Patent Ductus Arteriosus in Preterm Babies – When and How to Close

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Persistent patency of ductus arteriosus in preterm infants is well recognized in the era of modern preterm care. The prevalence of patent ductus arteriosus (PDA) in babies less than 1750 gram is 45% and it increases closer to 80% in very low birth weight (VLBW) babies less than 1200-gram weight (1). PDA with significant left to right shunt is associated with varied complications like Necrotizing enterocolitis (NEC), intra-ventricular hemorrhage (IVH), and chronic lung disease (CLD) in preterm babies (2). Effective and timely treatment of PDA enhances preterm survival and reduces risk of complications. Studies showed that closure of hemodynamically significant PDA is beneficial but the timing and best method of closure is not clear (3).

A hemodynamically significant duct is identified clinically by features of heart failure, bounding pulses, evidence of pulmonary over-circulation (tachypnea, tachycardia, and continued requirement of mechanical ventilation). An easily audible murmur often accompanies the hemodynamically significant duct, but this is typically absent if the duct is large and unrestrictive.

Echocardiography aids considerably in determining the hemodynamic significance of a PDA. A size of > 1mm/ Kg body weight is considered the minimum for the PDA to be of significance. However, a number of additional echocardiographic signs are helpful indicators of the hemodynamic significance of the PDA. The Doppler flow patterns across the PDA are useful. A very low diastolic flow velocity (< 10-20 mm Hg) across the PDA suggests a large flow across the PDA. A duct that is restrictive in diastole is unlikely to produce significant increase in the pulmonary blood flow. Diastolic flow reversal in the descending thoracic aorta at the level of the diaphragm is a consistent feature of a hemodynamically significant duct. A large left ventricle and left atrium are typically associated with large flows across the PDA. In presence of significant associated pulmonary hypertension the flow patterns across the PDA. Pulmonary arterial hypertension (PAH) is readily quantified by the peak systolic gradient across the PDA. In presence of severe PAH there is often late systolic flow reversal (Right to left flows) across the PDA. Diastolic flows across the PDA tend to remain left to right unless the pulmonary vascular resistance starts to exceed systemic vascular resistance.

Hemodynamically significant PDA may complicate the clinical outcome of preterm infants. Pharmacologic closure of PDA with indomethacin or ibuprofen seems to be the preferred initial management with high degree of success in many reports (3,4). Indomethacin provokes closure to majority of the cases but selected studies have shown that it may be ineffective in as high as 40% of cases (5). There may be reopening in as much as 35% of cases that initially responded to the drug (5). Indomethacin has been widely used for ductal closure in this situation but Indomethacin may affect renal, cerebral and gastrointestinal system leading to necrotizing enterocolitis, gastrointestinal hemorrhage or decrease in intra-cerebral oxygenation.

Also, in general indomethacin is most effective in closing the PDA in infants who need it the least

i.e. babies of 32-34 weeks gestational age and relatively larger infants who can better tolerate the hemodynamic effects of PDA. The younger the gestational age of the infant, the lesser is the likelihood of a response to indomethacin. Beyond 10 days postnatal age the ductus rarely responds to indomethacin.

Ibuprofen like Indomethacin belongs to the group of NSAIDs and is a cyclo-oxygenase inhibitor preventing the conversion of arachidonic acid to PGE_2 thus preventing patency of PDA. In the last few years, much evidence has emerged regarding the safety and efficacy of Ibuprofen for the treatment of preterm PDA. Ibuprofen does not impair cerebral auto regulation and has much less adverse effects on renal and mesenteric circulation.

A recent study conducted in a large number of preterm infants (6) suggests that Ibuprofen should be preferred as the first line of drug for closing PDA in preterm infants. Patients with oliguria, intraventricular hemorrhage, hyperbilirubinemia and thrombocytopenia were excluded in this trial; however, even in these situations Ibuprofen would not be safe.

In our experience in these 7 years, we have found oral Ibuprofen to be a safe and effective drug for closure of hemodynamically significant PDA in preterm infants. Two courses of the drug could be tried for effecting a pharmacologic closure, substantiated by echocardiography. However, significant PDAs nonresponsive to medical means and especially those disallowing the baby to be weaned off respiratory support need to be surgically ligated. This is best done in the NICU itself with the baby not having to be shifted to the cardiac operating room thereby preventing destabilization of the critically ill preterm. Larger randomized controlled trials for comparison with other drugs like Indomethacin and Mefenamic acid are warranted.

With the recent advancement in the neonatal cardiovascular surgery and postoperative care the risk of surgery in preterm PDA is very small. The cardiovascular surgeon can perform the ligation of PDA even off site in NICU thereby saving the complication of sick preterm transfer (3).

Traditionally the role of surgical ligation in management of PDA comes after the trial of medical management along with Ibuprofen or indomethacin. The indication of surgical ligation varies between different Neonatal Intensive care Units (NICU). Ligation can be considered in the following situations –

1. Failure of indomethacin or ibuprofen therapy
2. Hemodynamically significant PDA and presence of contraindications to indomethacin therapy. These contraindications include active bleeding, low platelet count, active or suspected NEC, creatinine > 2 mg% and known renal anomaly.
3. PDA with NEC. In these circumstances operative closure of PDA is always necessary before the NEC resolves and may be required as an emergency procedure.
4. Hemodynamically significant PDA after 10 postnatal days (6, 7,8).

Many studies have shown that there is no increased morbidity; mortality of surgical ligation and some studies claimed shorter ICU stays (9-12). A randomized controlled trial of early prophylactic ligation of PDA in < 1000-gram babies [84 babies] showed reduced risk of NEC in those who required supplemental oxygen (13). Whereas Brookes et al (2) in a study showed routine surgical ligation of PDA refractory to medical management may not reduce CLD, NEC and IVH. Bedside ligation of PDA in sick babies in NICU is also gaining popularity in view of reduction of transport related reduction of preterm newborns. This is a procedure now being carried out routinely in NICUs like ours in India, without much morbidity and excellent results. Trus and his colleagues have suggested that primary surgical ligation may provide the optimal management of PDA in carefully selected patients with extremely low birth weight less than 800 gm and larger LA/AO ratio (>1.5), who have high failure rate and significant complication in treatment with indomethacin (4).

The decision of surgical ligation of PDA in preterm babies should be individualized. Although indomethacin therapy is a reasonable treatment alternative, it is associated with significant complications. Ductus ligation may be preferable, especially in very low birth weight babies with significant PDA, because it is associated with low morbidity and almost certain degree of success (14). Recently, catheter based treatment has emerged as an alternative to surgery in selected preterm infants (15). Careful case selection through echocardiography is mandatory. Ducts that are < 3 mm in size with adequate ampulla can undergo coil occlusion. The procedure can be technically challenging and requires experienced operators. However, the morbidity of the procedure is minimal if the venous route is used and arterial puncture is avoided (16).

References:

1. Moore P, Brook MM, Heymann MA, Patent Ductus Arteriosus in Moss and Adams' Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adult. 6th edition, Lippincott Williams & Wilkins; 2000: 652-659.

2. Brooks JM, Travadi JN, Patole SK, Doherty DA and Simmer K in 'IS surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. Arch. Dis. Child. Fetal Neonatal Ed. 2005;90;235-239.

3. Mehta SK, Younosazai A, Peitz J , Achanti BP. Pharmacological Closure of the patent ductus arteriosus . Images Pediatr Cardiolo 2003;14:1-15.

4. Chung-I Chang . Surgical Treatment of Patent Ductus Arteriosus in Premature Infants with Extremely Low Birth Weight. Acta Cardiol Sin 2005;21:35-36.

5. Miyague NI. Preterm neonates with patent ductus arteriosus. Jornal de Pediatria - 2005;81:429-430.

6. Van Overmeire BV, Smets K, Lecoutere D, Vande Brock H, Weyler J, Degroote, *et al.* Comparison of Ibuprofen and Indomethacin for closure of patent ductus arteriosis. N Eng J Med 2000;343:674-681.

7. Joseph A. Kitterman, Shannon E. G. Hamrick, Roberta L. Keller. Patent Ductus Arteriosus, Intensive Care Nursery House Staff Manual, Eighth edition,UCSF Children's hospital, University of California, July 2003;Page 99-100.

8. Evans N . Patent Ductus Arteriosus, Department of Neonatal Medicine Protocol Book, Royal Prince Alfred Hospital Sydney, Australia, February 2001.

9. 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;164:1007-1009.

10. Malone PS, Roberts KD, Abrams LD, Jones S, Beasley J. Day-case ligation of patent ductus arteriosus in premature infants. J Ped Surg. 1987;22:284–285.

11. Hubbard C, Rucker RW, Realyvasquez F, Sperling DR, Hicks DA, Worcester CC, Amlie R, Huxtable RF, Bartlett RH, Gazzaniga AB. Ligation of the patent ductus arteriosus in newborn respiratory failure. J Ped Surg 1986;21:3-5.

12. Satur CRM, Walker DR, Dickinson DF. Day case ligation of patent ductus arteriosus in preterm infants: a 10-year review. Arch Dis Child. 1991;66:477-480.

13. Cassady G, Crouse DT, Kirklin JW, Strange MJ, Joiner CH, Godoy G Odrezin, GT, Cutter GR, Kirklin JK, Pacifico AD, 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. Eng J Med, 1989;320:1511-1516.

14. Little DC, Pratt TC, Blalock SE, Krauss DR, Cooney DR, Custer MD .Patent ductus arteriosus in micro preemies and full-term infants: the relative merits of surgical ligation versus indomethacin treatment. J Pediatr Surg. 2003 Mar;38(3):492-496.

15. Kannan BRJ, Anil SR, Padhi SS, Kumar RK: Catheter closure of the patent ductus arteriosus in sick ventilated infants, Indian Heart Journal 2004; 56: 232-234.

16. Kumar RK, Anil SR, Philip A, Sivakumar K, Bioptome-assisted coil occlusion of moderate-large patent arterial ducts in infants and small children, Catheterization and cardiovascular interventions 2004;62:266-271.