Research Article

ISSN 2689-1085

Journal of Pediatrics & Neonatology

Influence of Pulmonary Hypertension on Surgical PDA Ligation Outcomes in Preterm Neonates

Alexander Raskin MD[1*], Edward Kirkpatrick DO[1], Joanne M. Lagatta MD[2], Evelyn M Kuhn PhD[3] and Stephanie S. Handler MD[1]

[1]*Department of Pediatrics, Division of Pediatric Cardiology, Medical College of Wisconsin.*

[2]*Department of Pediatrics, Division of Neonatology, Medical College of Wisconsin.*

[3]*Business Intelligence and Data Warehousing, Children's Hospital of Wisconsin.*

[*]Correspondence:
Alexander Raskin, Department of Pediatrics, Division of Pediatric Cardiology, Medical College of Wisconsin.

Received: 14 May 2022; **Accepted:** 19 Jun 2022; **Published:** 24 Jun 2022

Citation: Raskin A, Kirkpatrick E, Lagatta JM, et al. Influence of Pulmonary Hypertension on Surgical PDA Ligation Outcomes in Preterm Neonates. J Pediatr Neonatal. 2022; 4(2): 1-6.

ABSTRACT

Background: *Pulmonary hypertension (PH) increases mortality in infants with bronchopulmonary dysplasia (BPD). As practice has shifted towards expectant management of patent ductus arteriosus (PDA), there is limited data guiding treatment with PH.*

Methods: *Retrospective single center cohort study of neonates <32 weeks gestation who underwent surgical PDA ligation before discharge. Ductal gradients by echocardiogram defined PH severity: severe PH as bidirectional/ right to left shunting, mild-to-moderate PH as greater than half-systemic pressure, no PH as less than half-systemic pressure. Primary outcome was mortality. Secondary outcomes were length of stay (LOS), duration of ventilation, post-operative inotropes, steroids, systemic pulmonary vasodilators, and incidence of BPD.*

Results: *Eighty patients, median gestational age 25 (23-31) weeks, underwent surgical PDA ligation between 2010-2016. Ten had severe PH, 54 mild-to-moderate PH, and 16 no PH. Severe PH group had significantly longer LOS, 173 vs. 143 days (p=.05). PH cohort had higher surgical weight, 1.71 kg vs. 1.06 kg (p=0.04). All deaths occurred in the PH group (6% vs. 0%), p=NS. No significant difference in ventilation, inotropes, steroids, pulmonary vasodilators, and BPD. Although, statistically insignificant, the PH group had higher rates of tracheostomies (18.8% vs. 6.25%).*

Conclusion: *Premature infants requiring PDA ligation with severe PH had longer overall LOS. All mortality occurred in the PH group. More data is needed to determine effect of PDA on lung disease and the development of PH.*

Keywords

Pulmonary hypertension, Patent ductus arteriosus, Neonates.

Introduction

Patent ductus arteriosus (PDA) is a common clinical finding in preterm neonates. The reported incidence of PDA is 20-60%, and it is inversely correlated with gestational age and birth weight [1]. The presence of PDA is associated with neonatal mortality and morbidity, such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular Hemorrhage (IVH), and retinopathy of prematurity (ROP) [2-5]. However, there is a lack of consensus on the management of PDA; clinical approaches are extremely variable depending on institutional and individual experiences [6]. Some investigations concluded that patient outcomes are not improved with treatment [7,8]. Furthermore, there is data suggesting increased adverse outcomes with both medical and surgical closure of PDA. The use of COX inhibitors for medical management is a risk factor for intestinal

perforation in very low birth weight infants, and surgical ligation has been associated with increased incidence of BPD [9].

As practice styles have shifted towards expectant management, persistence of PDA beyond three weeks has been shown to be associated with higher rates of BPD, NEC, ROP, longer length of hospital stay (LOS), and increased duration of mechanical ventilation [10]. Severity of BPD and duration of mechanical ventilation are independent risk factors for the development of Pulmonary Hypertension (PH), which affects up to 23% of premature infants [11,12]. Additionally, persistence of PDA by itself could contribute to the development of PH. Long standing left to right shunting across the PDA induces pulmonary vascular remodeling and increases pulmonary vascular resistance (PVR) [13]. It is less clear how the short-term presence of PDA affects the risk of chronic lung disease and development of PH. The development of PH significantly increases morbidity and mortality in BPD patients [14,15].

Despite PDA and PH being common amongst preterm neonates there is lack of literature assessing both of these factors together. The aim of this study was to investigate if clinical outcomes after PDA ligation were affected by the presence of PH.

Methods

We performed a retrospective single center cohort study. Inclusion criteria were neonates <32 weeks gestation who underwent surgical PDA ligation as part of their initial hospitalization between 2010-2016. Presence of PH was determined by preoperative echocardiographic ductal gradients. No PH was defined as predicted pulmonary artery pressure (PAP) less than half-systemic. Mild to moderate PH was categorized as PAP greater than half systemic and severe PH as suprasystemic PAP as evident by right to left or bidirectional ductal shunting. Variables that were included for analysis were gestational age, sex, birth weight, surgical weight, hospitalization length of stay (LOS), BPD severity, use of systemic steroids, systemic pulmonary vasodilators post operatively, tracheostomy at discharge, and mortality. Post-operative duration inotropes and mechanical ventilation were also included in the analysis. The PH and no PH groups were compared. A subanalysis was performed between the suprasystemic PH group vs. all other patients. Univariate analyses were done using Mann-Whitney-U tests for continuous variables and Fisher's exact tests for descriptive variables. All statistical analyses were done using SPSS Version 21.0 (Chicago, IL). A p-value of less than 0.05 was considered statistically significant.

Results

Eighty patients underwent surgical PDA ligation between 2010-2016. The median gestational age was 25 weeks (23-31 weeks). Of those, 10 had bidirectional PDA shunting and were classified as severe PH. An additional 54 patients were categorized as mild to moderate PH, and 16 had no PH (Figure 1).

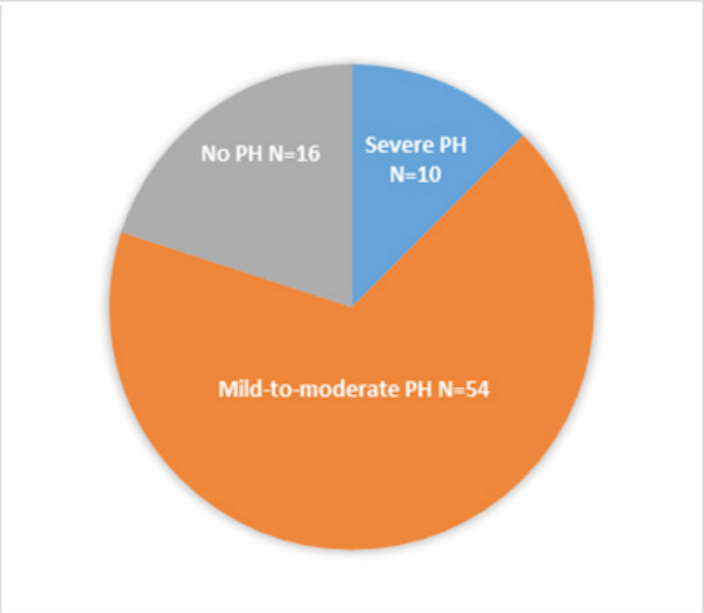

Figure 1: Patient Breakdown.

Table 1: Pulmonary Hypertension vs. No Pulmonary Hypertension.

	PH (N=64)	No PH (N=16)	
Sex Male Female	 33 (51.6%) 31 (48.4%)	 6 (37.5%) 10 (62.5%)	p=0.4
Gestational Age (weeks)	25.1 (23-31)	24.4 (23-26)	p=0.25
Birth Weight (kg) Mean Median	 0.74 (0.38-1.58) 0.68	 0.68 (0.48-1.14) 0.64	p=0.41
Surgical Age (days) Mean Median	 55.3 (10-233) 32	 34.5 (12-90) 32	p=0.4
Surgical Weight (kg) Mean Median	 1.71 (0.55-6.45) 1.11	 1.06 (0.58-2.07) 0.97	p=0.04*
Length of Stay (days)	151	130	p=0.58
Systemic Steroids	43 (67%)	13 (81%)	p=0.37
Inotropes Post OP (days)	2	1.1	p=0.28
Vent Days Post OP	16.9	20.3	p=0.61
Tracheostomy Discharge	12 (18.8%)	1 (6.25%)	p=0.45
Systemic Pulmonary Vasodilators Post OP	12 (18.8%)	0 (0%)	p=0.06
Mortality	4 (6%)	0 (0%)	p=0.3
BPD	Mild 7 Moderate-Severe 57	Mild 2 Moderate-Severe 16	p=0.86

For the first analysis, the PH group was compared against the no PH cohort (Table 1). There was a total of 64 patients in the PH group (severe PH + mild to moderate PH). The PH group was made up of 33 (51.6%) males and 31 (48.4%) females, and the no PH group consisted of 6 (37.6%) males and 10 (62.5%) females, p=0.4. There were no significant differences in gestational age between the 2 groups, 25.1 (23-31) weeks for PH and 24.4 (23-26) for no PH, p=0.25. There were no significant differences between

groups for birth weight, with median weight of 0.68 (0.38-1.58) kg for PH and 0.64 (0.48-1.14) kg for no PH, p=0.41. The median surgical age for both groups was 32 days, with a wider set of distribution for the PH group (10-233 days) vs. the no PH group (12-90 days), p=0.4. The surgical weight was significantly larger in the PH group, p=0.04 (Figure 2). The median surgical weight in the PH group was 1.11 (0.55-6.45) kg vs. 0.97 (0.58-2.07) in the no PH group. There was no significant difference in hospitalization LOS between groups (151 days in PH vs. 130 days in no PH), p=0.58. Utilization of systemic steroids was not significantly different between groups, p=0.37. PH patients required inotropes for 2 days postoperatively vs 1.1 days in the no PH group, p=0.28. On average, the PH group remained on a ventilator for 16.9 days postoperatively compared to the no PH group at 20.3 days, p=0.61. Patients in the PH group had a higher rate of tracheostomies at discharge 12 (18.8%) in contrast to 1 (6.25%), but this did not meet statistical significance, p=0.45 (Figure 3). The use of systemic pulmonary vasodilators approached statistical significance with 12 (18.8%) patients in the PH cohort and 0 (0%) in no PH, p=0.06. There was no difference in BPD severity between groups, p=0.86. Mortality was seen only in the PH group with 4 (6%) patients, p=0.30 (Figure 4).

A sub analysis was performed comparing the severe PH (10 patients) against all other patients (70 patients no PH + mild-moderate PH) (Table 2). The severe PH group was comprised of 8 (80%) males

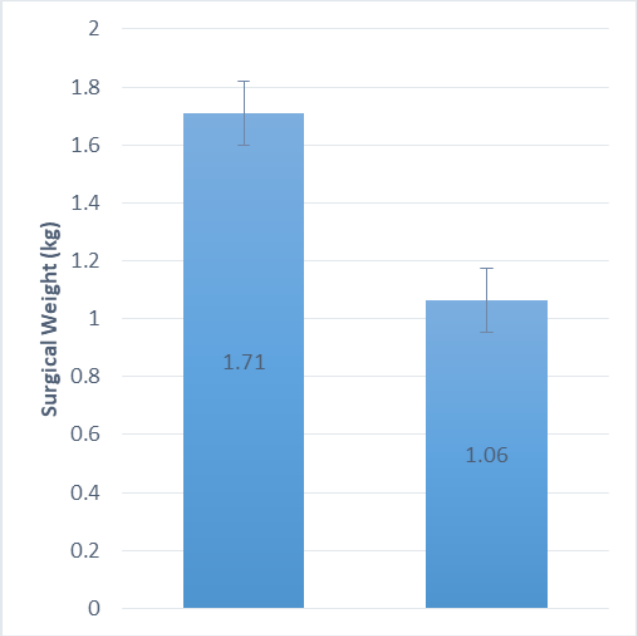

Figure 2: Surgical Weight.

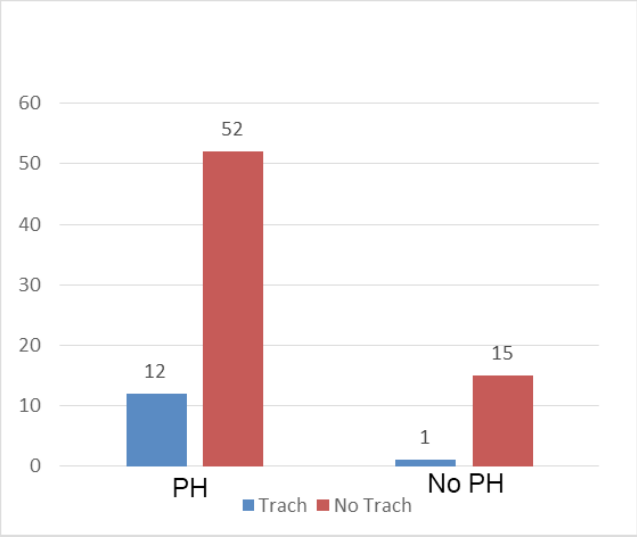

Figure 3: Tracheostomy at Discharge

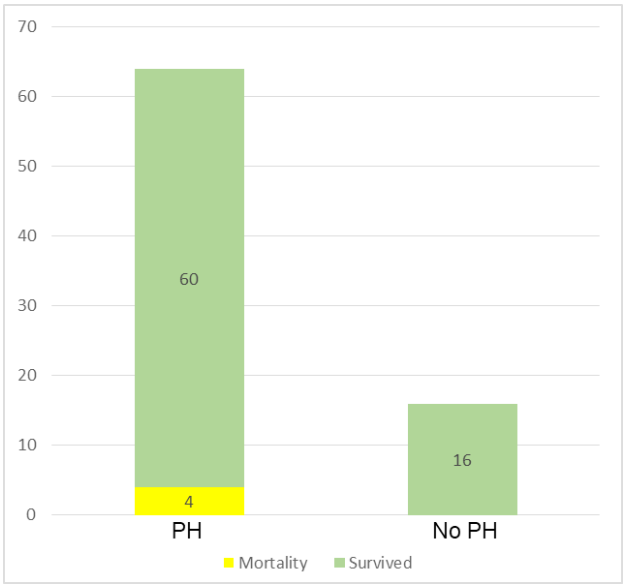

Figure 4: Mortality.

Table 2: Severe PH vs. All other patients.

	Severe PH (N=10)	No PH + Mild to Mod PH (N=70)	
Sex Male Female	 8 (80%) 2 (20%)	 31 (44%) 39 (56%)	p=0.05
Gestational Age (weeks)	25.1 (23-31)	25 (23-31)	p=0.81
Birth Weight (kg) Mean Median	 0.70 (0.4-1.26) 0.68	 0.73 (0.38-1.58) 0.66	p=0.69
Surgical Age (days) Mean Median	 59.5 (10-171) 53	 49.9 (10-233) 30	p=0.26
Surgical Weight (kg) Mean Median	 1.77 (0.74-4.58) 1.26	 1.55 (0.55-6.45) 1.08	p=0.29
Length of Stay (days)	173	143	p=0.049*
Systemic Steroids	7 (70%)	49 (70%)	p=1
Inotropes Post OP (days)	1.3	1.9	p=0.58
Vent Days Post OP	20.1	17.3	p=0.5
Tracheostomy Discharge	2 (20%)	11 (16%)	p=0.66
Systemic Pulmonary Vasodilators Post OP	3 (30%)	9 (13%)	p=0.17
Mortality	1 (10%)	3 (4%)	p=0.42
BPD	Mild 1 Moderate-Severe 9	Mild 8 Moderate-Severe 62	P=0.89

and 2 (20%) females; the other group consisted of 31 (44%) males and 39 (56%) females, p=0.05. The gestational age between the two groups was equivocal at 25.1 weeks (severe PH) and 25 weeks (all others), p=0.81. There was no significant difference in birth weight between the two groups, p=0.69. The median birth weight in the severe PH group was 0.68 (0.4-1.26) kg, and for all other patients the birth weight was 0.66 (0.38-1.58) kg. Patients with severe PH were older at time of surgery, median 53 (10-171) days, in comparison to all other patients, 30 (10-233) days, but this was not statistically significant, p=0.26. Severe PH patients had larger median surgical weight at 1.26 (0.74-4.58) kg vs. 1.08 (0.55-6.45) kg, p=0.29. The severe PH group had significantly longer hospitalization LOS at 173 days in comparison to 143 days for all other patients, p=0.05. Both groups utilized systemic steroids in 70% of the patients, p=1. There was no difference in the average utilization of inotropes (1.3 vs 1.9 days post operatively), p=0.58. Patients with severe PH required mechanical ventilation for 20.1 days post operatively, and the remaining patients remained on a ventilator for 17.3 days on average, p=0.5. Both groups had similar rates of tracheostomies at discharge, 2 (20%) for severe PH vs. 11 (16%), p=0.66. There was no significant difference in systemic pulmonary vasodilator use and BPD severity between the two groups, p=0.17 and p=0.89, respectively. The severe PH group had 1 (10%) mortality vs. 3 (4%), p=0.42.

Discussion

Previous work has demonstrated that right to left shunting across the PDA has been associated with increased mortality in preterm neonates [16]. In our cohort, mortality was not significantly increased after PDA ligation in the severe PH group, which was defined as presence of right to left or bidirectional shunting. However, it is clinically pertinent to highlight that all observed mortality occurred only in patients with PH. Another clinically relevant point is that the rate of tracheostomies was higher in the PH group, even though this did not meet statistical significance. It is unclear what the underlying driver for these differences is. Patients with PH were noted to have significantly larger surgical weights. This may suggest that delaying PDA closure until patients are larger may potentiate worsening lung disease, development of pulmonary hypertension, and increased morbidity. This theory is corroborated by Saldeño's data that associated persistence of PDA beyond three weeks with increased morbidity [10]. Conversely, later PDA ligation in PH patients maybe a reflection of their underlying clinical status. Worse lung disease may delay the timing of PDA ligation, contribute to the development of PH, and lead to increased LOS. Other factors that may have delayed PDA ligation and prolonged hospitalization, such as NEC and ROP, were not assessed in this study, but should be looked at in future investigations.

One of the limitations of this study was that echocardiography was used to establish the diagnosis PH. Echocardiography is the noninvasive screening tool of choice that provides estimated right ventricular and pulmonary artery pressures. However, a large unrestrictive PDA creates systemic right sided pressures without necessarily affecting PVR. Elevated PVR is the true hallmark of PH. Cardiac catheterization is required to confirm the diagnosis by direct hemodynamic measurement and calculation of PVR. Additionally, responsiveness to pulmonary vasodilators prior to initiation of treatment can be assessed during catheterization [17]. Bidirectional shunting or right to left shunting can only occur with elevated PVR, which is the reason these patients in our study were defined as severe PH. However, for patients with a large PDA and purely left to right, our study may have overestimated the incidence of PH. We advocate that patient with bidirectional shunting, RV dysfunction or other evidence of severe PH undergo catheterization to help with risk stratification. If PH is confirmed, effective pulmonary vasoactive therapy should be initiated prior to undergoing PDA closure. Niu and colleagues utilized a staged approach involving catheterization with balloon test occlusion to determine safety of ductal closure [18]. Additionally, advances in techniques and devices have allowed for safe and effective percutaneous PDA closure in premature neonates under 2 kg and feasible results attainable in children as small as 1200 grams [19-20]. This may mitigate some of the risks and adverse outcomes associated with surgical ductal ligation. Alternative treatment modalities such as medical management with acetaminophen has been shown to be safe and effective [21]. Both acetaminophen and percutaneous device closure should be further investigated to help determine if early PDA closure in preterm neonates reduces the risk of developing PH and improves long-term outcomes.

This study was limited by several factors. This was a retrospective study and therefore is susceptible to selection bias. Additionally, the relatively low sample sizes limited the power of this study. It is possible that with a larger sample size differences that are more significant will have been noted. Catheterization data confirming the diagnosis of PH was lacking. Relying on echocardiography may have overestimated the incidence PH. Data analyzing additional comorbidities such as NEC and ROP was not performed for this study.

Conclusion

Preterm infants with severe PH that underwent surgical PDA ligation had longer hospitalization LOS. Patients with PH were significantly larger at the time of surgery. All mortality occurred in the PH group. Although, statistically not significant, there were higher rates of tracheostomies at discharge in the PH group. Underlying lung disease may contribute to PH development and longer LOS. More data is needed to determine effect of PDA on lung disease and the development of PH.

References

1. Dice JE, Bhatia J. Patent ductus arteriosus: an overview. J Pediatr Pharmacol Ther. 2007; 12: 138-146.
2. Mitra S, Florez ID, Tamayo ME, et al. Effectiveness and safety of treatments used for the management of patent ductus arteriosus (PDA) in preterm infants: a protocol for a systematic review and network meta-analysis. BMJ Open. 2016; 6: 011271.
3. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr. 2005; 40: 184-188.
4. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr. 1979; 95: 865-866.
5. Lipman B, Serwer GA, Brazy JE. Abnormal cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatrics. 1982; 69: 778-781.
6. Ngo S, Profit J, Gould JB, et al. Trends in patent ductus arteriosus diagnosis and Management for Very low Birth Weight Infants. Pediatrics. 2017; 139: 20162390.
7. William E. Benitz. COMMITTEE ON FETUS AND NEWBORN. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016l; 137: 20153730
8. Chock VY, Punn R, Oza A, et al. Predictors of bronchopulmonary dysplasia or death in premature infants with a patent ductus arteriosus. Pediatr Res. 2013; 75: 570-575.
9. Abdel-Hady H, Nasef N, Shabaan AE, et al. Patent ductus arteriosus in preterm infants: do we have the right answers?. Biomed Res Int. 2013; 2013: 676192.
10. Saldeño YP, Favareto V, Mirpuri J. Prolonged persistent patent ductus arteriosus: potential perdurable anomalies in premature infants. J Perinatol. 2012; 32: 953-958.
11. Nagiub M, Kanaan U, Simon D, et al. Risk factors for

development of pulmonary hypertension in infants with bronchopulmonary dysplasia: systematic review and meta-analysis. Paediatr Respir Rev. 2017; 23: 27-32.

12. Vyas-Read S, Kanaan U, Shankar P, et al. Early characteristics of infants with pulmonary hypertension in a referral neonatal intensive care unit. BMC Pediatr. 2017; 17: 163.
13. Frank DB, Hanna BD. Pulmonary arterial hypertension associated with congenital heart disease and Eisenmenger syndrome: current practice in pediatrics. Minerva Pediatr. 2015; 67: 169-185.
14. Kim GB. Pulmonary hypertension in infants with bronchopulmonary dysplasia. Korean J Pediatr. 2010; 53: 688-693.
15. Baker CD, Abman SH, Mourani PM. Pulmonary Hypertension in Preterm Infants with Bronchopulmonary Dysplasia. Pediatr Allergy Immunol Pulmonol. 2014; 27: 8-16.
16. Bapat R, Aggarwal S, Natarajan G. A right-to-left or bidirectional ductal shunt in preterm neonates: grave implication. Am J Perinatol. 2011; 28: 709-714.
17. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015; 132: 2037-2099.
18. Niu MC, Mallory GB, Justino H, et al. Treatment of severe pulmonary hypertension in the setting of the large patent ductus arteriosus. Pediatrics. 2013; 131: 1643-1649.
19. Narin N, Pamukçu Ö, Baykan A, et al. Transcatheter closure of PDA in premature babies less than 2 kg. Anatol J Cardiol. 2016; 17: 147-153.
20. Morville P, Douchin S, Bouvaist H, et al. Transcatheter occlusion of the patent ductus arteriosus in premature infants weighing less than 1200 g. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2018; 103: 198-201.
21. Luecke CM, Liviskie CJ, Zeller BN, et al. Acetaminophen for Patent Ductus Arteriosus in Extremely Low-Birth-Weight Neonates. J Pediatr Pharmacol Ther. 2017; 22: 461-466.