Original Article

Targeted neonatal echocardiography for patent ductus arteriosus in neonates reduces the surgical ligation rate without affecting healthcare outcomes

Krishan Yadav[1], Audrey Hebert[2], Karen Lavie-Nevo[3], Mimi T. Y. Kuan[1]^, Michael Castaldo[1]^, Horacio Osiovich[1], Martin Hosking[1], Joseph Y. Ting[1,4]^

[1]Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada; [2]Department of Pediatrics, Laval University, Quebec City, QC, Canada; [3]Department of Pediatrics, Lady Davies Carmel Medical Center, Haifa, Israel; [4]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

Contributions: (I) Conception and design: K Yadav, A Hebert, K Lavie-Nevo, JY Ting; (II) Administrative support: MTY Kuan, JY Ting; (III) Provision of study materials or patients: K Yadav, MTY Kuan, JY Ting; (IV) Collection and assembly of data: K Yadav, A Hebert, K Lavie-Nevo, MTY Kuan; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Joseph Y. Ting. Department of Pediatrics, University of Alberta, 3-469 Edmonton Clinic Health Academy, 11405-87 Ave. NW Edmonton, AB T6G 1C9, Canada. Email: joseph.ting@ualberta.ca.

Background: Surgical ligation of patent ductus arteriosus (PDA) can be associated with long-term morbidity and adverse outcomes in neonates. Targeted neonatal echocardiography (TNE) has been increasingly used to improve the hemodynamic management. We aimed to evaluate the preoperative assessment impacts of the hemodynamic significance of PDA using TNE on PDA ligation rates and neonatal outcomes.

Methods: This observational study included preterm infants who underwent PDA ligation during two epochs (Epoch I: January 2013 to December 2014; Epoch II: January 2015 to June 2016). During Epoch II, a comprehensive TNE assessment was performed preoperatively to evaluate the hemodynamic significance of PDA. Primary outcome was the incidence of PDA ligation. Secondary outcomes included the incidence of postoperative cardiorespiratory instabilities, individual morbidities, and the composite outcome of death.

Results: A total of 69 neonates underwent PDA ligation. No difference in baseline demographics was found between the epochs. The incidence of PDA ligation in very low birth weight (VLBW) infants was lower during Epoch II than Epoch I [7.5% *vs.* 14.6%, rate ratio =0.51 (95% confidence interval =0.30–0.88)]. No differences were observed between epochs in the proportion of VLBW infants who developed post-operative hypotension or oxygenation failure. The composite outcome of death or major morbidity did not significantly differ between Epoch I and Epoch II (91.1% *vs.* 94.1%, P=1.000).

Conclusions: Incorporating TNE into a standardized hemodynamic assessment program, we demonstrated a 49% reduction in PDA ligation rate without any increase in postoperative cardiopulmonary instability or short-term neonatal morbidities in a cohort of VLBW infants.

Keywords: Ligation; neonatology; patent ductus arteriosus (PDA); echocardiography

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^ ORCID: Mimi T. Y. Kuan, 0000-0002-4751-6579; Michael Castaldo, 0000-0002-6736-6918; Joseph Y. Ting, 0000-0002-5246-8823.

Introduction

Patent ductus arteriosus (PDA) is a frequent complication among preterm infants in the neonatal intensive care unit (NICU). The incidence of PDA is inversely related to the infants gestational age, varying from 20% in infants born at 32 weeks to approximately 60% for those born at <28 weeks of gestation (1,2). Although pharmacological treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen is currently considered the first-line treatment option for the PDA, there is a lack of consensus regarding the definition of hemodynamically significant PDA and a standard therapeutic approach (3,4). Debate over the relationship between PDA and various neonatal morbidities has led to a more conservative approach to PDA treatment (5-7). Surgical ligation of the PDA is generally considered for infants in whom medical therapy has either failed or is contraindicated. This trend towards a more permissive, conservative approach may be partially related to fear regarding cardiovascular complications during surgery, immediate postsurgical period, and the impact of ligation on neurosensory outcomes (8-10). Different anesthetic agents and techniques may cause respiratory and metabolic derangements and affect perioperative outcomes (11). Physiological instability after ligation and the development of post-ligation cardiac syndrome (PLCS) occurs in 28–45% of patients, which is associated with a clinically significant increase in the fractional oxygen requirement (FiO_2), mean airway pressure (MAP), and use of vasopressors (12-16).

Highlight box

Key findings

- Incorporating comprehensive TNE-based triaging process to assess the hemodynamic significance of PDA reduced the incidence of PDA ligation without affecting the short-term outcomes in very low birth weight infants.

What is known and what is new?

- While pharmacological treatment is considered the first-line treatment option for PDA, there is a lack of consensus regarding the definition of hemodynamically significant PDA and a standard therapeutic approach.
- Combining clinical parameters and comprehensive TNE assessment of hemodynamic significant PDA to identify infants who need surgical treatment of PDA closure.

What is the implication, and what should change now?

- The TNE service led to improvement in hemodynamic evaluation and decision making. The reduced incidence of PDA ligation did not affect short-term outcomes of these infants.

Among preterm infants who needed surgical treatment of the PDA, recent literature indicates an increase in mortality and long-term morbidities, such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and neurodevelopmental impairment (NDI) at 2 years of age (17-20). Owing to both immediate postoperative complications and various neonatal morbidities related to surgical treatment, clinical and echocardiography-based patient selection criteria are imperative to identify infants who need surgical treatment for PDA closure to improve PDA-related neonatal outcomes.

The impact of echocardiography performed by trained neonatologists in the NICU has been well described (21,22). The targeted neonatal echocardiography (TNE) service led to improvement in the hemodynamic evaluation and decision making in neonatal intensive care (23). In 2015, TNE was incorporated as part of a comprehensive scheme to assess the hemodynamic significance of PDA in our unit. This information aided decision-making for medical treatment and ligation in the NICU at the British Columbia Women's Hospital, which has one of the highest ligation rates across Canada. This study aimed to determine the impact of the TNE-based triaging system on the rates of the PDA ligation and the associated perioperative complications. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-147/rc).

Methods

Study design and patients

This was an observational study conducted at the BC Women's and Children's Health Centre, a quaternary referral NICU, between January 2013 and December 2014 (retrospective) and from January 2015 to June 2016 (prospective). Population-based data of the total number of very low birth weight (VLBW) infants born at <34 weeks of gestation, including inborn and outborn, were obtained from the local neonatal database. All VLBW infants without any major congenital malformations or cardiac anomalies, except for PDA or patent foramen ovale, who were admitted to our NICU were enrolled in the study (*Figure 1*). A retrospective chart review was performed for all infants who underwent PDA ligation during Epoch I (January 2013 to December 2014), whereas prospective data were collected during Epoch II (January 2015 to June 2016). A dedicated comprehensive TNE program was

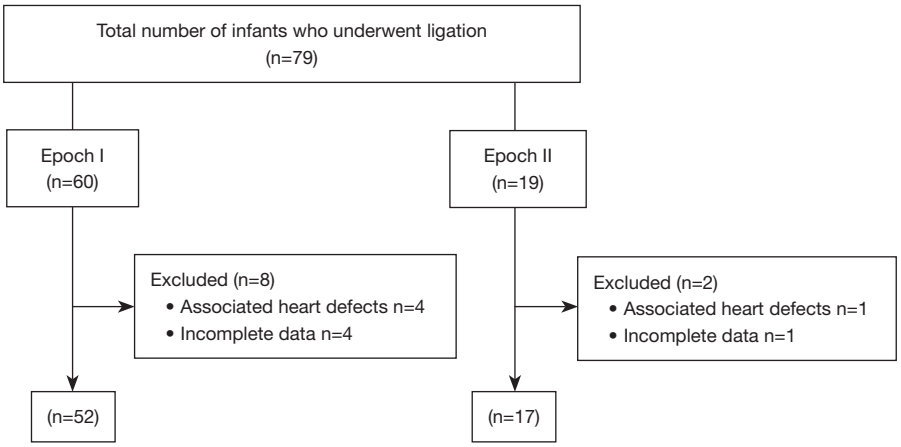

Figure 1 Flow diagram of patient enrollment in the study.

introduced to preoperatively assess the PDA's hemodynamic significance and to triage patients for ligation starting in January 2015. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the University of British Columbia Children and Women's Research Ethics Board (No. H15-01343) and individual consent for this study was waived as data were already being collected for standard clinical care purposes (secondary use of data).

Demographic and clinical parameters

Demographic and clinical data were collected preoperatively and at 24 hours post-PDA ligation. Data on neonatal demographics (gestational age at birth, birth weight, small for gestational age, sex, inborn *vs.* outborn, Apgar score at 5 min (24), and score for neonatal acute physiology II >20) (25,26), medical treatment for the PDA (indomethacin prophylaxis, use of NSAIDs or acetaminophen), and perioperative neonatal characteristics [age, gestational age and weight at surgery, perioperative high-frequency ventilation (HFV), FiO_2 requirement, MAP, inotrope use, ductal diameter, and doppler flow velocity across the PDA] were collected.

Postoperatively, data related to cardiopulmonary status (use of fluid bolus/steroid/inotrope for <24 hours, PLCS, and oxygenation failure) and major determinants of neonatal outcomes [mortality, intraventricular hemorrhage (IVH) of ≥ grade III, necrotizing enterocolitis (NEC) of ≥ stage II, ROP of ≥ stage III, and BPD] were obtained. Small for gestational age was defined as a weight below the 10th percentile for gestational age at birth. Grade III or IV IVH was defined according to the classification system reported by Papile *et al.* (27). NEC was diagnosed according to the modified Bell's staging criteria (28). BPD was defined as oxygen use at 36 weeks' corrected gestational age with oxygen use on the 28th day after birth. Severe ROP is defined as stage ≥3 according to the international classification of ROP (29).

Oxygenation failure was defined as an absolute increase of ≥20% in the MAP or FiO_2 compared to the preoperative value, for a minimum of 1 hour within the 24-hour post-ligation period. Ventilation failure was defined as the need for rescue high frequency ventilation due to the inability of conventional settings to maintain adequate ventilation support or a 20% increase in amplitude or peak inspiratory pressure of the pre-operative value as needed, for a minimum of 1 hour within the 24-hour post-ligation period. Post ligation cardiac syndrome was considered if the infant developed both oxygenation failure and systemic hypotension (SH), which was defined as blood pressure (systolic, diastolic, or mean values) below the third percentile expected for the gestational age that persisted for ≥1 hour within the 24-hour post-ligation period or for a shorter period if corrective intervention was provided. The hemodynamic significance of the PDA during Epoch II was determined preoperatively by the standard criteria using both clinical characteristics and echocardiographic parameters (*Table 1*).

PDA ligation triaging

Epoch I

One of the neonatologists from either our NICU or the

Table 1 Baseline demographic and perioperative neonatal characteristics and medical treatment

	Epoch I	Epoch II	P value
Demographic characteristics			
Gestational age (weeks)	25 [24, 26]	26 [24, 27]	0.344
Birth weight (grams)	822 [661, 941]	735 [611, 870]	0.411
Sex (male)	32/52 (61.5%)	11/17 (64.7%)	1.000
Inborn	27/50 (54.0%)	11/17 (64.7%)	0.627
Small-for-gestational age	5/52 (9.6%)	4/17 (23.5%)	0.209
5-minute Apgar score	7 [6, 8]	6 [5, 8]	0.542
SNAP II score >20	21/52 (40.4%)	8/17 (47.1%)	0.841
Medical treatment for PDA			
Indomethacin prophylaxis	10/52 (19.2%)	7/17 (41.2%)	0.134
Use of acetaminophen	1/50 (2.0%)	3/17 (17.6%)	0.047
PDA without medical treatment	9/50 (18.0%)	5/17 (29.4%)	0.322
Use of more than one treatment course	12/52 (23.1%)	5/17 (29.4%)	0.747
Perioperative neonatal characteristics			
Age at surgery (days)	26 [0.5, 33]	26 [17, 30]	0.535
Gestational age at surgery (weeks)	28 [27, 30]	29 [28, 31]	0.364
Body weight at surgery (grams)	1,098 [860, 1,315]	992 [802, 1,160]	0.377
Pre-operative HFV use	28/52 (53.8%)	11/17 (64.7%)	0.615
Pre-operative inotrope use	19/52 (36.5%)	8/17 (47.1%)	0.569
Pre-operative MAP (cmH_2O)	11 [10, 13]	11 [10.5, 12]	0.779
Pre-operative FiO_2 (FiO_2)	0.28 [0.25, 0.35]	0.35 [0.26, 0.44]	0.060
Pre-operative PDA size (mm)	2.3 [2.0, 3.0]	2.5 [2.1, 2.5]	0.959
Pre-operative ductal velocity (m/s)	2.1 [1.6, 2.4]	2.0 [1.2, 2.6]	0.901

Data are presented as median [interquartile range] or as a proportion of the total (%). SNAP, the score for neonatal acute physiology; PDA, patent ductus arteriosus; HFV, high-frequency ventilation; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen.

referral centre referred infants with a persistent PDA for surgical ligation. Echocardiography assessment and final pediatric cardiologist evaluation were performed. There were no predefined criteria for adjudication of hemodynamic significance of the PDA for ligation or standardization of the referral process. The postoperative care was at the discretion of the attending neonatologist. The data were collected retrospectively from patients who underwent PDA ligation.

Pre-operative assessment in Epoch II

A dedicated TNE program was introduced to improve clinical decision-making by assessing various echocardiographic parameters (evidence of pulmonary over-circulation and systemic hypoperfusion related to the PDA) and clinical parameters (evidence of pulmonary congestion, cardiomegaly and features suggestive of systemic hypoperfusion) based on published criteria (22,30). All infants diagnosed with presumed hemodynamically significant PDA were referred to the TNE team for further assessment. After excluding congenital heart diseases, TNE was performed by one neonatologist trained in neonatal hemodynamics, and the decision to perform the PDA ligation in these neonates was made based on clinical and echocardiographic criteria for hemodynamically significant patent ductus arteriosus (hsPDA). Studies were performed

using the Vivid I or E9 cardiovascular ultrasound system (GE Medical Systems, Milwaukee, Wisconsin, USA) with a 6- or 12-MHz high-frequency phased-array transducer probe. Standard two-dimensional, M-mode, color Doppler, pulse-wave Doppler, and continuous-wave Doppler images were obtained for transthoracic echocardiographic analysis. Left ventricular fractional shortening (LVFS) and left ventricular output (LVO) were used as surrogate markers of left ventricular (LV) systolic function. The aortic root annulus diameter was obtained from the standard parasternal long-axis view, and the aortic cross-sectional area was calculated as follows: $\pi \times (\text{aortic annulus diameter}/2)^2$. An apical 5-chamber view was used to visualize the left ventricular outflow tract. By applying a pulse-wave Doppler and positioning the 2-mm sample volume on the LV side of the aortic valve, the velocity curve was obtained, and the velocity-time integral (VTI) was traced. LVO was calculated as follows: (VTI × heart rate × aortic cross-sectional area) indexed to body weight. The other measurements were obtained as per a previous study (30). The isovolumic relaxation time (IVRT), the time interval between aortic valve closure and mitral valve opening, and the ratio of early-to-late-ventricular-filling velocities (E/A) ratio were obtained to assess diastolic dysfunction. The E/A ratio was measured by positioning a pulse-wave Doppler with a 2-mm sample volume across the mitral valve to measure the velocities across the valve in an apical 4-chamber view. The probe was then angulated anteriorly. Again, using pulsed Doppler, a 2-mm sample volume was positioned midway between the aortic and mitral valves to obtain a clear signal showing both the aortic outflow and the mitral inflow to obtain IVRT.

Post-operative care in Epoch II

A comprehensive targeted echocardiography study was performed by a TNE-trained neonatologist 1-hour post-surgery to assess myocardial performance and ventricular output. Infants who had a LVO of <200 mL/kg/min received an IV of milrinone (0.33 mcg/kg/min) after the initiation of normal saline bolus at 10 mL/kg. Milrinone was discontinued 24 hours later. To exclude postoperative pneumothorax, chylothorax, and lung hyperinflation secondary to altered lung compliance, a chest radiograph was performed for all patients within one hour postoperatively.

Management of hypotension

An infant was considered hypotensive if one of the systolic, diastolic, or mean blood pressure was less than the third percentile for corrected gestational age. The standard of care at our center is to give a fluid bolus for volume replacement and at least 1 inotropic agent (e.g., dopamine or dobutamine) at the discretion of the attending neonatologist before considering hydrocortisone treatment. Prophylactic hydrocortisone was not recommended.

Outcome measurements

The following healthcare outcome measurements were included at 24 h post-surgery: SH, oxygenation failure, ventilation failure, and post ligation cardiac syndrome. The primary outcome was the incidence of PDA ligation. The secondary outcomes were the incidence of postoperative cardiorespiratory instabilities, composite outcomes of death or major morbidity, and individual components of morbidity (IVH, NEC, ROP, and BPD).

Statistical analyses

Descriptive statistics [frequencies (%), mean ± SD, or median (interquartile range, IQR)] were used to characterize the demographics, echocardiographic parameters, and perioperative outcomes of infants undergoing medical therapy or surgical ligation of the PDA during the study period. Distributions of continuous variables were assessed visually. Between-epoch differences were assessed via the Mann-Whitney U-test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. All analyses were performed in R (version 4.0.3) using R Studio (version 1.3.1073), and statistical significance was set at $P<0.05$.

Results

A total of 69 infants who underwent the PDA ligation were eligible for the study, with 52 infants in Epoch I and 17 in Epoch II (*Figure 1*). The median gestational age was 25 weeks (IQR 24, 26) and 26 weeks (IQR 24, 27) in epochs I and II, respectively (P=0.344). All baseline demographic characteristics were similar in both epochs (*Table 1*), except that the use of acetaminophen (17.6% *vs.* 2.0%, P=0.047) was significantly higher during Epoch II than during Epoch I. Age, gestational age, and weight at the time of surgery were similar between the two epochs. Moreover, no significant differences were noted in other perioperative characteristics between the two study periods (*Table 1*).

Table 2 Postoperative characteristics and neonatal outcomes of infants

	Epoch I	Epoch II	P value
Postoperative cardiorespiratory status			
Use of fluid bolus <24 h	10/52 (19.2%)	4/17 (23.5%)	0.734
Use of steroid <24 h	18/52 (34.6%)	7/17 (41.2%)	0.772
Use of inotrope <24 h	15/52 (28.8%)	2/17 (11.8%)	0.206
Post-ligation cardiac syndrome[†]	6/52 (11.5%)	3/17 (17.6%)	0.679
Post-operative oxygenation failure[#]	26/52 (50.0%)	12/17 (70.6%)	0.168
Neonatal morbidities			
Composite outcome of mortality or major morbidity[‡]	41/45 (91.1%)	16/17 (94.1%)	1.000
Mortality	2/52 (3.8%)	1/17 (5.9%)	1.000
IVH ≥ grade III	4/52 (7.7%)	2/17 (11.8%)	0.631
NEC ≥ stage II	7/49 (14.3%)	1/17 (5.9%)	0.669
ROP ≥ stage III	3/47 (6.4%)	2/17 (11.8%)	0.602
BPD	40/47 (85.1%)	15/17 (88.2%)	1.000

[†], post-ligation cardiac syndrome: development of both oxygenation failure and systemic hypotension (defined as blood pressure <3rd percentile or the need for bolus volume >20 mL/kg or inotropes) within the first 24 h after ligation. [#], oxygenation failure: an absolute increase of at least 20% in the MAP or FiO_2, compared with the preoperative value, for a minimum of 1 h within the 24-h post-ligation period. [‡], mortality or at least one of the following major morbidities: IVH ≥ grade III, NEC ≥ stage II, ROP ≥ stage III, BPD. IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia. MAP, mean airway pressure; FiO_2, fraction of inspired oxygen.

The incidence of the PDA ligation as a proportion of all very low birth weight admissions in Epoch II was significantly lower than that in Epoch I [Epoch II =17/228 (7.5%) *vs.* Epoch I =52/356 (14.6%); rate ratio =0.51 (95% confidence interval =0.30–0.88)].

There were no significant differences in the number of infants requiring fluid bolus, administration of steroids or inotropes, or development of post ligation cardiac syndrome and postoperative oxygenation failure between the two epochs (*Table 2*).

The composite outcome of mortality or major morbidity was comparable in both epochs (91.1% *vs.* 94.1% in Epoch I and II, respectively; P=1.000). Two infants (3.8%) in Epoch I and one infant (5.9%) in Epoch II died during hospitalization. The proportion of individual major morbidities, such as IVH ≥ grade 3, NEC ≥ stage 2, BPD, and ROP ≥ stage 3 was similar between the two epochs (*Table 2*).

Discussion

Through the assessment of the hemodynamic significance of the PDA using TNE to standardize the process of triaging infants, we were able to demonstrate a reduction in the number of infants undergoing PDA ligation from 14.6% (Epoch I) to 7.5% (Epoch II). We did not identify differences in postoperative complications or neonatal morbidities in our cohort.

The trend towards a decrease in ligation appears to be consistent with that of the published literature, indicating a lack of benefit of major surgical procedures (31,32). Similar to previous studies, we found that an integrated hemodynamic approach based on clinical and echocardiographic parameters aids in the identification of infants who might benefit from the PDA ligation. Resende *et al.* demonstrated a reduction in the PDA ligation rate from 10.7% to 5.3% after introducing the comprehensive TNE program in the Central East Region of Ontario (22). A recent study by Isayama *et al.*, comparing proactive and selective approaches to the PDA treatment, found a lower PDA ligation rate in Japan than in Canada (1% *vs.* 13%), which may be explained by differences in the use of echocardiography for PDA assessment, different criteria for ligation and variation in admission populations, and outcomes measured (31).

Meticulous postoperative clinical assessment and comprehensive echocardiography to identify neonates at risk of post ligation cardiac syndrome in the immediate postoperative period aided the prevention of cardiorespiratory instability (32,33). In our study, during both epochs, postoperative cardiopulmonary characteristics, such as post ligation cardiac syndrome, oxygen failure, and use of inotropes or steroids, did not differ significantly. The introduction of a new protocol during Epoch II did not result in any difference in composite outcomes of mortality or major morbidity. The decrease in the PDA ligation rate was not associated with an increase in cardiorespiratory instability or adverse postoperative outcomes due to the possible selection of "sicker infants" for ligation.

The use of acetaminophen for the PDA treatment increased during Epoch II compared to Epoch I. This is consistent with the current trend towards the use of acetaminophen, which is predominantly administered as either late rescue therapy for infants waiting for ligation surgery or as a non-inferior pharmaceutical alternative to infants in whom non-steroidal anti-inflammatory drugs are contraindicated (34,35).

The strengths of this study include the reliable and uniform assessment of the hemodynamic significance of each PDA case by a single person using a comprehensive set of individually validated echocardiographic indices in conjunction with clinical features suggestive of significant impact on pulmonary and systemic circulation of ductal shunting, which decreased the inter-observer differences. In addition, data were collected prospectively during Epoch II, thereby minimizing the chances of missing data during the analysis. Finally, in this study, the infant population represents an age group that is at the highest risk of hemodynamically significant PDA.

Along with the well-recognized challenges associated with the small sample size, this study has additional limitations. The retrospective nature of the study during Epoch I may have limited the statistical analyses due to incomplete data. Echocardiography was performed by different echocardiography technicians and pediatric cardiologists during Epoch I. Inherent limitations in measuring the size of PDAs, such as the tortuosity of the duct or the limited acoustic window in infants who are ventilated with a high MAP, might also have affected the results. We were not able to compare the echocardiographic parameters among infants with and without PDA ligation in each epoch due to heterogeneity in the clinical practice and sonographic measurements. The referral criteria of outborn infants for the PDA ligation might vary among different centers.

Conclusions

In conclusion, we found that standardization of the triaging process by combining clinical parameters and comprehensive TNE assessment of the hemodynamic significance of PDA reduced the incidence of PDA ligation without affecting the short-term outcomes in VLBW infants. Further studies with larger sample sizes are needed to identify specific echocardiographic parameters associated with poor healthcare outcomes in VLBW infants undergoing surgical ligation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-147/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-147/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-147/coif). JYT reports that he receives salary support from the Investigator Grant Award Program of the British Columbia Children's Hospital Research Institute. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the University of British Columbia Children and Women's Research Ethics Board (No. H15-01343) and individual consent for this study was waived as data were already being collected for patient care purposes (secondary use of data).

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