Korean J Thorac Cardiovasc Surg 2014;47:444-450 □ Clinical Research □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) http://dx.doi.org/10.5090/kjtcs.2014.47.5.444

Surgical Ligation on Significant Patent Ductus Arteriosus in Very Low Birth Weight Infants: Comparison between Early and Late Ligations

Jun Ho Lee, M.D.[1], Sun Kyun Ro, M.D.[2], Hyun Ju Lee, M.D.[3], Hyun Kyung Park, M.D.[3], Won-Sang Chung, M.D.[1], Young Hak Kim, M.D.[1], Jeong Ho Kang, M.D.[1], Hyuck Kim, M.D.[1]

Background: We aimed to evaluate the efficacy and safety of early surgical ligation (within 15 days of age) over late surgical ligation (after 15 days of age) by a comparative analysis of very low birth weight (VLBW) infants undergoing surgical correction for symptomatic patent ductus arteriosus (PDA) over the course of 6 years in our hospital. ***Methods:*** We retrospectively reviewed all the medical records in the neonatal intensive care unit at Hanyang University Seoul Hospital, from March 2007 to May 2013, to identify VLBW infants (＜1,500 g) who underwent surgical PDA ligation. ***Results:*** The gestational age (GA) in the late ligation (LL) group was significantly younger than in the early ligation (EL) group (p=0.010). The other baseline characteristics and preoperative conditions did not differ significantly between the two groups. The intubation period before surgery (p＜0.001) and the age at surgery (p＜0.001) were significantly different. The postoperative clinical outcomes of the study patients, including major morbidity and mortality, are summarized. There were no significant differences in bronchopulmonary dysplasia, sepsis, or mortality between the EL and the LL groups. However, the LL group was significantly associated with an increased risk of necrotizing enterocolitis (p=0.037) and with a prolonged duration of the total parenteral nutrition (p=0.046) after adjusting for GA. ***Conclusion:*** Early surgical ligation for the treatment of PDA that failed to close after medical treatment or in cases contraindicated for medical treatment might be desirable to reduce the incidence of necrotizing enterocolitis and to alleviate feeding intolerance in preterm infants.

Key words: 1. Congenital heart disease (CHD)
2. Infant
3. Outcomes

INTRODUCTION

Patent ductus arteriosus (PDA) is a congenital anomaly involving the proximal descending thoracic aorta and is associated with increased morbidity and mortality in preterm infants. In particular, symptomatic PDA adversely affects the regional blood flow, resulting in necrotizing enterocolitis (NEC), particularly in very low birth weight (VLBW) infants.

Department of Thoracic and Cardiovascular Surgery, [1]Hanyang University Seoul Hospital, [2]Hanyang University Guri Hospital, [3]Department of Pediatrics, Hanyang University Seoul Hospital, Hanyang University College of Medicine
† This article was presented at the 45th Fall Meeting of the Korean Society for Thoracic and Cardiovascular Surgery, November 7, 2013.
‡ This article, written by Jun Ho Lee (lead author), was approved as a thesis for the Master of Thoracic and Cardiovascular Surgery, Hanyang University Graduate School, February 28, 2014.
Received: February 4, 2014, Revised: March 16, 2014, Accepted: March 20, 2014, Published online: October 5, 2014
Corresponding author: Hyuck Kim, Department of Thoracic and Cardiovascular Surgery, Hanyang University Seoul Hospital, Hanyang University College of Medicine, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 133-791, Korea
(Tel) 82-2-2290-8467 (Fax) 82-2-2290-8467 (E-mail) khkim@hanyang.ac.kr

Therefore, PDA frequently requires surgical treatment. The first surgical ligation for PDA was performed by Drs. Gross and Hubbard in 1938, and this operation opened a new era of pediatric cardiac surgery [1].

In utero, the ductus arteriosus shunts mostly right to left due to the high resistance of the pulmonary circulation. In the first several hours after birth, closure of the ductus arteriosus usually occurs due to increased arterial oxygen tension, which constricts the smooth muscle cells of the ductus. The ductus arteriosus closes spontaneously during the first four days after birth in 90% to 95% of full-term infants and 80% to 90% of premature infants born at 30 to 37 weeks of gestational age (GA) [2]. However, the rate of spontaneous ductus arteriosus closure is inversely proportional to birth weight. In particular, in VLBW infants, the closure of the ductus arteriosus is often delayed or fails altogether because of an increase in prostaglandin E1 in the blood. This failure results in a persistent left-to-right shunt.

PDA increases the risk of prolonged ventilation, pulmonary edema, pulmonary hemorrhage, and bronchopulmonary dysplasia (BPD). Additionally, the comorbidities associated with PDA include NEC, intestinal ischemia, renal hypoperfusion, retinopathy, cerebral hypoperfusion, and intraventricular hemorrhage (IVH) [3].

Although PDA ligation is a definitive treatment, there are few comparisons between early surgical ligation and conservative management for symptomatic PDA in the available literature. Prompt ductal closure is desirable to minimize the deleterious effects of PDA in preterm infants. However, the benefits or side effects of surgical ligation in preterm infants remain unclear.

Gerhardt and Bancalari [4] demonstrated that the surgical closure of PDA decreased the need for ventilatory support and the incidence of significant pulmonary morbidity. Cassady et al. [5] reported that early prophylactic ligation of PDA in preterm infants reduced the incidence of NEC. Perez et al. [6] demonstrated that PDA ligation was technically feasible and safe, even in premature, low birth weight infants. Finally, Little et al. [7] reported that delaying surgical ligation could increase the likelihood of developing morbidity and mortality.

In this context, we aimed to evaluate the efficacy and safety of early surgical ligation (within 15 days of age) over late surgical ligation (after 15 days of age) by a comparative analysis of VLBW infants undergoing surgical correction for symptomatic PDA during a 6-year period at Hanyang University Seoul Hospital.

METHODS

1) Study populations

We retrospectively reviewed all the medical records of the neonatal intensive care unit (NICU) at Hanyang University Seoul Hospital, from March 2007 to May 2013, in order to identify VLBW infants (＜1,500 g) who underwent surgical PDA ligation. Infants manifesting other congenital anomalies or congenital heart diseases and 3 infants who died within 15 days of birth were excluded.

A total of 320 VLBW infants have been treated in the NICU during the study period, and of them, 125 patients (39.1%) were diagnosed with symptomatic PDA. Excluding 61 patients who improved by medical treatment alone, in the end, 64 patients who underwent surgical correction for symptomatic PDA were enrolled in our study. Of these patients, 28 patients underwent surgical ligation at 15 days of age or earlier (EL group), whereas 36 patients underwent surgical ligation at 16 days of age or later (LL group) (Fig. 1).

2) Definitions

Symptomatic PDA indicated hemodynamically significant PDA, which was defined as tachycardia with a heart rate of 160 bpm or more, hyperdynamic precordium, murmur (≥grade II), worsening of the respiratory status, and cardiomegaly on a simple chest X-ray. Symptomatic PDA was defined as the ductus arteriosus having a diameter of 2 mm or more and a ratio of 1.5 or more of the size of the left atrium to the diameter of the aortic root on portable echocardiography (HD11 Diagnostic Ultrasound Imaging System and Transducers; Philips Ultrasound, Bothell, WA, USA).

BPD was defined using Jobe and Bancalari's criteria [8]. Sepsis was defined as the presence of at least one positive blood culture and clinical manifestations of infection. NEC was classified using Bell's modified staging criteria [9]. The stages of retinopathy of prematurity (ROP), previously known

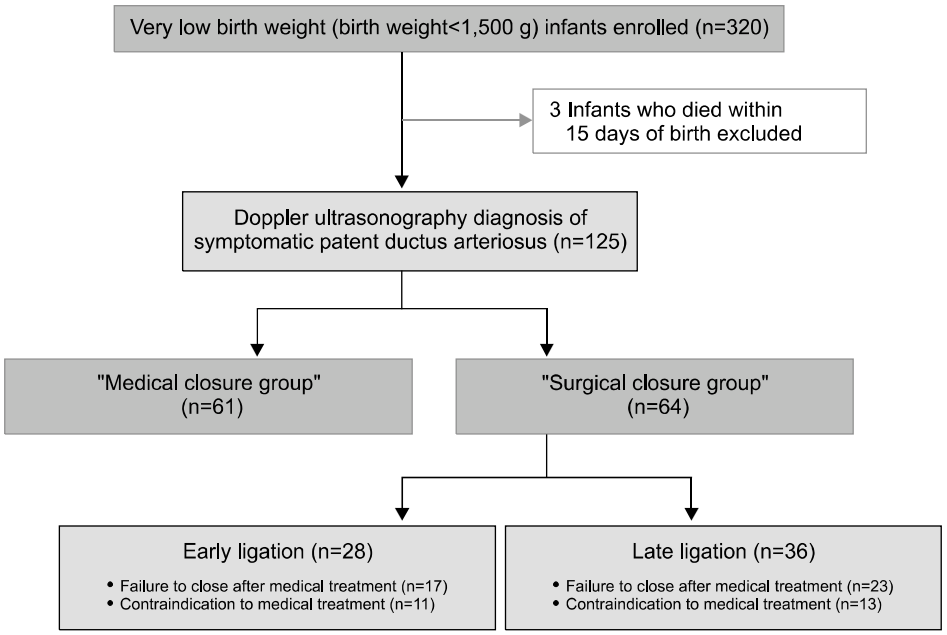

Fig. 1. Flow diagram of the study patients.

Table 1. Protocol for indomethacin and ibuprofen treatment

Age at 1st dose	1st	2nd	3rd
Indomethacin (mg/kg)[a]			
<48 hr	0.2	0.1	0.1
2–7 day	0.2	0.2	0.2
>7 day	0.2	0.25	0.25
Ibuprofen (mg/kg)[b]	10	5	5

[a]At 12–24-hour intervals. [b]At 24-hour intervals.

as retrolental fibroplasia, were defined by the International Classification of Retinopathy of Prematurity [10]. IVH was classified using Volpe's grading system [11].

3) Medical treatment

Most of the patients were initially treated with 2 to 3 cycles of indomethacin or ibuprofen. In most of the patients, indomethacin or ibuprofen was initially administered according to the treatment protocols as shown in Table 1, unless there were contraindications including poor urine output (<0.6 mL/kg/hr), high blood urea (>30 mg/dL), high serum creatinine (>1.8 mg/dL), thrombocytopenia (<60,000/mm^3), gastrointestinal bleeding, or intraventricular hemorrhage. Since 2009, our policy for medical treatment of symptomatic PDA has been changed from indomethacin to ibuprofen on the basis of the clinical evidence that ibuprofen is significantly less associated with the impairment of renal function, than indomethacin [12,13].

4) Surgery

The indications for surgical ligation include failure or contraindications of medical treatment and the occurrence of hemodynamic instability despite their use. All patients underwent surgical ligations in the NICU under general anesthesia. A left minimal transaxillary thoracotomy, via the 3rd or 4th intercostal space, was performed, and the ductus arteriosus was ligated using a single medium-sized titanium Horizon clip (Teleflex Medical, Research Triangle Park, NC, USA).

5) Data collection

All the patients' baseline characteristics including GA, birth weight, sex, Apgar score (at 1 minute and 5 minutes), maternal age, the use of ibuprofen, the first day of symptomatic PDA, duration of intubation before surgery, age at surgery, weight at surgery, antenatal steroid treatment, surfactant use, and echocardiographic findings such as size of the PDA and the left atrial-to-aortic root diameter were retrospectively reviewed. Additionally, data concerning preoperative comorbidity such as pulmonary hemorrhage, upper gastrointestinal hemorrhage, pneumothorax, acute respiratory distress syndrome, and IVH were also collected (Tables 2–4). The

Table 2. Baseline characteristics of the study patients

Variable	Early ligation group (n=28)	Late ligation group (n=36)	p-value
Gestational age (wk)	27.1±2.2	25.7±1.6	0.010
Birth weight (g)	883±190	817±188	0.17
Male gender (%)	15 (53.6)	15 (41.7)	0.45
Apgar score at 1 min	1.8±0.9	1.6±1.2	0.51
Apgar score at 5 min	3.9±1.2	3.2±1.5	0.06
Antenatal steroid (%)	18 (64.2)	26 (72.2)	0.57
Maternal age (yr)	31.4±2.9	30.7±3.2	0.38
Surfactant use (%)	27 (96.4)	36 (100.0)	0.44
Length of hospital stay (day)	98.1±54.8	94.0±26.0	0.70

Values are presented as mean±standard deviation or number (%).

Table 3. Preoperative conditions of the study patients

Variable	Early ligation group (n=28)	Late ligation group (n=36)	p-value
Pulmonary hemorrhage	5 (17.9)	10 (27.8)	0.39
Upper gastrointestinal hemorrhage	4 (14.3)	8 (22.2)	0.53
Pneumothorax	1 (3.6)	0	0.07
Acute respiratory distress syndrome	13 (46.4)	22 (61.1)	0.31
Intraventricular hemorrhage	13 (46.4)	17 (47.2)	1.00
Ibuprofen use	14 (50)	17 (47.2)	0.34

Values are presented as number (%).

Table 4. Operative conditions of the study patients

Variable	Early ligation group (n=28)	Late ligation group (n=36)	p-value
First day of symptomatic patent ductus arteriosus	3.1±2.1	3.8±2.6	0.24
Intubation before surgery (day)	9.1±4.5	18.2±9.4	<0.001
Age at surgery (day)	10.2±3.6	24.5±7.6	<0.001
Weight at surgery (g)	839.2±193.1	892.2±298.3	0.42
Patent ductus size (mm)	2.4±0.7	2.2±0.8	0.21
Left atrial/aortic diameter (mm)	1.5±0.3	1.5±0.4	0.67

Values are presented as mean±standard deviation.

early clinical outcomes included early mortality and morbidity, such as BPD, sepsis, NEC, prolonged parenteral nutrition (>28 days), retinopathy of prematurity (ROP; stage ≥3), periventricular leukomalacia (PVL), and prolonged length of hospital stay (Fig. 2).

6) Statistical analysis

Categorical variables were expressed as numbers and percentages and compared using Pearson's χ^2 test or Fisher's exact test. Continuous variables were reported as means± standard deviations and compared using the Student unpaired t-test or the Mann-Whitney U-test, as appropriate. The odds ratios of early ligation to late ligation affecting the clinical outcomes were obtained through a logistic regression analysis. Statistical significance is denoted by p-values<0.05. PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.

RESULTS

As shown in Tables 2 and 3, the GA in the LL group was significantly lower than in the EL group (27.1±2.2 weeks vs. 25.7±1.6 weeks, p=0.010). The other baseline characteristics and preoperative conditions did not differ significantly between the two groups. As shown in Table 4, the intubation period before surgery (9.1±4.5 days vs. 18.2±9.4 days, p <0.001) and age at surgery (10.2±3.6 days vs. 24.5±7.6 days, p<0.001) were significantly different.

The postoperative clinical outcomes of the study patients, including major morbidity and mortality, are illustrated in Fig. 2. There were no significant differences in BPD, sepsis, or mortality between the EL and the LL groups. The incidence of ROP was significantly different before adjusting for GA, but after adjusting for GA, it was not significantly

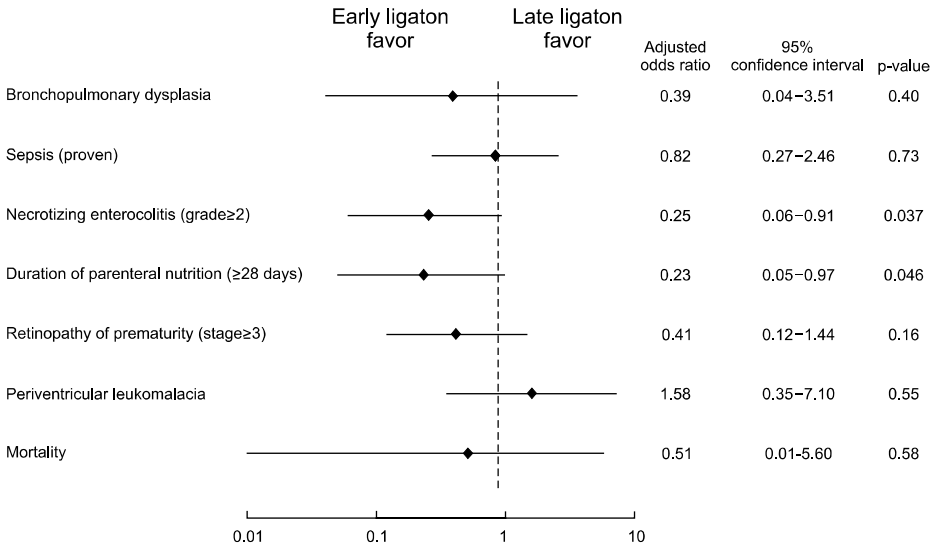

Fig. 2. Postoperative clinical outcomes of the study patients. Adjusted for gestational age, which was a significant difference between the early ligation and the late ligation groups.

different (p=0.163). However, the LL group was significantly associated with an increased risk of NEC (odds ratio, 0.25; p=0.037) and with a prolonged duration of the total parenteral nutrition (TPN) (odds ratio, 0.23; p=0.046) after adjusting for GA.

No infants died during the surgical procedures. Two patients required reoperation due to residual PDA, as diagnosed by postoperative transthoracic echocardiography.

DISCUSSION

Our results indicated that the incidence of NEC and the duration of TPN were significantly decreased in premature infants with early surgical ligation of symptomatic PDA that was refractory to medical treatment. We did not find evidence that late ligation was associated with BPD, sepsis, ROP, PVL, or mortality.

The number of cases of NEC (grade≥2) and the duration of TPN (≥28 days) in the EL group were reduced compared with those in the LL group. In the present study, this finding could have occurred because the GA in the EL group was significantly older than in the LL group. PDA closure has been inversely correlated with GA. However, after adjusting for GA, the adjusted p values for NEC and the duration of TPN were still less than 0.05, indicating that the incidence of NEC and the duration of TPN were significantly decreased in the EL group.

In the category of perinatal factors, GA in the EL group was significantly longer than that in the LL group. GA was associated with the course of PDA closure, including clinical closure and anatomical closure. With clinical closure in premature infants, constriction of the sensitive smooth muscle cells of the ductus is decreased because of the low response to oxygen and the high sensitivity to prostaglandin E1 and nitric oxide [14,15]. During anatomical closure in VLBW infants, hypoxia and immaturity of the ductal closure mechanism interfere with closure progress. Thus, the possibility of the reopening of the ductus arteriosus is high after successful clinical closure in lower GA groups, such as the LL group [16].

PDA is a common problem in preterm infants and has been associated with increased hospital morbidity and mortality [17]. In premature infants, PDA increased the risk of prolonged ventilation and resulted in oxygen requirements, as well as increased rates of BPD [18] and pulmonary hemorrhage [19]. However, in the present study, there were no significant differences in BPD between the EL and the LL groups. The diastolic steal of blood flow through the PDA has been associated with intestinal ischemia, renal hypoperfusion, NEC, reduced middle cerebral artery blood flow velocity [20], and an increased risk of IVH [21]. In particular, impaired intestinal blood flow can cause feeding intolerance and NEC, and a previous study confirmed that the early prophylactic ligation of PDA in VLBW infants reduced the

incidence of NEC [5]. In our study, we concluded the early surgical ligation for the treatment of PDA might be desirable to reduce the incidence of NEC and to improve feeding intolerance in preterm infants.

Medical treatment has proven to be the initial choice of therapy. However, there have been side effects such as renal impairment, IVH, and NEC [22]. Surgical treatment has been recommended after initial medical treatment has failed or has been contraindicated because there have also been complications with surgical closure, such as cardiopulmonary dysfunction, chylothorax, vocal cord and diaphragmatic paralysis, infection, unstable blood pressure, and death [23,24].

In VLBW infants with hemodynamically significant PDA, the decision for the optimal timing of surgical closure is important [25]. However, there have been few reports comparing early surgical ligation and late surgical ligation for symptomatic PDA. Tantraworasin et al. [26] demonstrated that the surgical closure of PDA in premature infants was safe, but early ligation did not appear to be more beneficial than late ligation. These authors defined the early surgery group as infants operated upon within 21 days after birth. In contrast, Lee et al. [3] reported that early PDA closure in extremely low birth weight infants (＜1,000 g) by either medical or surgical treatment, was necessary within the first week of life. Additionally, Hsiao et al. [27] reported that early ligation (within 14 days of birth) of medically refractory PDA in VLBW infants (＜1,500 g) improved enteral feeding tolerance and reduced TPN and ventilator use. These findings are consistent with those of our study. Additionally, two previous studies demonstrated that prolonged medical therapy before PDA ligation increased hospital morbidity and hospital stays. The authors of these studies recommended that early PDA ligation be performed as soon as medical treatment was unsuccessful [17,25]. In our study, the surgical closure of PDA was safe in preterm infants, and early ligation appeared to be more beneficial than late ligation.

To diagnose symptomatic PDA earlier, it is very important to perform echocardiography within the first 24 hours after birth. Furthermore, for early PDA closure, it is important to confirm the response to treatment by echocardiography [28]. Teamwork and cooperation between cardiac surgeons and neonatologists are absolutely necessary to optimize the clinical course of the patient through optimal planning of the ideal timing for surgical ligation.

In addition, according to the policy of our hospital, postoperative echocardiography for all the operated infants was performed in the NICU immediately after surgery and two infants were re-operated upon to close the PDA completely as soon as they were diagnosed by postoperative echocardiography, with the maintenance of general anesthesia.

We performed a retrospective study; it was not possible to perform a randomized, controlled trial. The number of subjects was limited by the appearance of VLBW infants with symptomatic PDA who were refractory to medical treatment not being frequent during the study period. The long-term outcomes, positive and negative, must be evaluated further. Additionally, future studies are required to determine whether the potential benefits of the surgical closure of the ductus arteriosus are balanced against the possible side effects of the surgical procedure.

In conclusion, early surgical ligation for the treatment of PDA that failed to close after medical treatment or in cases contraindicated for medical treatment might be desirable, to reduce the incidence of NEC and to improve feeding intolerance in preterm infants.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Emani SM. *Patent ductus arteriosus, coarctation of the aorta, and vascular rings. In: Sellke FW, Nido PJ, Swanson SJ, editors. Sabiston and Spencer surgery of the chest.* 8th ed. Philadelphia: Saunders; 2010. p. 1781-95.
2. Reller MD, Ziegler ML, Rice MJ, Solin RC, McDonald RW. *Duration of ductal shunting in healthy preterm infants: an echocardiographic color flow Doppler study.* J Pediatr 1988; 112:441-6.
3. Lee HJ, Sim GH, Jung KE, et al. *Delayed closure effect in preterm infants with patent ductus arteriosus.* Korean J Pediatr 2008;51:1065-70.
4. Gerhardt T, Bancalari E. *Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation.*

Biol Neonate 1980;38:96-105.
5. Cassady G, Crouse DT, Kirklin JW, et al. *A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth.* N Engl J Med 1989;320:1511-6.
6. Perez CA, Bustorff-Silva JM, Villasenor E, Fonkalsrud EW, Atkinson JB. *Surgical ligation of patent ductus arteriosus in very low birth weight infants: is it safe?* Am Surg 1998; 64:1007-9.
7. Little DC, Pratt TC, Blalock SE, Krauss DR, Cooney DR, Custer MD. *Patent ductus arteriosus in micropreemies and full-term infants: the relative merits of surgical ligation versus indomethacin treatment.* J Pediatr Surg 2003;38:492-6.
8. Jobe AH, Bancalari E. *Bronchopulmonary dysplasia.* Am J Respir Crit Care Med 2001;163:1723-9.
9. Kamitsuka MD, Horton MK, Williams MA. *The incidence of necrotizing enterocolitis after introducing standardized feeding schedules for infants between 1250 and 2500 grams and less than 35 weeks of gestation.* Pediatrics 2000;105:379-84.
10. International Committee for the Classification of Retinopathy of Prematurity. *The International Classification of Retinopathy of Prematurity revisited.* Arch Ophthalmol 2005;123: 991-9.
11. Volpe JJ. *Intraventricular hemorrhage in the premature infant: current concepts.* Part I. Ann Neurol 1989;25:3-11.
12. Van Overmeire B, Smets K, Lecoutere D, et al. *A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus.* N Engl J Med 2000;343:674-81.
13. Su PH, Chen JY, Su CM, Huang TC, Lee HS. *Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants.* Pediatr Int 2003;45:665-70.
14. Clyman RI, Chan CY, Mauray F, et al. *Permanent anatomic closure of the ductus arteriosus in newborn baboons: the roles of postnatal constriction, hypoxia, and gestation.* Pediatr Res 1999;45:19-29.
15. Clyman RI, Waleh N, Black SM, Riemer RK, Mauray F, Chen YQ. *Regulation of ductus arteriosus patency by nitric oxide in fetal lambs: the role of gestation, oxygen tension, and vasa vasorum.* Pediatr Res 1998;43:633-44.
16. Weiss H, Cooper B, Brook M, Schlueter M, Clyman R. *Factors determining reopening of the ductus arteriosus after successful clinical closure with indomethacin.* J Pediatr 1995; 127:466-71.
17. Vida VL, Lago P, Salvatori S, et al. *Is there an optimal timing for surgical ligation of patent ductus arteriosus in preterm infants?* Ann Thorac Surg 2009;87:1509-15.
18. Bancalari E, Claure N, Sosenko IR. *Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition.* Semin Neonatol 2003;8:63-71.
19. Kluckow M, Evans N. *Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage.* J Pediatr 2000;137: 68-72.
20. Weir FJ, Ohlsson A, Myhr TL, Fong K, Ryan ML. *A patent ductus arteriosus is associated with reduced middle cerebral artery blood flow velocity.* Eur J Pediatr 1999;158:484-7.
21. Osborn DA, Evans N, Kluckow M. *Effect of early targeted indomethacin on the ductus arteriosus and blood flow to the upper body and brain in the preterm infant.* Arch Dis Child Fetal Neonatal Ed 2003;88:F477-82.
22. Cherif A, Jabnoun S, Khrouf N. *Oral ibuprofen in early curative closure of patent ductus arteriosus in very premature infants.* Am J Perinatol 2007;24:339-45.
23. Sosenko IR, Fajardo MF, Claure N, Bancalari E. *Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial.* J Pediatr 2012;160:929-35.e1.
24. Koehne PS, Bein G, Alexi-Meskhishvili V, Weng Y, Buhrer C, Obladen M. *Patent ductus arteriosus in very low birthweight infants: complications of pharmacological and surgical treatment.* J Perinat Med 2001;29:327-34.
25. Raval MV, Laughon MM, Bose CL, Phillips JD. *Patent ductus arteriosus ligation in premature infants: who really benefits, and at what cost?* J Pediatr Surg 2007;42:69-75.
26. Tantraworasin A, Woragidpoonpol S, Chuaratanapong S, Sittiwangkul R, Chittawatanarat K. *Timing of surgical closure of patent ductus arteriosus in preterm neonates?* Asian Cardiovasc Thorac Ann 2012;20:12-8.
27. Hsiao CC, Wung JT, Tsao LY, Chang WC. *Early or late surgical ligation of medical refractory patent ductus arteriosus in premature infants.* J Formos Med Assoc 2009;108: 72-7.
28. Kluckow M, Seri I, Evans N. *Functional echocardiography: an emerging clinical tool for the neonatologist.* J Pediatr 2007;150:125-30.