Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2023.23066

Experiences in Patent Ductus Arteriosus Closure of Preterm Infants Transported to Another Center for Surgical Ligation

Savaş Dedeoğlu[1], Ahmet Şaşmazel[2]

[1]Department of Pediatrics, Üsküdar University Faculty of Medicine, İstanbul, Turkey
[2]Department of Pediatric Cardiovascular Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey

What is already known on this topic?

- *Patent ductus arteriosus (PDA) results in increased pulmonary blood flow and stealing flow from systemic circulation due to left-to-right shunt. Serious complications for the cardiovascular system, including pulmonary edema, respiratory insufficiency, and heart failure, as well as intracranial hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and death may be observed.*

What this study adds on this topic?

- *Surgical PDA ligation is indicated in cases of failure of medical treatment or in situations such as contraindications to pharmacological agents and fluid restriction policies. We share our experiences of premature infants having surgical ligation of PDA in another center. This is the first study to explore the results of surgical ligation of PDA in external centers to which babies had to be transported.*

ABSTRACT

Objective: The timing of surgical patent ductus arteriosus ligation in preterm infants remains controversial. Early ligation (<2 or 3 weeks of life) benefits preterm infants with a lower incidence of bronchopulmonary dysplasia and necrotizing enterocolitis. We present patent ductus arteriosus ligation experience in premature infants who had been transported for closure to an outside centre other than the hospital they were hospitalized.

Materials and Methods: We retrospectively evaluated 17 consecutive patients who had undergone surgery of premature infant patent ductus arteriosus closure during the period of March 2009–December 2020. Patent ductus arteriosus had been clipped in 17 patients.

Results: The median birth weight and age were 930 g and 28 gestation weeks, respectively. The birth age of the sub-groups were A: ≤28 weeks and B: >28 weeks and birthweight were group I: ≤800 g and group II: >800 g. The median day of PDA ligation wasa 20 days, and patients with birthweight ≤800 g were ligated later than patients weighing >800 g. Two patients had intracranial hemorrhage, 6 had bronchopulmonary dysplasia, and 2 were dead. We found that exposure to large patent ductus arteriosus and low birth age in preterm babies was associated with longer hospitalization duration, preoperative mechanical ventilation time, and sepsis.

Conclusion: Infants exposed to moderate-to-large patent ductus arteriosus requiring intubation and resistant to medical therapy for more than 2 weeks should have surgical ligation as soon as possible.

Keywords: Surgical PDA ligation, premature infants, timing

INTRODUCTION

Patent ductus arteriosus (PDA) is the most frequently seen congenital cardiac lesion in neonates younger than 30 weeks of gestational age (GW).[1] A prolonged PDA may cause a left heart volume overload and pulmonary overcirculation as a result of the left-to-right shunt.[2]

An increased risk of bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD), prolonged assisted ventilation, necrotizing enterocolitis (NEC), pulmonary hemorrhage, intraventricular hemorrhage, renal impairment, and mortality have all been linked to the delayed closure of a hemodynamically significant PDA. Currently, different types of treatments available are (1) cyclooxygenase inhibitor–based pharmaceutical treatment and (2) surgical repair. Surgery is often reserved for individuals in whom pharmaceutical treatment is inadequate or inappropriate.[3,4] In preterm infants, it significantly reduces mortality and does not increase CLD, retinopathy of prematurity (ROP), or neurodevelopmental impairment (NDI). Lateral, posterolateral, and axillary thoracotomies are the most common surgical techniques for ligation of PDA.

Corresponding author:
Savaş Dedeoğlu
✉ savasdedeoglu@gmail.com
Received: April 6, 2023
Accepted: July 3, 2023
Publication Date: August 15, 2023

Cite this article as: Dedeoğlu S, Şaşmazel A. Experiences in patent ductus arteriosus closure of preterm infants transported to another center for surgical ligation. *Turk Arch Pediatr.* 2023;58(5):503–508.

To date, the timing of surgical PDA ligation in preterm infants remains controversial. Early ligation (<2 or 3 weeks of life) benefits preterm infants with a lower incidence of BPD and NEC.[5-8] In this study, we present our PDA ligation experience in premature infants who had not responded to medical treatment and were transferred for closure to an another center other than the hospital they had been hospitalized.

MATERIALS AND METHODS

We retrospectively evaluated 17 consecutive patients who had undergone surgery of premature infant PDA closure during the period of March 2009-December 2020.

All the patients were preterm neonates who required surgical ligation despite pharmacological agents or showed a large left-to-right shunt on echocardiograms and remained in congestive heart failure after failed attempts at medical closure with ibuprofen. Surgical ligation was also determined for preterm babies with contraindications to ibuprofen/paracetamol. A pediatric cardiologist (S.D.) had performed transthoracic echocardiography on all the infants, who were on mechanical ventilators and/or receiving medication for cardiac failure.

A moderate-to-large PDA was defined by a ductus internal diameter measuring >1.5 mm and 1 or more of the following echocardiographic criteria: a left atrium-to-aortic root ratio of 1:6, ductus flow velocity 2.5 m/s, and/or reversed diastolic flow in the descending aorta. The PDA was defined as small if it was less than 1.5 mm measured at the narrowest color Doppler flow intersection of the left pulmonary artery and PDA.[9] PDA exposure duration was expressed in days. The day of birth was considered day 0. Regardless of the previous duration or level of oxygen therapy, BPD was classified according to the Jensen's mode of respiratory support administered at 36 weeks' postmenstrual age.[10]

Infants in need of surgical ligation of PDA had been transported to another hospital. All operations (n = 17, 100%) were performed in the operating room. The PDA was clipped through an anterior minithoracotomy at the second intercostal space. After the surgery, all but 1 of the patients were transferred back to the hospital from which they had come. The other needed a median sternotomy due to complications; he was moved to the intensive care unit until sufficiently stable for transport.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences, Version 20.0 (IBM Corp.; Armonk, NY, USA). Scale data were described as mean ± SD for normal distributions and median (minimum–maximum value) for skewed distribution and categorical variables were expressed as frequency (percentage). Statistical analysis differences in normally distributed variables between 2 independent groups were compared by the Student's *t*-test, Mann–Whitney *U*-test was applied for comparisons of the non-–normally distributed data, and categorical variables were compared using the Pearson's chi-square test. Spearman's correlation analysis was used to evaluate the degrees of relation between variables. Statistical significance was assumed at $P < .05$.

RESULTS

Study Population and General Outcome

The median GW of the 17 infants who underwent PDA ligation through anterior minithoracotomy was 28 weeks (range 23-35). Nine patients (53%) were female, and 8 (47%) were male. There was no statistically significant difference in terms of sex. The median birthweight was 930 g (range 560-2690). Besides PDA, preoperative echocardiographic study revealed patent foramen ovale in 12 patients, atrial septal defects in 3 patients, and ventricular septal defects in 1 patient. The demographics and clinical characteristics of the patients are listed in Table 1.

The median PDA diameter was 2.0 mm and ranged from 1.8 to 4.0 mm. Twelve of the 17 infants (71%) had received at least 1 pharmacological treatment for PDA closure before ligation (Table 1). The median day of PDA ligation was 20.5 days of life and ranged between 10 and 76 days of life.

The median length of hospital stay was 82.5 days (range 17-168 days). Eighty-six percent of infants (12/14) had sepsis during hospitalization. Eight of 12 infants (66.7%) had other comorbidities, including BPD and intracranial hemorrhage (ICH). Six infants had BPD, 4 of whom were ligated at day 20. One patient with BPD had a syndrome with multiple congenital anomalies and died of multiorgan failure at 144 days of age. Two infants had ICH. One was born at 23 GW and weighed 560 g. He had a moderate PDA and received only 1 pharmacological treatment for PDA due to hematological problems. His PDA was ligated on the 35th day of life. The other infant with ICH was born at 26 GW, weighed 800 g, received 2 attempts of ibuprofen, and was ligated for PDA on day 22. Both infants with ICH had a long hospital stay of 168 and 82 days, respectively.

Two infants (12%) died. One with BPD has already been mentioned above. The other was a male infant of 820 g born at 25 GW who had a large ductus. An anterolateral thoracotomy was performed in the infraclavicular ductal region, and the PDA was ligated. However, 4 days postoperatively, a 2 cm raised, mobile, palpable bulge was observed under the PDA ligation incision mark. The bulge was more prominent when the baby was crying. On ultrasonography, a small portion of the lung was found to be herniating between the ribs at the palpable bulge (Figure 1). A possible explanation for this herniation was that the stitches of the intercostal muscles had broken open after the ligation.

Subgroup Analysis According to the Birth Age, Birthweight, and Day of Patent Ductus Arteriosus Ligation

As shown in Table 2, there were no significant differences between the subgroups of birth age (≤28 weeks vs. >28 weeks) or birthweight (≤800 g vs. >800 g) in terms of sex, PDA diameter, day of PDA ligation, use of inotropic support, pre- or postoperative ventilation duration, hospitalization duration, or the occurrence of sepsis.

Additionally, as shown in Table 3, there were no differences between patients ligated before and after 20 days (≤20 days vs. >20 days) considering sex, birthweight, use of inotropic support, pre- or postoperative ventilation duration, hospitalization

Table 1. Demographic and Clinical Characteristics of the Premature Infants

	Number of Patients	Median (25th-75th Percentile)	Range (Minimum–Maximum)
Sex, female/male, n (%)	17	9 (53)/8 (47)	
Birth age, GW	17	28 (26-29)	23-35
Birthweight, g	17	930 (750-1417)	560-2690
Apgar	16	5 (4.25-7.75)	2-8
Comorbidities, n (%)	17	12 (71)	
None		9 (53)	
Ambiguous genitalia		1 (6)	
Syndromic		2 (12)	
Intubation, n (%)	13	13 (100)	
At birth		8 (61.5)	
First 24 hours		1 (8)	
First 48 hours		4 (30.5)	
Surfactant exposure, n (%)	12	9 (75)	
Once		2 (17)	
≥2		7 (58)	
Heart failure, n (%)	17	14 (82)	
Inotropic support	17	10 (58.8)	
Dobutamine		5 (29.4)	
Dopamine and digoxin		5 (29.4)	
PDA diameter, mm	17	2.0 (2.0-3.0)	1.8-4.0
Pharmacological treatment for PDA closure	17	12 (71)	
None		1 (6)	
One course		7 (41)	
More than once		4 (24)	
Day of PDA ligation	16	20.5 (15.0-40.25)	10-76
Preoperative ventilation duration, days	12	19.0 (10.5-33.0)	0-71
Postoperative ventilation duration, days	12	18.5 (5.0-67.7)	2-92
Hospitalization duration, days	12	82.5 (57.5-105)	17-168
Presence of sepsis, n (%)	14	12 (86)	
Early sepsis, n (%)		6 (43)	
Late sepsis, n (%)		6 (43)	
Hospitalization comorbidities, n (%)	12	8 (66.7)	
None		4 (33.3)	
Intracranial hemorrhage		2 (16.7)	
Bronchopulmonary dysplasia		6 (50)	
Outcome, n (%)	17		
Alive		15 (88)	
Exitus		2 (12)	

PDA, patent ductus arteriosus.

duration, sepsis, or mortality (Table 3). However, infants ligated ≤20 days had lower birth ages than infants ligated more than 20 days [median 26 GW (25-27) vs. 29 GW (28-38) ($P < .001$)].

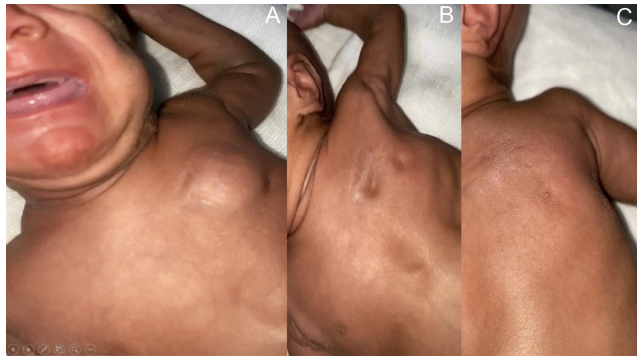

Figure 1. (A) Chest wall bulging while baby was crying. (B) Incision region during inspiration. (C) Chest wall while baby was in calm state.

DISCUSSION

Previous studies have reported that infants <28 weeks of gestation and exposed to a large PDA for 10 days have a significantly higher incidence of comorbidities than do those exposed to shorter durations of ductus patency or with a small ductus.[11-13] PDA persists in 70% of premature infants for up to several weeks after birth.[14] Early closure of the duct may reduce neonatal morbidities such as hypotension and hemorrhagic pulmonary edema and reduce the need for intensive respiratory support.[15] There is little information about whether exposure to a large PDA shunt or extended duration of exposure increases later neonatal morbidities, such as BPD and ICH.[16] Prolonged exposure to moderate-to-large PDAs causing prolonged duration of pulmonary hyperemia and systemic hypoperfusion may lead to worsening pulmonary status and poorer nutritional status at late ligation.[17] Also, longer exposure to PDA and mechanical ventilation are associated with worse neurodevelopmental outcomes.[18]

Surgical ligation of symptomatic PDA is mostly performed in cases where ibuprofen medication has failed or is contraindicated. Especially among very-low-birthweight (VLBW) infants, PDA closure rates with medical treatment are low.[19,20] There are reports suggesting that surgical PDA ligation is associated with an increased incidence of CLD, BPD, NEC, and ROP.[21,22] In reports from the early 2000s, logistic regression analysis was used to observe the effects of PDA-associated variables (presence of symptomatic PDA, the ductus response to indomethacin, and the use of surgical ligation) on the incidence of NEC, BPD, NDI, and death.[23,24] These studies have shown that surgical ligation of PDA is significantly associated with the development of BPD. However, it is important to note that in certain cases, BPD may occur independently of factors such as premature birth, low birth weight, mechanical ventilation, oxygen therapy, or other known risk factors that are commonly associated with BPD during the perinatal and neonatal periods. Although the study designs were not randomized controlled trials (RCTs) comparing surgical to medical PDA closure, the findings in these studies suggested an increased risk of 1 or more of the following outcomes related to surgical ligation: CLD, ROP, and neurosensory impairment.

Jhaveri et al[9] reported the results of 2 different approaches to infants born at age <27 GW who failed indomethacin treatment

Table 2. Subgroup Analysis According to the Birth Age and Birth weight

	Birth Age		*P*	Birth Weight		
	≤28 weeks	>28 weeks		≤800 g	>800 g	
	n = 8	n = 9		n = 6	n = 11	*P*
Sex, female, n (%)	5 (62.5)	4 (44)	.64$^{\chi 2}$	4 (67)	5 (45.5)	.62$^{\chi 2}$
PDA diameter, mm	2.0 (2.0-2.9)	2.0 (2.0-3.0)	.74^{u}	2.0 (1.95-2.7)	2.0 (2.0-3.0)	.40^{u}
Pharmacological treatment before ligation (no, once, ≥2)	0/1/4	1/4/2	.20^{u}	0/1/4	1/4/2	.20^{u}
Day of PDA ligation	22 (16-38)	20 (13-55.5)	.92^{u}	35 (20.5-57)	16 (11-41)	.14^{u}
Inotropic support, n (%)	5 (62.5)	5 (56)	1.0$^{\chi 2}$	3 (50)	7 (64)	.64$^{\chi 2}$
Postop ventilation duration,** days	44 (14.5-68.5)	5.0 (2.0-73.0)	.43^{u}	44 (14.5-68.5)	5.0 (20-73.0)	.34^{u}
Hospitalization duration,** days	102 (82.5-135)	65.0 (20.0-106.0)	.34^{u}	102 (82.5-135)	65.0 (20.0-106)	.14^{u}
Hospitalization comorbidities*	5 BPD 2 ICH	1 BPD		3 BPD 2 ICH	3 BPD	
Sepsis (no, early, late)**n	0/3/4	2/3/2	.26$^{\chi 2}$	0/2/4	2/4/2	.21$^{\chi 2}$

Continous data presented as median (25th-75th percentile) and categorical data presented as n (%).
BPD, bronchopulmonary dysplasia; ICH, intracranial hemorrhage.
*Data available for 16 patients.
**Data available for 14 patients. $^{\chi 2}$Pearson's chi-squared test. ^{u}Mann–Whitney *U*-test.

Table 3. Comparisons of Patients According to the Ductal Ligation Day

	PDA Ligation Day < 20	PDA Ligation Day > 20	
	n = 8	n = 9	*P*
Sex, female, n (%)	4 (67)	5 (45.5)	.64$^{\chi^2}$
Birthweight, g	780 (680-1118)	1400 (910-2340)	.027^{u}
Birth age, gestational weeks	26 (25-27)	29 (28-38)	<.001^{u}
Inotropic support, n (%)	5 (62.5)	5 (56)	1.0$^{\chi^2}$
Preoperative ventilation duration days	19 (14.5-31)	15 (7-52)	.64^{u}
Postoperative ventilation duration,** days	44 (11-68.5)	12 (2-73)	.43^{u}
Hospitalization duration,** days	102 (73.5-135)	72.0 (20.0-106)	.34^{u}
Sepsis (no, early, late),** n	0/3/4	2/3/2	.26$^{\chi^2}$
Exitus, n (%)	0	2 (25)	.47$^{\chi^2}$

Continuous data are presented as median (25th-75th percentile), and categorical data are presented as n (%).
PDA, patent ductus arteriosus.
**Data available for 14 patients. χ^2Pearson's chi-squared test. ^{u}Mann–Whitney *U*-test.
PDA, patent ductus arteriosus.

of the same center. In the first period, they tried an early surgical approach in which feedings were stopped, and all PDAs were ligated, while in the second period, a more conservative approach was adopted in which feedings continued, and PDAs were ligated only if cardiopulmonary compromise developed. All infants in both periods had similar rates of perinatal/neonatal risk factors as well as ventilator management. Interestingly, even though infants in the second period were exposed to larger PDA shunts for longer durations, the rates for CLD, sepsis, ROP, neurological injury, and death were still similar for both sets of patients.

On the other hand, in a recently reported meta-analysis comparing early with late ligation, the authors concluded that the early surgery might have a better respiratory outcome and nutritional status for PDA in preterm or VLBW infants.[25] There were no differences in mortality or postoperative complications between early and late ligations. The meta-analysis described late surgical ligation (the cutoff time of early and late ligation was 2-3 weeks of life) and included studies that involved patients who underwent surgical ligation because of ibuprofen/paracetamol failure, regardless of medical treatment before surgery.

In the PDA-TOLERATE trial results, which tolerated moderate-to-large PDAs for the first week in infants <28 weeks of gestation, PDA persisting beyond 10 days was associated with an increased risk of BPD and prolonged intubation requirement.[26]

In our country, surgical PDA ligation has been utilized as a "rescue" therapy for patients who fail medical intervention. This practice formed the basis of this study. We tried at least 1 course of medical treatment for ductal closure before deciding on surgical ligation. Therefore, in this study, we did not compare medical to surgical closure of PDA. The relatively small size of our study may have made it difficult to detect significant differences among some of our PDA exposure subgroups. Even though there were no significant differences in the neonatal demographic characteristics among the infants exposed to a moderate-to-large PDA for ≤20 days and those exposed for >20 days except birth age, unmeasured differences in practice, such as eagerness for the transfer, might have affected the rate of hospitalization comorbidities, including BPD and ICH.

Our patients had been transferred from their own health centers for surgical ligation and then transferred back just after the operation. Thermoregulatory instability and technical problems, such as loss of intravenous lines, malfunction, and inappropriate ventilation, are among the risks of transferring babies.[27] Although we did not encounter any problems in our patients, this is one of the major concerns of neonatologists working in health centers incapable of infant surgery and reticent about giving their consent to early surgical ligation of PDA.

We found that longer exposure to PDA was associated with a significant increase in the risk of developing hospitalization comorbidities, including ICH, BPD, sepsis, and longer ventilation duration. Six of our patients had BPD. Although we are unable to offer good estimations of the duration of the "waiting time," the transport to a center with the surgical capacity to have the PDA ligated may have adversely affected outcomes for some of our patients.

The limitations of the study were first we had few patients to make comparisons and secondly the data were collected retrospectively from records.

In conclusion, even though we have a limited number of patients, we share our experiences of premature infants having surgical ligation of PDA in another center. This is the first study to explore the results of surgical ligation of PDA in centers to which babies had to be transported. According to our observation, infants with moderate-to-large PDAs requiring intubation and resistant to medical therapy for more than 2 weeks should have surgical ligation as soon as possible. Our findings support the need for RCTs to reexamine the benefits and risks of surgical ligation timing for PDA.

Data Availability Statement: Data are available as per your request.

Ethics Committee Approval: This study was approved by the Ethics Committee of Üsküdar University of Medical Sciences, İstanbul, Turkey (Üsküdar University, REC:61351342/November 2, 2022). This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients' parents who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Data Collection and/or Processing – S.D., A.S.; Analysis and/or Interpretation – S.D.; Critical Review – S.D., A.S.

Acknowledgments: The authors would like to appreciate Assoc. Prof. Dr. Reyhan Dedeoğlu for support in editing the manuscript.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. *Pediatrics*. 2010;125(5):1020-1030. [CrossRef]
2. Noori S, Seri I. The VLBW neonate with a hemodynamically significant patent ductus arteriosus during the first postnatal week. In: Kleinman CS, Seri I, eds. *Hemodynamics and Cardiology. Neonatal Questions and Controversies*. Philadelphia, PA: Saunders Elsevier; 2008:179.
3. Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? *Curr Opin Pediatr*. 2004;16(2):146-151. [CrossRef]
4. 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(1):69-75. [CrossRef]
5. Jaillard S, Larrue B, Rakza T, Magnenant E, Warembourg H, Storme L. Consequences of delayed surgical closure of patent ductus arteriosus in very premature infants. *Ann Thorac Surg*. 2006;81(1):231-234. [CrossRef]
6. Lee JH, Ro SK, Lee HJ, et al. Surgical ligation on significant patent ductus arteriosus in very low birth weight infants: comparison between early and late ligations. *Korean J Thorac Cardiovasc Surg*. 2014;47(5):444-450. [CrossRef]
7. Ibrahim MH, Azab AA, Kamal NM, et al. Outcomes of early ligation of patent ductus arteriosus in preterms, multicenter experience. *Medicine*. 2015;94(25):e915. [CrossRef]
8. Fonseca E, Georgiev SG, Gorenflo M, Loukanov TS. Patent ductus arteriosus in preterm infants: benefits of early surgical closure. *Asian Cardiovasc Thorac Ann*. 2014;22(4):391-396. [CrossRef]
9. Jhaveri N, Moon-Grady A, Clyman RI. Early surgical ligation versus a conservative approach for management of patent ductus arteriosus that fails to close after indomethacin treatment. *J Pediatr*. 2010;157(3):381-7.e1. [CrossRef]
10. Jensen EA, Dysart K, Gantz MG, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. *Am J Respir Crit Care Med*. 2019;200(6):751-759. [CrossRef]
11. Thébaud B, Lacaze-Mazmonteil T. Patent ductus arteriosus in premature infants: A never-closing act, 5/6. *Paediatr Child Health*. 2010;17(5):267-270. [CrossRef]
12. Clyman RI, Hills NK, Liebowitz M, Johng S. Relationship between duration of infant exposure to a moderate to large patent ductus arteriosus shunt and the risk of developing bronchopulmonary dysplasia or death before 36 weeks. *Am J Perinatol*. 2020;37(2):216-223. [CrossRef]
13. Mirza H, Garcia J, McKinley G, et al. Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants. *J Perinatol*. 2019;39(12):1648-1655. [CrossRef]
14. Sung SI, Chang YS, Chun JY, et al. Mandatory closure versus non intervention for patent ductus arteriosus in very preterm infants. *J Pediatr*. 2016;177:66-71.e1. [CrossRef]
15. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(2):F99-F104. [CrossRef]
16. Sellmer A, Bjerre JV, Schmidt MR, et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(6):F505-F510. [CrossRef]
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(5):1509-1509. [CrossRef]
18. Youn Y, Seo YM, Yum SK, Sung IK. Patent ductus arteriosus ligation on neurodevelopmental outcomes at corrected 2 years. *Ital J Pediatr*. 2019;45(1):110. [CrossRef]
19. Trus T, Winthrop AL, Pipe S, Shah J, Langer JC, Lau GY. Optimal management of patent ductus arteriosus in the neonate weighing less than 800 g. *J Pediatr Surg*. 1993;28(9):1137-1139. [CrossRef]
20. Avsar MK, Demir T, Celiksular C, Zeybek C. Bedside PDA ligation in premature infants less than 28 weeks and 1000 grams. *J Cardiothorac Surg*. 2016;11(1):146. [CrossRef]
21. Bancalari E, Claure N, Gonzalez A. Patent ductus arteriosus and respiratory outcome in premature infants. *Biol Neonate*. 2005;88(3):192-201. [CrossRef]
22. Malviya MN, Ohlsson A, Shah SS. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. *Cochrane Database of Systematic Reviews*. 88(3):192-201. [CrossRef]
23. 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(6):1165-1174. [CrossRef]
24. Kabra NS, Schmidt B, Roberts RS, et al. 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(3):229-234. [CrossRef]

25. Hualin Y, Fan M, Yifei L, Kaiyu Z, Yimin H, Chaomin W. The optimal timing of surgical ligation of patent ductus arteriosus in preterm or very-low-birth-weight infants a systematic review and meta-analysis. *Medicine*. 2020;99(9): e19356.
26. Clyman RI , Liebowitz M, Kaempf J, et al. PDA-TOLERATE trial: an exploratory randomized controlled trial of treatment of moderate-to-large patent ductus arteriosus at 1 week of age. *J Pediatr*. 2019;205:41-48.e6. [CrossRef]
27. Jennings RB Jr, Innes BJ, Wirth FH, et al. Bedside patent ductus ligation in prematures. *Circulation*. 1975;52(suppl 2):101.