.996) and increased with PAH (aOR: 30, 95% CI: 2.1, 415), major surgery (aOR; 2.8, 95% CI: 1.3, 6.3), and PAH and surgery (aOR: 10.3, 95% CI: 2.5, 42.1).
CONCLUSION: Among preterm patients with evolving BPD, PAH and surgery are independently associated with mortality.

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) contributes to significant morbidity and mortality in preterm infants, impacting ~10 000–15 000 infants annually in the United States alone.[1] Pulmonary arterial hypertension (PAH), a cardiovascular complication of abnormal vascular growth, occurs in 25–38%[2–6] of preterm infants with BPD and is associated with a four- to fivefold increase in odds of mortality.[3,7]

There are relatively few studies describing outcomes in patients with PAH who undergo surgery. In adults undergoing major joint replacement surgery, PAH is associated with a fourfold increase in mortality.[8] For patients with PAH, there must be careful titration of anesthetic medications and maintenance of hemodynamic stability to prevent worsening of PAH in the perioperative period.[9–12] A referral pulmonary hypertension program reported that among pediatric patients undergoing non-cardiac surgical procedures, the odds of major perioperative complications increased by a factor of 8 in association with baseline suprasystemic PAH.[13]

Preterm infants are at increased risk of poor outcomes when major surgery is performed. Morriss *et al.* classified surgery into major surgery (presumed general anesthesia) and minor surgery (presumed non general anesthesia) in a cohort of very low birth weight infants in the National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network. They found increased adjusted odds of death or neurodevelopmental impairment in all surgery patients and in the subgroup of major surgery patients, but not in the subgroup of minor surgery.[14] However, a retrospective series of 22 infants with severe BPD undergoing anti-gastroesophageal reflux surgery in a single center described that all of the patients survived the procedure; 18 of these patients had PAH.[15]

Owing to the scarcity of data on mortality after surgery in preterm patients with BPD and PAH, we sought to assess whether mortality in patients with evolving BPD is independently associated with PAH and with surgery.

METHODS

Design

This was a retrospective birth cohort study of preterm infants with gestational age (GA) $23^{0/7}$ to $36^{6/7}$ weeks and evolving BPD (defined as ⩾28 days of oxygen exposure with lung disease) delivered between 1 May 2001 and 31 December 2014 at Parkland Memorial Hospital (PMH) in Dallas, TX, USA. We chose 1 May, 2001 as a starting date for this study, because 30 April, 2001 was our latest day of recruitment for the NICHD Preemie Inhaled Nitric Oxide Study, a trial that examined the effectiveness of inhaled nitric oxide as a therapy for severe respiratory failure in premature infants.[16] This trial increased awareness of PAH and utilization of inhaled nitric oxide as a treatment modality. The study was approved by the Institutional Review Board at University of Texas Southwestern Medical Center and a waiver of consent was granted.

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Study population

The study population included all preterm infants with gestational age (GA) $23^{0/7}$ to $36^{6/7}$ weeks and evolving BPD. Exclusion criteria were: critical congenital heart disease,[17] pulmonary vein stenosis diagnosed prior to the first surgery, severe congenital anomalies and persistent pulmonary hypertension (PPHN). Patients with patent ductus arteriosus (PDA), ventricular septal defect or atrial septal defect were not excluded from the study. Potential patients for this study were identified by searching the PMH prospective neonatal intensive care unit (NICU) database.

Classification

Infants were classified into three groups on the basis of surgery after 28 days: no surgery, minor surgery and major surgery, based on the most severe surgery, according to criteria published by Morriss *et al.*[14]

Presence of PAH was assessed after 28 days of life for patients who did not have surgery, or within a perioperative window of 1 month prior to or 2 weeks post surgery. To confirm the diagnosis of PAH, available echocardiograms or echocardiogram reports were reviewed by a pediatric cardiologist (CR), who was unaware of the clinical condition. Patients were classified as:

1) Confirmed PAH, based on one or more of the following:
   (a) Echocardiogram diagnosis based on the classification defined by Mourani *et al.*,[18] in which PAH is defined by any of the following: estimated right ventricular systolic pressure >40 mm Hg; ratio of right ventricular systolic pressure to systemic systolic blood pressure >0.5; any cardiac shunt with bidirectional or right-to-left flow; any degree of ventricular septal wall flattening;
   (b) Improvement of oxygen saturation by at least 30% with treatment (increased oxygen administration, inhaled nitric oxide, or vasodilators such as Sildenafil or Bosentan).

2) Comparison Group (without confirmed PAH):
   (a) Patients with clinical diagnosis or suspicion of PAH but not confirmed by echocardiogram or response to treatment as described above;
   (b) Patients with no documented clinical diagnosis or suspicion of PAH.

Variables

The primary outcome variable was death prior to discharge from the initial hospitalization, irrespective of whether the infant was discharged from PMH or from the adjacent referral children's hospital, Children's Medical Center Dallas.

Variables collected from the NICU database included: PAH, GA, birth weight, ethnicity, gender, 5-min Apgar score, administration of antenatal steroids before delivery, congestive heart failure, administration of indomethacin for PDA, administration of postnatal systemic steroids for treatment of BPD, culture proven sepsis, culture proven meningitis, necrotizing enterocolitis stage II or greater (NEC), seizures confirmed by electroencephalogram, type and dates of surgical interventions and congenital malformations.

Medical records were reviewed for all patients suspected of having PAH from the NICU database, to collect information on timing of diagnosis, to determine if temporal variables (that is, sepsis, meningitis, NEC, seizures) were present in the perioperative window described above, and to determine the type of anesthesia used for surgery. In addition, medical records were reviewed in all infants for whom malformation severity was not clearly defined.

Statistical analysis

The primary outcome was assessed by stepwise logistic regression to adjust for confounding variables that were present at 28 days. To avoid collinearity with GA, birth weight was converted to birth weight *Z*-score for GA and gender (using tables from Olsen *et al.*[19]). Other analyses included χ^2 analysis, Fisher's exact test, Student's *t*-test, Mann–Whitney test, and Cochran–Mantel–Haenszel test. We used SPSS version 23 (IBM Corporation) and considered two-tailed tests with *P*-values <0.05 as statistically significant.

Sample size analysis

Sample size was calculated based on 10% surgical mortality among preterm infants[20] and an estimated PAH-associated odds ratio (OR) of mortality of 4–5 compared with preterm infants without PAH.[3,7] We estimated that we would require a sample size of at 144 patients (assuming that 20% of the patients would have PAH), or 240 patients (assuming that 10% would have PAH), to have a two-sided alpha of 0.05 and 80% power to detect an OR of 5, and 214 and 350 patients, respectively, to detect an OR of 4.

On the basis of preliminary data from the NICU database, we estimated we would need to collect data over 10–15 years. For multivariate analysis we limited the number of variables in the final model to one per 10 patients who died before discharge; as 33 patients died, only three variables were included. Stepwise logistic regression was used to select the most significant variables among all variables that were present at 28 days. Interaction was tested using an additive model comparing patients with PAH who underwent major surgery, those without PAH who underwent surgery and those with PAH who did not undergo surgery with the controls, who had no PAH and did not undergo surgery.

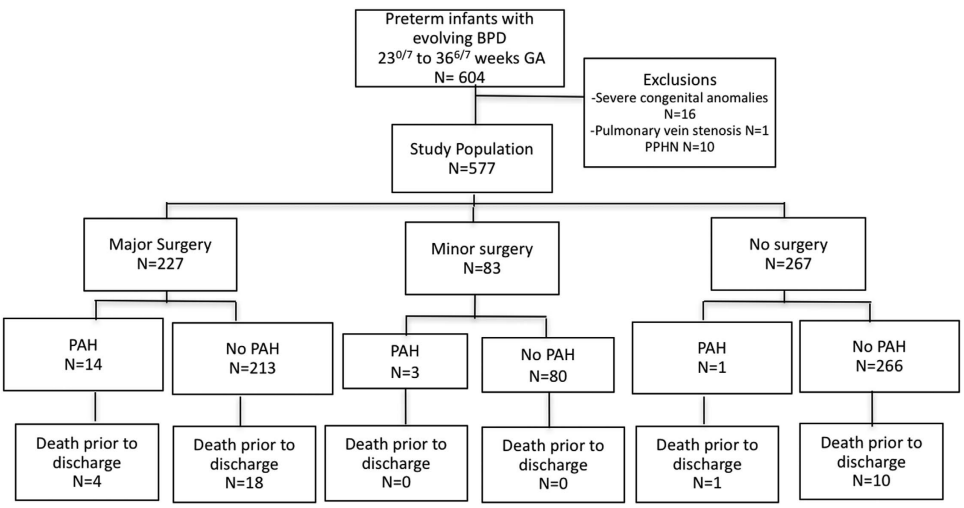

Figure 1. Flow diagram showing final classification and mortality. BPD, bronchopulmonary dysplasia; GA, gestational age; PAH, pulmonary arterial hypertension.

Table 1. Patient characteristics

	Confirmed PAH (n = *18*)	*Comparison group* (n = *559*)	P-*value*
Gestational age, weeks	27.3 ± 3.7	26.6 ± 2	0.39
Birth weight (g)	904 ± 397	922 ± 280	0.80
Birth weight *Z*-score	− 0.91 ± 0.81	− 0.15 ± 1.14	0.01
Small for gestational age	6 (35)	94 (17)	0.09
Ethnicity, % Hispanic	5 (28)	390 (70)	< 0.01
Sex, % male	8 (44)	242 (43)	0.92
5-min Apgar Score	6 (5, 8)	7 (6, 8)	0.26
Antenatal steroids (%)	7 (39)	276 (49)	0.38
Duration of mechanical ventilation (days)	106 ± 41	53 ± 30	< 0.01
Duration of continuous positive airway pressure (days)	35 ± 27	30 ± 18	0.26
Congestive heart failure (%)	1 (6)	15 (3)	0.40
Indomethacin for PDA (%)	5 (28)	284 (51)	0.05
Postnatal steroids for BPD (%)	11 (61)	108 (19)	< 0.01
Sepsis (%)	6 (33)	215 (39)	0.66
Meningitis (%)	0 (0)	16 (3)	1.00
NEC, Stage II+ (%)	1 (6)	64 (11)	0.71
Seizures (%)	1 (6)	16 (3)	0.42
Surgery (%)	16 (89)	229 (41)	< 0.01

Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus. Values are presented as mean ± s.d.; median (interquartile range) or number (%).

RESULTS

Patient characteristics

The NICU database identified 604 patients with evolving BPD (Figure 1). Twenty-seven patients were excluded: one with pulmonary vein stenosis prior to surgery, sixteen with severe congenital malformations and ten with PPHN. Thus, the study population included 577 preterm infants with evolving BPD, of whom 227 had major surgery, 83 had minor surgery and 267 had no surgery (Figure 1). Among 577 patients with evolving BPD, 33 (6%) died prior to discharge. Mortality was higher ($P < 0.05$) in those with major surgery (9.7%), but not in those with minor surgery (0%), in comparison with those who did not have surgery (4.1%). Therefore, we combined those with no surgery and those with minor surgery in further analyses. Supplementary Table 2 describes the frequency of surgical procedures in the population.

Table 1 shows the neonatal characteristics of BPD patients. Eighteen patients had confirmed PAH. Patients with confirmed PAH were less likely to be Hispanics, had lower birth weight *Z*-scores, and had longer duration of mechanical ventilation and higher frequency of postnatal steroids for BPD and of surgery than controls (Table 1). Confirmed PAH was more frequent in patients born at 33–36 weeks (2/9, 22%) than in those born at 23–28 weeks GA (13/481, 3%), and those born at 29–32 weeks (3/87, 3%) ($P < 0.05$). The majority (15/18) of patients were diagnosed using echocardiographic criteria, though three patients were diagnosed based on a significant response to PAH treatment. The result of the echocardiogram review was consistent with chart review for diagnosis of PAH, with the exception of one patient with whom there was subjective difference in interpretation of septal flattening, who was nonetheless treated clinically as PAH based on real time echocardiogram interpretation and therefore classified as confirmed PAH.

Among patients who underwent major surgery, mortality was 4/14 (29%) among those with PAH and 18/213 (8%) among those without PAH (Figure 1). Among those who had no surgery or minor surgery, mortality was 1/4 (25%) among those with PAH and 10/346 (3%) among those without PAH. Mortality decreased with gestational age (adjusted odds ratio (aOR): 0.69; 95% confidence interval (CI): 0.55, 0.87), birth weight *Z*-score (aOR: 0.69, 95% CI: 0.47, 0.996) and increased with PAH (aOR: 30, 95% CI: 2.1, 415), major surgery (aOR: 2.8, 95% CI: 1.3, 6.3) and both PAH and major surgery (aOR: 10.3, 95% CI: 2.5, 42.1).

DISCUSSION

The major finding of our study is that mortality in patients with evolving BPD, adjusted for GA and birth weight *Z*-score, is associated with PAH and with major surgery. We found no evidence for interaction between PAH and surgery. Mortality of patients undergoing minor surgery was not significantly different from those who did not undergo surgery.

Our results are consistent with several recent publications that demonstrate an increased mortality in association either with major surgery[14] or with PAH in this population.[2–4,7,21,22]

Strengths of our study include a birth cohort design; the use of a prospective, validated database; well-defined echocardiographic criteria for PAH, confirmed by study cardiologist for most patients and chart review in all those with PAH. The latter was essential to differentiate PPHN from PAH that develops with chronic lung disease; patients with PPHN were excluded from the study. As the pathogenesis of PPHN differs from that of PAH,[23] we felt that it was important to separate these two entities and focus specifically on PAH that develops with chronic lung disease.

Limitations of this study include retrospective design, single site study, small sample size and lack of a prospective protocol to diagnose PAH in BPD patients. Small sample size prevented adjustment for all possible confounding variables (including maternal pre-eclampsia, asthma or smoking and severity of BPD). It is possible that the difference in mortality between the PAH and comparison groups could be in part related to increased BPD severity in patients with PAH, suggested by the longer duration of mechanical ventilation and higher percentage of those who received systemic steroids for BPD. We were unable to classify BPD by severity because the study started in 2001, before implementation of the physiologic definition of BPD and of the NIH consensus definition of BPD. Our NICU has never used well-defined criteria for diagnosis of PAH, nor a systematic protocol of serial echocardiograms to detect PAH in patients with BPD. Application of strict echocardiographic criteria for PAH for this study was limited to interpretation of previously interpreted echocardiogram reports. When images were available, clarification was provided from a pediatric cardiologist (CR), however, the only

patients that were reviewed were those suspected of PAH from the NICU database; therefore, it is possible that we have missed patients with PAH or details about patients in the comparison group.

A recent report from the American Heart Association and American Thoracic Society recommends screening infants with established BPD for PAH as well as serial echocardiograms to monitor response to PAH-targeted therapy.[24] Both Nagiub *et al.*,[25] and Mourani *et al.*,[18] describe algorithms for diagnosing PAH non-invasively via echocardiograms that would be worthy of further study. Furthermore, the Mourani study[18] and a recent study by Bhat *et al.*,[21] prospectively studied PAH in preterm infants, yet neither of these studies address the common issue of surgery in this population.

We conclude that mortality in patients with evolving BPD, adjusted for GA and birth weight *Z*-score, is associated with PAH and with major surgery. Larger, prospective studies with a systematic protocol for serial echocardiograms and a rigorous definition of PAH are needed to further elucidate whether mortality among preterm infants with BPD is affected by an interaction between surgery and PAH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Lindsay DeVries: She wrote the first draft of the manuscript. She conceptualized and designed the study. She reviewed data from the database, medical records, participated in the interpretation of the data, critically reviewed, revised and approved the final manuscript. Roy J. Heyne: He conceptualized and designed the study. He participated in the interpretation of the data, critically reviewed and approved the final manuscript. Claudio Ramaciotti: He conceptualized and designed the study. He reviewed and interpreted echocardiograms using pre-specified criteria and echocardiogram readings for patients with unavailable echocardiograms, participated in the interpretation of the data, critically reviewed and approved the final manuscript. Steven Brown: He conceptualized and designed the study. He completed all statistical analyses, participated in the interpretation of the data and critically reviewed the manuscript. Mambarambath A. Jaleel: He conceptualized and designed the study. He participated in the interpretation of the data, critically reviewed and approved the final manuscript. Vishal Kapadia: He conceptualized and designed the study. He participated in the interpretation of the data, critically reviewed and approved the final manuscript. Patti J. Burchfield: She collected and entered data into the database and extracted the data for this study; she participated in the interpretation of the data, critically reviewed the manuscript and approved the final manuscript. Luc P Brion: He conceptualized and designed the study. He participated in the interpretation of the data, critically reviewed, revised and approved the final manuscript.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)