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ARTICLE

Post-ligation cardiac syndrome is associated with increased morbidity in preterm infants

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Abstract

Objective The influence of post-ligation cardiac syndrome (PLCS), a complication of patent ductus arteriosus (PDA) ligations, on neonatal outcomes is unknown. The purpose of this study was to determine the risks of PLCS on severe pulmonary morbidity and severe retinopathy of prematurity (ROP).

Study design Retrospective cohort study of infants who underwent a PDA ligation between 2006 and 2015. Data were collected on patients with and without PLCS. The primary outcome was the difference in severe bronchopulmonary dysplasia (BPD) between groups. Secondary outcomes included discharge with home oxygen and severe ROP.

Result A total of 100 infants that underwent PDA ligation during the study period were included in the study; 31 (31%) neonates developed PLCS. In adjusted analysis, PLCS was associated with increased risk for severe BPD (RR 1.67, 95% CI: 1.15–2.42) and home oxygen therapy (RR: 1.47, 95% CI: 1.09–1.99) only. No association with severe ROP was seen (RR: 1.48; 95% CI: 0.87–2.52).

Conclusion PLCS is associated with severe neonatal pulmonary morbidity, but not with severe ROP. Further investigation is warranted to validate these results.

Introduction

Patent ductus arteriosus (PDA) has been associated with neonatal morbidity, including necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), hemorrhagic pulmonary edema, retinopathy of prematurity (ROP), and death [1–3]. With the goal of preventing these morbidities, closure of the PDA is frequently attempted with prostaglandin inhibitors such as ibuprofen or indomethacin. If pharmacologic interventions are unsuccessful or contraindicated, surgical ligation can be performed. Approximately 20% of all neonates ≤32 weeks in the United States will develop a persistent PDA and 10–21% of them will undergo PDA ligation [4, 5]. Although considerable variation in practice exists, the belief that a PDA ligation is both beneficial and necessary in the symptomatic neonate remains a prevailing sentiment among neonatologists [4, 6]. However, the benefits of PDA ligation have recently been challenged as an association with severe neonatal morbidities has been demonstrated, which has raised concerns about this common practice in neonatal intensive care units (NICUs) [7–13].

The post-PDA ligation course is often complicated by an acute respiratory and hemodynamic instability that occurs in the first 24 h following the procedure. Post-ligation cardiac syndrome (PLCS), with its distinct symptoms of systemic hypotension and either ventilation and/or oxygenation failure, complicates 30–44% of all PDA ligations [14, 15]. Neonatal mortality following PDA ligation complicated by systemic hypotension has been reported to be as high as 33%, but there is a paucity of data on other neonatal outcomes associated with this post-ligation phenomenon [16]. Although PLCS is a biologically plausible mechanism to explain the association between PDA ligation and increased neonatal morbidity, its effect on neonatal outcomes remains largely uninvestigated. We hypothesized that PLCS was associated with neonatal morbidity, including severe BPD,

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severe ROP, and need for home oxygen therapy at discharge.

Methods

This retrospective observational study was conducted at a tertiary NICU with ~1000 admissions annually, most of whom are outborn. Data for the study were collected from January 2006 to February 2015. The study received Institutional Review Board approval.

Eligible neonates were those <34 weeks gestational age (GA) at birth and admitted to the NICU for surgical closure of the PDA. Pre-established exclusion occurred for the following reasons: (1) complex congenital heart disease; (2) back transfer to referral hospital prior to assessment of the primary outcome; (3) death prior to assessment of the primary outcome; and (4) known or suspected genetic syndrome. One hundred patients met inclusion criteria for the study, 31 developed PLCS and 69 patients did not develop PLCS. The decision to ligate a PDA is based on the clinical scenario, echocardiographic findings, and comprehensive review of each case individually. Prior to ligation cases are frequently discussed at the morning cardiology report attended by neonatologists, cardiologist, and pediatric cardiothoracic surgeons.

The electronic medical records of all neonates who had undergone surgical ligation during the study period were retrospectively reviewed for inclusion. Records were analyzed to determine if neonates met criteria for PLCS. The following definitions, adopted from Jain et al. [14], of systemic hypotension within 24 h of ligation plus a component of either ventilation failure and/or oxygenation failure during that same timeframe were necessary for the diagnosis of PLCS:

1. Systemic hypotension: the need to initiate a new inotropic agent or to increase an inotropic agent by >20% of preligation dosing lasting at least 1 h.
2. Oxygenation failure: an increase in preligation fraction of inspired oxygen (FiO2) and/or mean airway pressure (MAP) by >20% lasting at least 1 h.
3. Ventilation failure: a need for high frequency ventilation (HFOV) secondary to an inability to maintain adequate ventilation on conventional modes or a rise of preligation amplitude by >20% if already on HFOV lasting at least 1 h.

Individual patient data were not evaluated to determine specific post-ligation management of systemic hypotension, if present. In general, postoperative hypotension is managed initially at our institution with a normal saline bolus. If the patient does not respond to initial volume expansion, then dopamine is started at 3–5 mcg/kg/min, and advanced as needed to achieve target blood pressure. If dopamine infusions >10 mcg/kg/min are needed, hydrocortisone is administered at 1 mg/kg every 12 h following a loading dose of 1–2 mg/kg. If a third line agent is necessary, epinephrine is often the drug of choice.

The primary outcome was severe BPD, defined as the need for ≥0.30 FiO2 and/or positive pressure ventilation (PPV) at 36 weeks PMA or discharge, whichever came first, for infants <32 weeks GA at birth. For infants ≥32 weeks GA at birth, severe BPD was defined as the need for ≥0.30 FiO2 and/or PPV at 56 days postnatal age or discharge, whichever came first. The secondary outcomes were need for home oxygen therapy and severe ROP, defined as ≥stage III or needing intervention with either bevacizumab or laser therapy. The attending physician determined the need for home oxygen therapy at the time of discharge. All patients with persistent oxygen requirements are attempted to be weaned off of oxygen prior to discharge. Starting in October 2011 patients on oxygen at 36 weeks corrected gestational age underwent an oxygen reduction test to determine the lowest FiO2 necessary to maintain adequate oxygen saturations. Patients with PLCS were compared to patients without PLCS for the primary and secondary outcomes.

Statistics

On the basis of estimates of having 90 total subjects meeting enrollment criteria with 32 patients in the disease group and 58 in the non-disease group, we calculated a power of 82% to detect a difference in the primary outcome between groups using χ^2 with a 0.05 two-sided significance level, a disease group proportion of 80%, and a non-disease group proportion of 50%. Descriptive statistics are reported as means ± standard deviation for continuous variables and frequency with percentage for categorical variables. Differences in outcomes between PLCS and non-PLCS groups were assessed using two-sided independent *t*-tests for continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate based on cell size. Highly skewed variables are reported as median and interquartile range (IQR) and tested using the Wilcoxon rank-sum test. The independent association of PLCS and outcomes was modeled using multivariable modified Poisson regression with robust error variance represented and results are reported as relative risks and 95% confidence intervals. Typical analyses utilize logistic regression to estimate adjusted odds ratios, which are then generally interpreted as relative risks. However, in this study, as the events being modeled were not rare, odds ratios were poor estimates of relative risks. To address this issue, we estimated adjusted relative risks directly using a modified Poisson regression model [17]. Possible confounding was accounted for by creating a

Table 1 Patient demographics and characteristics

	Post-ligation cardiac syndrome	
	Yes ($n = 31$)	No ($n = 69$)
Gestational age (wk)	25.8 ± 2.2	25.8 ± 2.1
Birth weight (g)	740.0 [605.0, 953.0]	790.0 [660.0, 995.0]
SGA (%)	6 (19.4)	8 (11.6)
Age at admission (d)*	3.8 ± 6.9	10.9 ± 18.4
Male (%)	14 (45.2)	37 (53.6)
PDA size (mm)	2.7 ± 0.8	2.6 ± 0.8
LA Size (mm)*	9.6 ± 2.4	11.5 ± 3.3
NSAID (%)	23 (74.2)	51 (75.3)
IVH ≥ grade III (%)	10 (32.3)	13 (18.8)
NEC (%)	3 (9.6)	15 (21.7)
RSS (median (IQR))*	4.0 (3.0, 6.7)	3.1 (2.4, 4.8)
Duration of mechanical ventilation (d)	15.0 (10.0, 22.0)	16.0 (10.0, 32.0)
Vasopressor (%)	5 (16.1)	6 (8.7)
Weight at ligation (g)*	970.0 (705.0, 1180.0)	1030.0 (900.0, 1470.0)
Postnatal age at ligation (d)*	19.5 ± 10.4	29.3 ± 19.1
Intraoperative fluids (ml/kg)	14.9 ± 9.1	19.4 ± 13.1
Respiratory support (%)		
No support	0 (0.0)	1 (1.4)
Nasal cannula	0 (0.0)	5 (7.2)
CPAP	1 (3.2)	4 (5.8)
CMV	17 (54.8)	41 (59.4)
HFOV	13 (41.9)	18 (26.1)

Data are presented as median (interquartile range), mean ± standard deviation, or a number (percentage)

SGA small for gestational age, *PDA* patent ductus arteriosus, *NSAID* nonsteroidal anti-inflammatory drug, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *RSS* respiratory severity score (MAP × FiO2), *CPAP* continuous positive airway pressure, *CMV* conventional mechanical ventilation, *HFOV* high frequency oscillatory ventilation

*$P < 0.05$

propensity score derived from a multivariable logistic regression model on PLCS. This propensity score was then included as a model covariate to adjust for imbalance between groups. Variables included in the propensity to be PLCS model were gender, age at admission, GA at birth, birth weight, weight at ligation, time from birth to ligation, preligation left atrial (LA) size, small for gestational age (SGA), and preligation respiratory severity score (RSS). The RSS is equal to the MAP multiplied by FiO2 (RSS = MAP × FiO2).

All statistical tests were two-sided and conducted at the alpha = 0.05 level. All statistical tests account for variance inequality if it existed. Statistical analysis was done using The SAS software v 9.4 (SAS Institute Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 127 patients <34 weeks GA were identified as having a PDA ligation between January 2006 and February 2015. All PDA ligations were performed by a board-certified pediatric cardiothoracic surgeon. Twenty-seven patients were excluded from the analysis: 17 for back transfer to the referring hospital prior to assessment of the primary outcome, 9 for critical congenital heart disease or confirmed genetic syndromes, and 1 for incomplete records. The subject with incomplete records was missing ventilator settings and vital signs from the medical record immediately following PDA ligation, making determination of PLCS status impossible. Among the 100 remaining patients included in the study, 31 (31%) developed PLCS and 69 patients (69%) did not develop PLCS. Neonates with and without PLCS had similar GA, birth weight, sex, and PDA size prior to ligation. Postnatal age at admission and at ligation, weight at ligation, LA size, and preligation RSS were the only demographic, clinical, and echocardiographic characteristics that differed significantly between groups (Table 1).

Patients with PLCS were more likely to have severe BPD (72.4% vs 46.3%, $P = 0.02$), severe ROP (55.2% vs 30.3%, $P = 0.02$), and need for home oxygen support at discharge (82.1% vs 53.8%, $P = 0.01$) than patients without PLCS. There was no difference in death before discharge (9.7% vs 5.8%, $P = 0.67$) (Table 2). Following multivariable adjustment with propensity matched scoring, PLCS remained significantly associated with severe BPD (RR: 1.67; 95% CI: 1.15–2.42) and need for home oxygen therapy (RR: 1.47; 95% CI: 1.09–1.99). Severe ROP was no longer significant (RR: 1.48; 95% CI: 0.87–2.52) (Fig. 1). Subjects without PLCS were significantly more likely to survive without severe BPD or severe ROP (RR: 1.54; 95% CI: 1.14–2.06).

Table 2 Unadjusted neonatal outcomes

	Post-ligation cardiac syndrome		*P*
	Yes ($n = 31$)	No ($n = 69$)	
Severe BPD (%)	21 (72.4)	31 (46.3)	0.02
Severe ROP (%)	16 (55.2)	20 (30.3)	0.02
Home oxygen therapy (%)	23 (82.1)	35 (53.8)	0.01
Death (%)	3 (9.7)	4 (5.8)	0.67

Data presented as a number (%)

BPD bronchopulmonary dysplasia, *ROP* retinopathy of prematurity

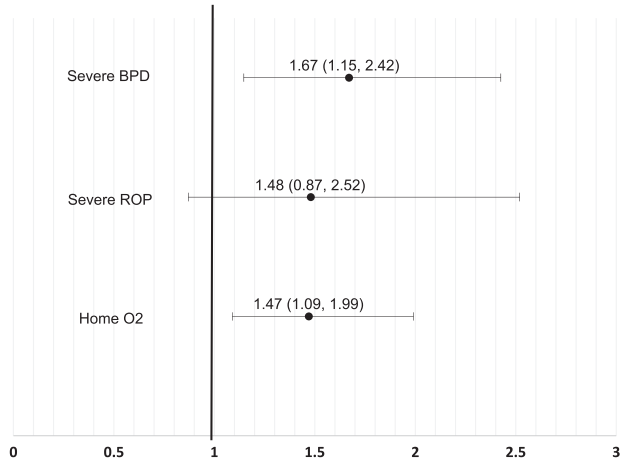

Fig. 1 Adjusted RR (95% CI) for the primary and secondary outcomes. BPD bronchopulmonary dysplasia, ROP retinopathy of prematurity

There were 7 deaths prior to discharge in the cohort (Table 2). Four deaths occurred prior to 36 weeks postmenstrual age, 2 in each group respectively, and were thus excluded from the analysis for the primary outcome. Subjects who died prior to hospital discharge were not included in the secondary outcomes analysis of need for home oxygen and severe ROP unless surgical intervention for ROP had occurred prior to death. As a result, all 7 patients who died prior to hospital discharge were excluded from the analysis of need for home oxygen therapy and 5 were excluded from the analysis of severe ROP, 2 with and 3 without PLCS, respectively.

As both intraoperative fluid volume and anesthesia can affect postoperative hemodynamics, intraoperative fluid administration and sedation were analyzed. There was no difference in the amount of intraoperative fluid volume per body weight received between groups (14.9 ± 9.1 vs 19.4 ± 13.1, $P = 0.12$). Similarly, there was no significant difference between the dose per kilogram of intraoperative sedation and paralytics between groups (data not shown). Total length of hospitalization in days (130.4 ± 56.2 vs 123.7 ± 44.4, $P = 0.52$) and length of hospitalization from ligation to discharge (110 ± 55.6 vs 94.3 ± 41.1, $P = 0.18$) did not differ between groups.

Discussion

PDA ligation has been associated with neonatal morbidity, including BPD and severe ROP [9–11, 13]. We performed this hypothesis driven retrospective cohort study to examine whether PLCS was positively associated with neonatal short-term morbidities. We demonstrated that PLCS contributes to increased neonatal pulmonary morbidity, in keeping with our hypothesis. PLCS was not associated with severe ROP.

The PDA with high volume left-to-right shunting increases pulmonary blood flow potentially leading to impaired gas exchange, an indication for surgical ligation. In theory, removal of the ductal circulation will improve the pulmonary mechanics of the patient and decrease the risk of neonatal respiratory morbidity. In practice, however, the results of a PDA ligation and pulmonary outcomes have been mixed. Chang et al. [18] showed in an animal model that pulmonary mechanics and alveolar surface area failed to improve following PDA ligation. Similarly, Waleh et al. [19] demonstrated an upregulation of genes associated with pulmonary inflammation following PDA ligation in baboons. Preterm infants have stiff, noncompliant left ventricles relative to term counterparts. Diastolic dysfunction, which may be exacerbated by PDA ligation, may lead to pulmonary venous congestion and further impair pulmonary mechanics [20]. We postulate that these maladaptive pulmonary responses to PDA ligation, coupled with the cardiovascular changes also seen, lead to pulmonary decompensation in the immediate postoperative period. The increased ventilator assistance necessary to support the patient with PLCS may be the catalyst for increased pulmonary morbidity as seen in our cohort. Although other authors have shown an association between PDA ligation and BPD [7, 10, 11, 13], it is unclear whether this association would continue to be found after removing patients with PLCS from their respective analyses as this factor was not controlled for in any study.

In addition to respiratory compromise, hypotension also occurs frequently following PDA ligation. Evidence has been emerging in recent years illustrating the causal pathways of this phenomenon. Clyman et al. found that cortisol production, vital in the maintenance of normal blood pressure, fails to increase adequately in response to surgical stress in a subset of ligated patients. In these cases, low serum cortisol values were secondary to failed signaling from the developmentally immature hypothalamus-pituitary axis rather than primary adrenal failure [21]. Unfortunately, preoperative stress dose hydrocortisone did not reduce cardiovascular instability following PDA ligation, suggesting that other etiologies for post-ligation hypotension existed [22]. McNamara et al. initially revealed that PDA ligation abruptly alters the loading conditions of the heart by increasing left ventricular afterload and reducing preload, a fact subsequently confirmed by other authors [20, 23, 24]. These abrupt cardiovascular changes impair left ventricular function and output with subsequent pulmonary venous congestion and cardiopulmonary decompensation [14]. These failed organ-specific responses to the stress of PDA ligation, either in isolation or combination, lead to hypotension.

Identifying infants at high risk for PLCS is important clinically and would be helpful in making decisions regarding not only in whom to perform PDA ligation but also to determine optimal timing so as to avoid both short and long-term sequelae. Certain preligation factors, including the degree of respiratory support prior to ligation, gestational age, and postnatal age at surgery have all previously been shown to be correlated with the development of hypotension following surgical ductal ligation [15, 16, 25]. Teixeira et al. [15] demonstrated the risk of post-ligation hypotension to be lower if ligation was delayed. Similarly, in our cohort, increasing postnatal age at ligation, while potentially prolonging exposure to a symptomatic PDA, did not increase the risk for cardiopulmonary instability. In fact, delaying ligation appeared to be protective. One possibility is that patients without PLCS were less ill prior to ligation, allowing surgical intervention to be delayed. While the RSS was higher in those with PLCS, the preligation duration and mode of mechanical ventilation did not differ between groups. In addition, other markers of preligation illness severity, including NEC and severity of intraventricular hemorrhage, were not significantly different. We speculate that delaying ligation may allow compensatory maturational changes of the cardiovascular system and hypothalamic–pituitary–adrenal axis thereby lessening the risk of PLCS. Caution is encouraged when interpreting these findings, as this study was not designed to investigate the merits of delaying ligation. There may be many untoward outcomes by delaying ligation in a patient with a symptomatic PDA based solely on our results.

Milrinone is a phosphodiesterase 3 inhibitor that reduces cardiac afterload and its targeted use following PDA ligation can decrease the rate of post-ligation hypotension and respiratory failure [14, 26]. It is not known whether prevention of PLCS with milrinone improves neonatal outcomes, but remains a promising therapeutic option for patients with PLCS. Targeted milrinone therapy in select patients with impaired left ventricular output after PDA ligation is an exciting topic for future research and warrants future investigation given the morbidities we have shown to be associated with PLCS.

Contrary to prior authors, we did not see an association between PLCS and mortality before discharge [25]. Harting et al. [16] demonstrated a mortality rate of 33% among surgically ligated neonates with postoperative hemodynamic deterioration. The overall mortality in our study population was only 7%, without a significant difference between groups. Our patients may have been more hemodynamically stable as only 11% were requiring vasopressors preoperatively compared to 20% in the cohort of Harting et al. [16]. In addition, our cohort was older at the time of ligation, which potentially impacted survival.

Our findings must be interpreted with caution, as there are certain limitations to our study. This was a retrospective study and is subject to the limitations of the design, specifically the ability to control for all potential confounders. The study was conducted at a single center and lacked a standardized definition of what constitutes a hemodynamically significant PDA. The center is a large metropolitan referral center. Patients referred for PDA ligation consideration came from many NICUs within the referral area resulting in variable postnatal management and a heterogeneous cohort. Despite these limitations, the considerably high incidence of neonatal pulmonary morbidity that occurred in patients with PLCS may have significant clinical impact owing to the long-term consequences of BPD on respiratory health and neurodevelopmental outcomes. Additional investigations are needed to confirm our results and to ascertain which infants are likely to develop PLCS.

Conclusion

In this retrospective review, PLCS was associated with severe pulmonary morbidity, including severe BPD and need for home oxygen therapy. PLCS was, however, not associated with the development of severe ROP. The increased respiratory support necessary to support the patient with PLCS likely contributes to the increased pulmonary morbidity seen in this study.

Compilance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. Pediatrics. 2009;123:e138–44.
2. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr. 2015;166:1488–92.
3. Brooks JM, Travadi JN, Patole SK, Doherty DA, Simmer K. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. Arch Dis Child Fetal Neonatal Ed. 2005;90:F235–239.
4. Lokku A, Mirea L, Lee SK, Shah PS. Trends and outcomes of patent ductus arteriosus treatment in very preterm infants in Canada. Am J Perinatol. 2016;34:441–50.
5. Weinberg JG, Evans FJ, Burns KM, Pearson GD, Kaltman JR. Surgical ligation of patent ductus arteriosus in premature infants: trends and practice variation. Cardiol Young. 2016;26:1107–14.

6. Kulkarni A, Richards J, Duffy D. Survey of management of patent ductus arteriosus in neonatal units across England. Arch Dis Child Fetal Neonatal Ed. 2013;98:F465–466.
7. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010;30:241–52.
8. Bourgoin L, Cipierre C, Hauet Q, Basset H, Gournay V, Roze JC, et al. Neurodevelopmental outcome at 2 years of age according to patent ductus arteriosus management in very preterm infants. Neonatology. 2016;109:139–46.
9. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics. 2007;119:1165–74.
10. Clyman R, Cassady G, Kirklin JK, Collins M, Philips JB 3rd. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. J Pediatr. 2009;154:873–6.
11. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet. 2016;387:1827–36.
12. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. J Pediatr. 2007;150:229–34. 234.e221
13. Weisz DE, More K, McNamara PJ, Shah PS. PDA ligation and health outcomes: a meta-analysis. Pediatrics. 2014;133:e1024–1046.
14. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr. 2012;160:584–89. e581
15. Teixeira LS, Shivananda SP, Stephens D, Van Arsdell G, McNamara PJ. Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to early need for intervention. J Perinatol. 2008;28:803–10.
16. Harting MT, Blakely ML, Cox CS Jr, Lantin-Hermoso R, Andrassy RJ, Lally KP. Acute hemodynamic decompensation following patent ductus arteriosus ligation in premature infants. J Invest Surg. 2008;21:133–8.
17. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159:702–6.
18. Chang LY, McCurnin D, Yoder B, Shaul PW, Clyman RI. Ductus arteriosus ligation and alveolar growth in preterm baboons with a patent ductus arteriosus. Pediatr Res. 2008;63:299–302.
19. Waleh N, McCurnin DC, Yoder BA, Shaul PW, Clyman RI. Patent ductus arteriosus ligation alters pulmonary gene expression in preterm baboons. Pediatr Res. 2011;69:212–6.
20. El-Khuffash AF, Jain A, McNamara PJ. Ligation of the patent ductus arteriosus in preterm infants: understanding the physiology. J Pediatr. 2013;162:1100–6.
21. Clyman RI, Wickremasinghe A, Merritt TA, Solomon T, McNamara P, Jain A, et al. Hypotension following patent ductus arteriosus ligation: the role of adrenal hormones. J Pediatr. 2014;164:1449–55. e1
22. Satpute MD, Donohue PK, Vricella L, Aucott SW. Cardiovascular instability after patent ductus arteriosus ligation in preterm infants: the role of hydrocortisone. J Perinatol. 2012;32:685–9.
23. McNamara PJ, Stewart L, Shivananda SP, Stephens D, Sehgal A. Patent ductus arteriosus ligation is associated with impaired left ventricular systolic performance in premature infants weighing less than 1000 g. J Thorac Cardiovasc Surg. 2010;140:150–7.
24. El-Khuffash AF, Jain A, Dragulescu A, McNamara PJ, Mertens L. Acute changes in myocardial systolic function in preterm infants undergoing patent ductus arteriosus ligation: a tissue Doppler and myocardial deformation study. J Am Soc Echocardiogr. 2012;25:1058–67.
25. Moin F, Kennedy KA, Moya FR. Risk factors predicting vasopressor use after patent ductus arteriosus ligation. Am J Perinatol. 2003;20:313–20.
26. Sehgal A, Francis JV, Lewis AI. Use of milrinone in the management of haemodynamic instability following duct ligation. Eur J Pediatr. 2011;170:115–9.