Role of prophylactic surgical ligation of patent ductus arteriosus in extremely low birth weight infants: Systematic review and implications for clinical practice

Rafat Mosalli, Khalid AlFaleh[1], Bosco Paes[2]

Departments of Pediatrics, Omm Al-Qura University, Mecca, [1]King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [2]McMaster University, Hamilton, Ontario, Canada

ABSTRACT

Objectives : **To investigate the effectiveness and safety of prophylactic surgical ligation of patent ductus arteriosus (PDA) on mortality and morbidity of preterm infants weighing less than 1000 g at birth.**

Materials and Methods : **The study conducted a systematic search of available database from 1996-2008. Retrieved articles were assessed for eligibility and data was abstracted independently by two reviewers. Decisions to include studies for review and the methodological quality of included studies were asssessed in duplicate based on predetermined criteria. No language restrictions were applied.**

Results : **Only one eligible study that enrolled 84 extremely low birth weight infants was identified. Prophylactic surgical ligation of PDA resulted in a statistically significant reduction of severe stage II or III necrotizing enterocolitis, [RR 0.25, 95% CI (0.08, 0.83), *P* value 0.02, number needed to treat 5]. The study, however, found no statistically significant difference in mortality, intraventricular hemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity.**

Conclusions : **Current evidence does not support the use of prophylactic surgical ligation of PDA in the management of the preterm infants.**

Keywords : Extremely low birth weight infants, patent ductus arteriosus, surgical ligation, systematic review

DOI : 10.4103/0974-2069.58313

INTRODUCTION

Patent ductus arteriosus (PDA) is the most common cardiac condition among preterm infants. It affects approximately 40-55% of preterm infants born at less than 29 weeks gestation and/or weighing fewer than 1500 g at birth.[1-3] In spite of significant advances in neonatal care over the last two decades, the approach to PDA management remains one of the most controversial topics in neonatal medicine.

PDA remains hemodynamically significant in preterm infants for a variety of reasons including decreased ductal sensitivity to partial pressure of oxygen, increased circulating prostaglandin E2, and increased ductal tissue sensitivity to prostaglandin E2 and nitric oxide.[4,5] A hemodynamically significant PDA is associated with left to right shunting of systemic blood with subsequent pulmonary overcirculation and a diastolic steal that results in hypoperfusion of vital organs. In extremely low birth weight (ELBW) infants, symptomatic PDA increases the risk of prolonged ventilation and oxygen requirements, pulmonary hemorrhage[6] and bronchopulmonary dysplasia (BPD).[7-9] The diastolic steal is associated with renal hypoperfusion,[10] intestinal ischemia, necrotizing enterocolitis (NEC), reduced middle cerebral artery blood flow velocity[11-14] and decreased superior vena cava (SVC) flow with concurrent increased risk of intraventricular hemorrhage (IVH).[15,16] If not managed appropriately, complications of symptomatic PDA may lead to death.[17] The increased number of

Address for correspondence: Dr. Rafat Mosalli, Umm Al-Qura University, Department of Pediatrics, P.O Box 7607, Mecca, Saudi Arabia.
E-mail:rafatmosali@hotmail.com

surviving preterm infants has led to a higher number of infants requiring medical or surgical intervention for PDA. Standard therapies include fluid restriction and use of cyclooxygenase inhibitors such as indomethacin or ibuprofen.

Surgical ligation is used when medical treatment fails or is contraindicated.[18-20] There is no consensus on the best time of treatment and optimal management strategy among this high-risk vulnerable population. Prophylactic indomethacin has been shown to have favorable intermediate outcomes such as reduction in risk of significant PDA, need for surgical ligation, severe intraventricular hemorrhage[21,22] and pulmonary hemorrhage.[23] Prophylactic indomethacin has not been shown to alter long-term outcomes including the rate of survival without neurosensory impairment at 18 months of corrected age[22] Given the limitation of medical treatment, prophylactic surgical closure of PDA may be a reasonable alternative in a high risk population, since it results in ultimate ductal closure and, therefore, might prevent associated neonatal morbidities.

Routine surgical ligation of a PDA refractory to medical treatment is widely practiced[24-27] However, there is no clear evidence that surgical ligation of a hemodynamically significant PDA is associated with improved long term outcome in preterm infants. Furthermore, surgery may potentially result in significant morbidity such as pneumothorax, hypothermia, intra-operative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy and thoracic scoliosis. On the other hand, there are reports suggesting that surgical ligation may be the preferred first line of treatment when compared to indomethacin in preterm infants less than 800 g.[3,25] Even though there may be a general consensus on the use of indomethacin as initial therapy for a symptomatic PDA while reserving surgical ligation for indomethacin failures, this therapeutic approach may not represent the optimal management of PDA in ELBWinfants who are at greatest risk for PDA.[28]

The primary objective of this systematic review was to determine the impact of prophylactic surgical ligation of PDA on mortality and morbidities in preterm infants less than 1000 g at birth as compared to no prophylaxis or use of prophylactic cyclooxygenase inhibitors. The secondary objective was to investigate the role of prophylactic ligation in a subgroup of high risk infants weighing less than 750 g at birth.

MATERIALS AND METHODS

The systematic review protocol was approved by the Cochrane Neonatal Review Group (CNRG). The selection criteria included studies that were randomized or quasi-randomized clinical trials, and the participants were preterm infants with less than 28 weeks gestation or less than 1000 g at birth who were on assisted ventilation and/or supplemental oxygen without clinical signs of a hemodynamically significant PDA.

The intervention was prophylactic surgical ligation of the PDA (i.e. procedure done during the first 72 hours of life in asymptomatic ELBW infants) versus no prophylactic intervention or medical prophylaxis (cyclooxygenase inhibitors) without dose specification.

The criteria for an asymptomatic or "silent ductus" include echocardiographic demonstration of a left to right shunt across the PDA, presence of a ductal size greater than 1.5 mm, left atrial: Aortic root ratio over 1.3 or end diastolic reversal of aortic blood flow in the absence of clinical signs such as a murmur, bounding pulses, overactive precordium and hemodynamic or respiratory compromise attributable to the PDA. The outcome measures were all causes of neonatal mortality at 36 weeks postmenstrual age and BPD defined as oxygen requirement at 36 weeks postmenstrual age. Other secondary outcomes were IVH; severe grade III–IV, IVH as per Papile criteria,[28] severe NEC (stage II or more) as per Bell's criteria[29] periventricular leukomalacia (PVL) defined as cystic changes in the periventricular area, retinopathy of prematurity (ROP) (defined by ICORP classification, any ROP and severe ROP stage 3 or worse), nosocomial sepsis, defined as positive bacterial blood or cerebrospinal fluid cultures taken beyond five days of age, time to establish full enteral feeds (days), duration of ventilation and supplemental oxygen, duration of hospital stay, neurodevelopment impairment i.e. rates of cerebral palsy, cognitive delay defined as a Mental Development Index score of less than 70 (2 SD below the mean of 100) on the Bayley Scales of Infant Development II,[30] deafness, blindness or their composite reported at 18 months corrected age or later, pneumothorax and vocal cord palsy.

The following databases were used for identification of studies: OVID MEDLINE-National Library of Medicine (1966 to December 2008) using the following subject headings (MeSH) and text word terms: "Neonate(s), newborn(s), infant(s), PDA, ligation, indomethacin, ibuprofen, cyclooxygenase inhibitors and publication type 'controlled trial'. No language restrictions were applied. Other databases including EMBASE (1980 to December 2008), the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 4, 2008) were searched. Two review authors conducted the electronic database search independently. A manual search of the abstract books published from the Society of Pediatric Research (SPR) and the European Society of Pediatric Research (ESPR) for the period of 1985-2008 was performed. Additional citations were sought using references in articles retrieved from searches. Subject experts were contacted to identify the

unpublished and ongoing studies. Two review authors independently screened candidate articles to check the eligibility for inclusion in the review.

Standard methods of Cochrane collaboration and its neonatal group were used to assess the methodological quality (validity criteria) of the trials. For each trial, information was sought regarding the method of randomization, blinding and reporting of all outcomes of all infants enrolled in the trial. Each criteria was assessed as yes, no, can't tell. Retrieved articles were assessed for eligibility and data abstracted independently by two review authors. Discrepancies were resolved by discussion and consensus.

RESULTS

Initial electronic search using OVID MEDLINE and EMBASE yielded 106 MEDLINE and 86 EMBASE potentially relevant citations. After reading abstracts, two articles were identified as potentially relevant. Review of full text articles identified a study[31] investigating the use of prophylactic PDA surgical ligation in preterm infants. Only one study[32] was excluded because surgery was done after one week of birth for infants needing ventilation or oxygen support and the intervention was not prophylactic. There was total agreement among both review authors with regard to the search process.

Cassady *et al.* carried out a single center, randomized controlled trial.[31] Eighty-four preterm infants less than 1000 g were enrolled in both study arms. The surgical intervention group (n = 40) had a PDA ligation within 24 hours of life following a pre-specified protocol while the control group (n = 44) received standard care defined as:

1. Nasal CPAP initially for hypoxemia due to RDS or pulmonary edema.
2. Endotracheal intubation and ventilation for respiratory failure (PCO_2 greater than 70) or refractory apnea.
3. Bedside echo and radionuclide studies routinely performed to detect silent ducts.

Ligation was performed on infants with a clinically "silent" PDA who required supplemental oxygen in the first 24 hours of life but had a hemodynamically significant duct based on predefined criteria which included a pulmonary to systemic flow ratio greater than 3.0 or ventilator dependence with a large systemic-pulmonary PDA shunt confirmed by echocardiography and Doppler examination. Neither group received any cyclooxygenase inhibitor during or before the study period. Infants with echo defined criteria or hemodynamically significant PDA underwent subsequent surgical ligation. The main outcome measures were survival to one year after birth, NEC (Bell's stage III, IV), IVH defined by cranial ultrasound, BPD and ROP. Long term neurosensory outcomes were not assessed. The study was suspended after 14 months since only a few physicians were available to conduct the study properly.

Outcomes measured

Death

The prespecified outcome of all causes of neonatal mortality at 36 weeks postmenstrual age was not presented in the study. The author presented data with regard to death within 28 days of birth and within one year of life. 16/40 infants died within 28 days of life in the treatment group as compared to 20/44 in the control group [RR 0.88, 95% CI (0.53, 1.45), *P* value 0.62]. A total of 25/40 infants died within one year of age in the treatment group as compared to 26/44 in the control group [RR 1.06, 95% CI 0.75, 1.49), *P* value 0.75].

Severe grade III, IV intraventricular hemorrhage

The study saw 16/35 infants in the prophylactic ductal ligation group who developed grade III or IVH as compared to 23/41 in the control group [RR 0.81, 95% CI (0.52, 1.28), *P* value 0.37]. Data with regard to all grades of IVH were not presented in the published manuscript.

Severe necrotizing enterocolitis

There was significant reduction of severe NEC in the prophylactic surgical group. The assessment of this outcome was blinded. Only 3/40 infants in the prophylactic ductal ligation group developed severe stage III or IV NEC as compared to 13/44 in the control group [RR 0.25,95% CI (0.08,0.83), *P* value 0.02, number needed to treat (NNT) 5] [Figure 1].

Bronchopulmonary dysplasia

The definition used for BPD was different from the prespecified definition (i.e. oxygen requirement at 36 weeks postmenstrual age). In the report by Cassady *et al.*, BPD was defined using the criteria of Bancalari *et al.* (histological finding or radiographic criteria). 15/24 infants in the prophylactic ligation group developed BPD as compared to 14/24 in the control group [RR 1.07, 95% CI (0.68, 1.69), *P* value 0.77].

Retinopathy of prematurity

The criteria and method of measurement of this outcome was not specified in the manuscript. 7/22 infants in the prophylactic group developed ROP as compared to 10/21 in the control group [RR 0.67, 95% CI (0.31, 1.43), *P* value 0.30]. Out of these, only one infant had severe stage III or IV ROP in the prophylactic ligation group as compared to three in the control group [RR 0.32, 95% CI (0.04, 2.8), *P* value 0.30].

Subgroup analysis

The secondary objective of this review was to investigate the role of prophylactic surgical ligation in a subgroup of high risk infants weighing less than 750 g at birth. No data

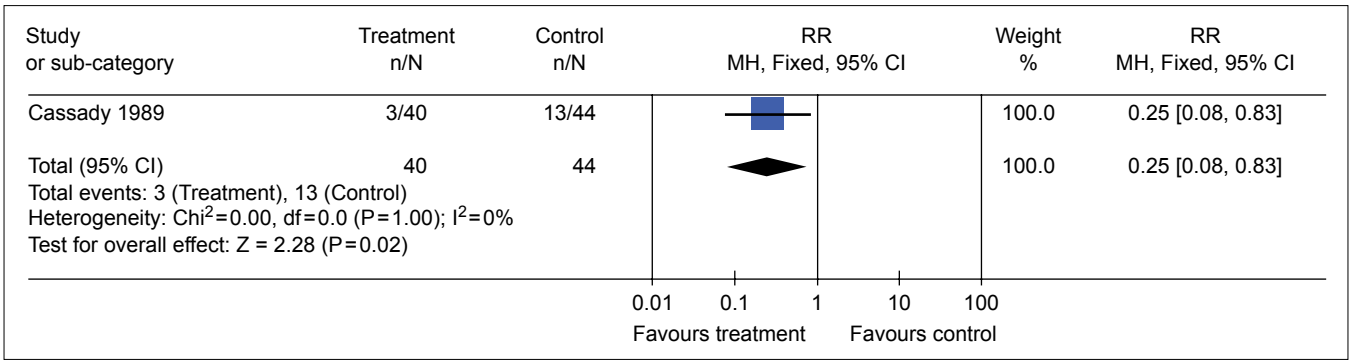

Figure 1: Comparison of prophylactic ductal ligation versus control group: Outcome for severe necrotizing enterocolitis

was found in the included trial that relates specifically to this high-risk group. Data with regard to nosocomial sepsis, hospital stay, pneumothorax, vocal cord palsy, periventricular leukomalacia, and long term neurosensory impairment were not presented in this study.

DISCUSSION

We found only one study (Cassady *et al.*) that compared the effect of early prophylactic PDA ligation in ELBW infants versus later or no intervention eligible for inclusion in this review. Prophylactic surgical ligation of the duct resulted in no significant differences in mortality, IVH, BPD and ROP between the two study groups. Interestingly, the study showed a significant reduction of severe NEC in the prophylactic surgical group as compared to infants who received selective treatment for hemodynamically significant PDA (20 vs. 79%). While it is possible this is a result of a true effect, it is important to note that feeds were introduced earlier in the control group. Strong conclusions cannot be made since the study is underpowered to detect minimally important clinical differences in outcomes other than NEC.

Ligation of the ductus arteriosus is not without risks and it is often associated with significant hypotension and postoperative cardio respiratory instability secondary to cardiovascular physiologic adaptation. There is limited information on the ability of preterm infants to compensate for the dramatic changes in left ventricular afterload following ligation.[33] Surgical ligation also poses risks of potential morbidity from infection, pneumothorax, chylothorax and vocal cord paralysis. Surgical ligation may not be easily accessible to all centers. In addition, evidence is accumulating regarding PDA ligation and its association with a higher incidence of BPD, ROP and unfavorable neurodevelopment outcomes.[34-38] Surgical ligation was found to be significantly associated with chronic lung disease independent of gestational age, variables related to PDA care and other pertinent perinatal and neonatal risk factors.[36]

Since the publication of the included trial, the practice of neonatal medicine has advanced significantly. Over the last 16 years, many trials were published addressing the efficacy of prophylactic cyclooxygenase inhibitors (i.e. indomethacin and ibuprofen) in reducing the incidence of PDA and other short and long-term morbidities in ELBW infants. The use of prophylactic indomethacin reduces the incidence of PDA by more than 50%, surgical ligation of the duct by 50% and severe grade III and IV IVH by 35% with no apparent adverse effect in long term neurosensory outcomes.[21,39] With the high rate of spontaneous closure, availability of effective safe medical therapies, potential short and long-term complications of prophylactic surgical ligation, and the recent doubts raised concerning the need to close all significant PDA's in preterm infants,[40-42] there is no obvious role for prophylactic surgical ligation in the management of preterm infants.

Current evidence demonstrates that prophylactic indomethacin given to preterm infants reduces the incidence of symptomatic PDA, severe IVH, and serious pulmonary hemorrhage.[21-23] Despite the reduction of the aforementioned morbidities (all of which are associated with poor long-term outcome), no improvements in long-term neurosensory outcome were noted. Giving indomethacin to an unselected group of infants, irrespective of the ductal size, is a possible explanation.[43] It has been suggested that future studies aimed at preventing IVH and improving neurodevelopment outcome using medical agents to close the PDA should be directed at infants with large, hemodynamically significant PDA in the first hours of life.[43,44]

The conclusions of our review are weakened by the inclusion of only one, small trial that addressed the intervention under study.

Implications for practice

Despite numerous trials regarding ductal closure, the risks and benefits of interventional strategies versus

conservative treatment, both in the short and long term, remain unanswered. Two large multicenter RCTs produced a wave of change in the use of indomethacin between 1991-2004 which impacted the incidence of PDA. The National Institute of Child Health and Development's (NICHD) National Research Network Registry showed that the increased use of indomethacin following the Ment trial in 1994, resulted in a significant reduction in the incidence of PDA in infants with less than or equal to 25 weeks gestation up to greater than or equal to 28 weeks with a corresponding decrease in PDA ligation in infants less than 26 weeks.[45,46] The publication of the TIPP trial in 2001, which similarly showed a reduction in severe IVH but without an improvement in neurocognitive outcome led to a subsequent decrease in the use of indomethacin between 2002-2004, with a corresponding increase in ductal ligation.[22] Although the anticipated effect size (greater than or equal to 20%) was not achieved in the TIPP trial, the results from the NICHD indicated that the results of the study significantly impacted clinical practice. It can be argued that the use of indomethacin prophylaxis offers measurable clinical benefits and given the lack of adverse long term neurological sequelae based on 12 year follow-up, perhaps should be reserved for patients in neonatal intensive care nurseries where the incidence of IVH and PDA are high.[47,48]

With regard to the choice between ibuprofen versus indomethacin for ductal closure, a recent phase III RCT demonstrated the safety and efficacy of intravenous ibuprofen while a systematic review confirmed that both drugs were equally effective without differences in relevant morbidities and mortality.[49,50] More importantly, indomethacin has a protective effect on IVH unlike ibuprofen but the latter is associated with a reduced risk of oliguria.[50,51] Treatment decisions should therefore be made based on clinical status and potential drug side effects.

CONCLUSION

Our systematic review of literature revealed that prophylactic surgical ligation of the PDA did not decrease mortality or the incidence of BPD in ELBW infants. A significant reduction in the incidence of stage II or III NEC was noted.

Prophylactic surgical therapy is not indicated in the management of the preterm infants in view of the lack of statistically significant benefit, the high rate of spontaneous closure, availability of effective and safe medical therapies, and the potential short and long-term complications of surgical ligation. A well powered large randomized controlled trial to investigate early targeted prophylactic use of cyclooxygenase inhibitors (within first 24 hours of life and based on echocardiographic criteria) in reducing neonatal morbidities and long-term neurosensory outcomes in ELBW infants is warranted. We recognize that echocardiography is not readily available in the majority of centers, but this should not detract from the importance of designing a pragmatic trial based on ductal severity to clearly delineate those infants that truly merit intervention without posing additional risk.[40,44] In the absence of efficiently conducted trials targeting infants specifically with a hemodynamically significant ductus arteriosus for treatment, it may be considered ethically unsound to use cyclooxygenase inhibitors without proper justification.

ACKNOWLEDGMENT

We would like to thank Dr. Roger Soll for his thoughtful advice throughout the process of our review preparation.

REFERENCES

1. Mouzinho AI, Rosenfeld CR, Risser R. Symptomatic patent ductus arteriosus in very-low-birth-weight infants: 1987-1989. Early Hum Dev 1991;27:65-77.
2. Reller MD, Rice MJ, McDonald RW. Review of studies evaluating ductal patency in the premature infant. J Pediatr 1993;122:S59-62.
3. Trus T, Winthrop AL, Pipe S, Shah J, Langer JC, Lau GY. Optimal management of patent ductus arteriosus in the neonate weighing less than 800g. J Pediatr Surg 1993;28:1137-9.
4. Clyman R. Developmental physiology of the ductus arteriosus. Fetal and Neonatal Cardiology. Philadelphia: WB Saunders; 1990. p. 64-75.
5. 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.
6. Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr 2000;137:68-72.
7. Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: Changes in pathogenesis, epidemiology and definition. Semin Neonatol 2003;8:63-71.
8. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr 1979;95:865-6.
9. Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995;126:605-10.
10. Hammerman C. Patent ductus arteriosus. Clinical relevance of prostaglandins and prostaglandin inhibitors in PDA pathophysiology and treatment. Clin Perinatol 1995;22:457-79.
11. Martin CG, Snider AR, Katz SM, Peabody JL, Brady JP. Abnormal cerebral blood flow patterns in preterm infants with a large patent ductus arteriosus. J Pediatr 1982;101:587-93.

12. Nestrud RM, Hill DE, Arrington RW, Beard AG, Dungan WT, Lau PY, *et al*. Indomethacin treatment in patent ductus arteriosus. A double-blind study utilizing indomethacin plasma levels. Dev Pharmacol Ther 1980;1:125-36.
13. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr 1994;125:270-7.
14. 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.
15. Dudell GG, Gersony WM. Patent ductus arteriosus in neonates with severe respiratory disease. J Pediatr 1984;104:915-20.
16. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/ intraventricular hemorrhage in premature infants. Pediatrics 2003;112:33-9.
17. Cotton RB, Stahlman MT, Kovar I, Catterton WZ. Medical management of small preterm infants with symptomatic patent ductus arteriosus. J Pediatr 1978;92:467-73.
18. Clyman RI. Recommendations for the postnatal use of indomethacin: An analysis of four separate treatment strategies. J Pediatr 1996;128:601-7.
19. Kitterman JA, Edmunds LH Jr, Gregory GA, Heymann MA, Tooley WH, Rudolph AM. Patent ducts arteriosus in premature infants. Incidence, relation to pulmonary disease and management. N Engl J Med 1972;287:473-7.
20. Wagner HR, Ellison RC, Zierler S, Lang P, Purohit DM, Behrendt D, *et al*. Surgical closure of patent ductus arteriosus in 268 preterm infants. J Thorac Cardiovasc Surg 1984;87:870-5.
21. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev 2002;3:CD000174.
22. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, *et al*. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966-72.
23. Alfaleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B. Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: Results from the trial of indomethacin prophylaxis in preterms. Pediatrics 2008;121:e233-8.
24. Chen KB, Tu KT, Cheng HC, Wu YL, Chang JS. The anesthetic management of a preterm infant weighing 500grams undergoing ligation of patent ductus arteriosus - A case report. Acta Anaesthesiol Sin 1999;37:89-92.
25. Palder SB, Schwartz MZ, Tyson KR, Marr CC. Management of patent ductus arteriosus: A comparison of operative v pharmacologic treatment. J Pediatr Surg 1987;22:1171-4.
26. Pokharel R, Hisano K, Yasufuku M, Ataka K, Okada M, Yoshimoto S, *et al*. Ligation of medically refracted patent ductus arteriosus (PDA) in an extremely low body weight premature infant. Surg Today 1998;28:1290-4.
27. Satur CR, Walker DR, Dickinson DF. Day case ligation of patent ductus arteriosus in preterm infants: A 10 year review. Arch Dis Child 1991;66:477-80.
28. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
29. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al*. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
30. Bayley N. Manual for the Bayley Scales of Infant Development. 2nd ed. San Antonio, Tex: Psychological Corporation; 1993.
31. Cassady G, Crouse DT, Kirklin JW, Strange MJ, Joiner CH, Godoy G, *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.
32. Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 1978;93:647-51.
33. Teixeira LS, McNamara PJ. Enhanced intensive care for the neonatal ductus arteriosus. Acta Paediatr 2006;95:394-403.
34. 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.
35. Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study. J Pediatr 1983;102:895-906.
36. 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.
37. Malviya M, Ohlsson A, Dhah S. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants.Cochrane Database Syst Rev 2008;1:CD003951.
38. Raval MV, Laughon MM, Bose CL, Phillips JD. Patent ductus arteriosus ligation in premature infants: Who really benefits, and at what cost? J Peaditr Surg 2007;42:69-75.
39. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants.Cochrane Database Syst Rev 2003;2:CD003745.
40. Bose CL, Laughon MM. Patent ductus arteriosus: Lack of evidence for common treatments. Arch Dis Child Fetal Neonatal Ed 2007;92:F498-502.
41. Laughon M, Bose C, Clark R. Treatment strategies to prevent or close a patent ductus arteriosus in preterm infants and outcomes. J Perinatol 2007;27:164-70.
42. 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;16:146-51.
43. 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.
44. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: The need for disease staging. Arch Dis Child Fetal Neonatal Ed 2007;92:F424-7.
45. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Vohr B, Allan W *et al*. Low-dose indomethacin and prevention of

intraventricular hemorrhage: A multicenter randomized trial. Pediatrics 1994;93:543-50.

46. Clyman RI, Saha S, Jobe A, Oh W. Indomethacin prophylaxis for preterm infants: The impact of 2 multicentered randomized controlled trials on clinical practice. J Pediatr 2007;150:46-50.
47. Vohr BR, Allan WC, Westerveld M, Schneider KC, Katz KH, Makuch RW *et al.* School-age outcomes of very low birth infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics 2003;111:e340-6.
48. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics 2009;123:1037-44.
49. Aranda JV, Clyman RC, Cox B, Van Overmeire B, Wozniak P, Sosenko I, *et al.* A randomized,double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus areteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol 2009;26:235-45.
50. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2008;1:CD003481.
51. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli F. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr 1999;135:733-8.

Source of Support: Nil, **Conflict of Interest:** None declared