Review Article

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Patent Ductus Arteriosus: Advances and Controversies

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Introduction

Significant patent ductus arteriosus (PDA) is detected in nearly one-third of very-low-birth-weight neonates admitted to neonatal intensive care units.[1] Management of PDA in preterm neonates has been a conundrum ever since Powell, in 1963, reported the surgical closure of PDA in a preterm infant with respiratory distress syndrome.[2] Even after continued research, the indications and the optimal timing of closure of PDA in preterm infants still remain unclear. There is an uncertainty regarding the treatments that have a positive effect on both short-term and long-term outcomes. Here is an update on the present-day evidence regarding these aspects of PDA.

Physiologic Significance of Patent Ductus Arteriosus

Traditionally, it was thought that ductal shunting is not important immediately after birth and assumes clinical significance only after 3 to 5 days of postnatal life. There was a notion that ductus arteriosus of very preterm infants has minimal constriction in the early hours after birth and that early shunts are either balanced or right to left and hence not hemodynamically significant. This

notion has been challenged in recent times due to the increased use of ultrasound for diagnostic studies in preterm infants. Early functional echocardiography (echo) has now demonstrated that shunting is usually from left to right and is hemodynamically significant. This hemodynamically significant PDA (hsPDA) has been reported to occur through poorly constricted ductus even during the early hours after birth.[3]

In preterm infants, significant left-to-right shunt may cause pulmonary overcirculation and systemic hypoperfusion early after birth. Pulmonary overcirculation has been hypothesized to result in pulmonary edema and alveolar protein leakage, leading to surfactant inhibition, reduced lung compliance, increased ventilator requirements, and a possibly increased risk of brochopulmonary dysplasia (BPD).[4] Systemic hypoperfusion may similarly lead to end-organ hypoperfusion, myocardial dysfunction, and systemic hypotension with a resultant increase in morbidities such as necrotizing enterocolitis (NEC), altered intracerebral blood flow (ductal steal), intraventricular hemorrhage (IVH), and periventricular leukomalacia.[5]

Significant left-to-right shunting in PDA, in preterm infants, may be considered pathologic because of its association with increased risk of mortality, morbidity, and neurodevelopmental impairment in early childhood. Due to this pathologic nature of PDA, the management of hsPDA in preterm infants is based on its closure and prevention.

Outcomes of Ductal Closure

Various clinical trials have looked at the short-term and long-term outcomes of medical and surgical closure of PDA in preterm infants. Some of the trials have reported a reduction in the incidence of pulmonary hemorrhage and intracranial hemorrhage; however, none of these studies have reported any long-term benefits of closure of the ductus. The lack of evidence regarding the overall benefit of closure, despite the strong association between PDA and increase in mortality and morbidity in preterm infants, has led to the new thinking on the management strategy for such infants.[6]

Timing of Ductal Closure

Timing of closure of the ductus may play an important role in determining the outcome of the management strategy. Closure strategies can be considered at 5 stages of evolution of a symptomatic PDA, namely prophylactic closure, presymptomatic closure, symptomatic closure, closure on development of early signs of organ failure, and closure on onset of heart failure. Three of these strategies that need further consideration are discussed as follows:

1. Prophylactic closure

Prophylactic approach involves treating PDA in the first 24 hours of birth according to predefined weight and gestational age criteria. This is the best studied strategy in the management of PDA. A meta-analysis of 19 trials involving 2872 infants and the Trial of Indomethacin Prophylaxis in Preterms (TIPP) study (with a slightly larger study group) show that prophylactic closure using indomethacin reduces the need for PDA treatment and ligation later and prevents major IVH, without affecting mortality or long-term neurodevelopmental outcomes.[7,8]

A Cochrane systematic review of 6 randomized controlled trials (RCTs) of prophylactic ibuprofen enrolling 869 infants shows that ibuprofen reduces the need for later treatment including ligation but does not affect other outcomes, particularly IVH.[9]

2. Early presymptomatic closure (early targeted approach)

The hsPDA in preterm infants does not produce physical signs immediately. Classic clinical symptoms of hsPDA such as increased precordial activity, murmur, high bounding pulse, and increased ventilator requirements have been shown to develop only about 2 to 4 days later in the clinical course.[10] Hence, in the early period, functional echo may be the only method for early identification of hsPDA that is likely to remain open and cause significant left-to-right shunting.

The hsPDA is generally defined by[11]

- Duct diameter ≥ 1.4 mm/kg

- Left atrium to aorta (LA:Ao) ratio ≥ 1.4 with a sensitivity of 79% and specificity of 95%: This may however not be present always as the left atrium may decompress into the right atrium via the foramen ovale
- Increased left pulmonary artery diastolic flow velocity (mean diastolic flow velocity > 0.42 m/s and diastolic flow velocity > 0.20 m/s)
- Absent or reversed descending aorta diastolic flow

In a pilot RCT (DETECT trial), this early targeted echo-based treatment protocol was evaluated. Echo was done within the first 12 hours of birth in infants below 29 weeks of gestation. Infants with large ducts were randomized (double blind)—44 infants to indomethacin group and 48 infants to placebo group. The study had to be stopped midway due to the withdrawal of indomethacin from the Australian market. However, among the infants studied, PDA closure was found to significantly reduce the incidence of pulmonary hemorrhage although there was no significant effect of closure on the primary outcome of death or cranial ultrasound.[12]

Other similar trials (Baby-OSCAR in UK [ISRCTN84264977] and TRIOCAPI in France [ClinicalTrials.gov identifier: NCT01630278]) are now considering the effect of early targeted echo-based closure of PDA while recruiting infants for their studies. Although this strategy of early targeted approach seems to be the most promising way forward, cases need to be individualized and the approach cannot be recommended universally until more information is available.

3. Symptomatic closure

Attempting for closure of ductus after the infants become symptomatic not only exposes a minimum number of them to the risks of treatment but may also result in delay in the treatment of hsPDA. Although this is one of the least-studied approaches in recent times, it is the most widely practiced approach all over the world.[13]

Biochemical markers, such as B-type natriuretic peptide (BNP), have also been studied recently as markers for screening and diagnosis of hsPDA in preterm infants. Serial BNP measurement has been proposed as a useful tool to assess the hemodynamic significance and indomethacin responsiveness of PDA.[14]

Effect of Timing of Ductal Closure on Treatment Outcome

Prophylactic closure and early targeted echo-based closure are found to reduce the incidence of pulmonary hemorrhage and IVH and also the need for surgical ligation, but they may also unnecessarily expose some of the preterm infants to the hazards of therapy such as negative effects on the gastrointestinal and renal systems.

In addition to these strategies, presymptomatic therapy with the onset of hemodynamic symptoms is found to reduce the risk of development of NEC in preterm infants with PDA.[15,16] However, a recent finding surprisingly shows that nonintervention in hsPDA compared with mandatory closure reduces the risk of BPD in extremely low-birth-weight infants.[17]

Medical Interventions for Ductal Closure

There is less controversy on the methods of medical closure of a significant PDA. Drugs such as indomethacin, ibuprofen, and paracetamol may be used for pharmacologic closure. Majority of the studies have used indomethacin for ductal closure. Ibuprofen is also proved to be equally effective with fewer side effects on the renal, cerebral, and mesenteric blood flow. Oral route of administration of ibuprofen has been found to be more effective than the intravenous route.[18] Recent strategies such as high-dose regimen and use of oral and intravenous paracetamol are newer alternatives to the established modes of treatment.[19]

Surgical ligation of the ductus is rarely used these days as it may worsen the outcome and as it is a universal trend to follow less aggressive approaches for the management of preterm PDA.[20] The procedure may be considered only in instances where the infants have failed 2 courses of pharmacologic treatment and

continue to be ventilator dependant with echocardiographic evidence of a large duct.[3]

Management of Patent Ductus Arteriosus in 2017

Finally, there is enough evidence now to state that medical or surgical closure of PDA during the first 2 weeks after birth does not result in better long-term outcome.[21]

However, Nick Evans states, "All this hand-wringing over the evidence is not particularly helpful to the practicing clinician who wants to know what to do. Despite all the copy decrying our lack of understanding of treatment of PDA, the proposed trials remain elusive because they are so difficult to perform."[3]

PDA may not always be the cause but can also be the effect of the underlying problems and leads to increase in mortality and morbidity in preterm infants. Hence, in day-to-day practice, patient selection may be the way forward, as PDA is not an all-or-none issue. Prophylactic closure is probably unnecessary as it exposes a large number of extremely preterm infants to unwanted effects of medications. Very early echo-based treatment of PDA is a promising approach that needs more evidence to be recommended as a universal strategy.[21] If no echo diagnosis is available as in a resource-limited setting, traditional strategy of closure when the ductus becomes symptomatic is the other most-accepted strategy. Although risky, the current evidence-based strategy seems to avoid medical interventions for ductal closure in hsPDA.

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