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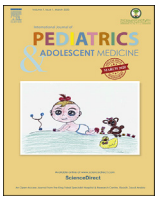

PDA: Does it matter?

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ABSTRACT

Management of persistent patent ductus arteriosus (PDA) continues to be a challenging issue. The attitude toward PDA has shifted in the opposite direction during the last 20 years, from advocating an aggressive and early closure toward a call for watchful observation. While persistent PDA may cause challenges in the medical management of preterm neonates secondary to volume overload, pulmonary edema or hemorrhage, hypotension, and impaired tissue perfusion, its contribution toward long-term neonatal morbidities including bronchopulmonary dysplasia (BPD), ROP, NEC, and NDI has not been substantiated. By advocating conservative management, it is clear now that the majority of the PDA cases show spontaneous closure and do not require treatment. However, there has not been agreement regarding what constitutes a hemodynamically significant PDA and when, if any, it should be targeted for treatment. With increasing concern regarding possible associated complications with PDA ligation, a new trend for transcatheter approach to PDA closure is expanding. In this review, we summarize current understanding of the pathophysiology, diagnosis, and management of PDA in preterm infants, and we make some recommendations regarding evidence-based approach.

1. Introduction

Patent ductus arteriosus (PDA) remains one of the commonest pediatric diagnoses in preterm neonates. Its prevalence is proportional to the gestational age (GA), with higher incidence in extremely low-birth-weight (ELBW) neonates, reaching 70% in infants < 28 weeks of GA [1]. The persistence of PDA has traditionally been thought to be a pathological condition requiring treatment. However, more recently, the approach toward this issue has become more conservative. It is not surprising that the approach to the management of PDA has shifted dramatically, from initial suggestions toward aggressive treatment including early surgical ligation to, more recently, advocating watchful observation. Although there remains a place for the treatment of PDA, controversies regarding patient selection, surgical treatment, and associated morbidity persist. In this paper, we will discuss historical concerns regarding the complications of PDA, initial approach to treatment, and recent evidence regarding patient selection for treatment versus observation.

2. Natural history of PDA

With the aggressive push to close all moderate-to-large PDA, left untreated, the outcome of PDA has not been known. The TIPP study shed early light on the incidence of spontaneous closure of PDA in patients treated with prophylactic indomethacin verses placebo [2]. In the placebo group, 50% of untreated babies had no PDA. Unfortunately, among the other 50% with persistent PDA, 276 out of the 601 neonates were treated with indomethacin and another 74 underwent surgical ligation, thus obscuring the long-term outcome of untreated PDA.

With recent approach becoming more tolerant of PDA, such prospect became possible. In 2017, Semberova et al. reported on their clinical experience with the conservative management of PDA in 280 very low-birth-weight (VLBW) infants. After hospital discharge, the PDA spontaneously closed in 85% of infants who were diagnosed with PDA but untreated. The average duration for spontaneous closure was proportional to the GA, with a median duration of 71 days for infants <26 weeks of GA and 6 days for infants ≥30 weeks of GA [3]. Furthermore, Clyman et al. included

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202 neonates of <28 weeks of GA at the end of the first week of life who had moderate-to-large PDA and randomized them to either early routine or conservative treatment. The infants had a mean GA of 25.8 (1.1) weeks and were enrolled between the age of 6 and 14 days (mean, 8.1 [2.2] days). At enrollment, 49% of the infants were intubated and 48% required nasal ventilation or continuous positive airway pressure (CPAP), indicating significant respiratory support. Of all infants screened, 41% did not qualify because of constricted PDA, signifying spontaneous closure. Of the 98 infants randomized to conservative treatment, only 48 (49%) required rescue treatment, while only five (5%) required surgical ligation [4]. These data suggest that the majority of the PDA cases in ELBW even in those requiring significant respiratory support do close spontaneously without the need for medical or surgical treatment. However, some still "need" treatment, thus changing the goal post from treating all to trying to identify which PDA needs treatment.

3. Pathophysiology of PDA complications

PDA has long been blamed for contributing to multiple neonatal morbidities including bronchopulmonary dysplasia (BPD), NEC, and renal impairment secondary to steel phenomenon and to the development of chronic pulmonary hypertension. The mechanisms implicated in the pathogenesis of BPD are multiple. Persistent ductus results in increased systemic to pulmonary shunting, especially as pulmonary vascular resistance decreases with improved pulmonary conditions. The increased pulmonary blood flow eventually leads to loss of physiological compensation, resulting in pulmonary edema and endothelial injury. PDA is also associated with impaired pulmonary mechanics and altered alveolar surface area. Furthermore, the presence of a patent ductus has been associated with increased risk of pulmonary hemorrhage. These alterations overall or in part make necessary the use of prolonged and more aggressive ventilation, leading to CLD and BPD. Pharmacological treatment leading to closure of the PDA prevents the deterioration of pulmonary function and alveolar development.

PDA has also been associated with the development of renal impairment and possible NEC secondary to decreased systemic perfusion and steal syndrome. Pharmacological treatment of PDA has been associated with improved blood pressure and urine output, supporting this association. Lastly, persistent left-to-right shunting across a persistent ductus can lead to elevated pulmonary pressure and chronic pulmonary hypertension, with its associated morbidity and mortality. It is no surprise that many neonatal authorities have advocated medical or surgical closure of PDA as soon as possible [5].

4. Is PDA truly associated with higher incidence of morbidity?

Most of the evidence indicating PDA in the development of neonatal morbidity, especially BPD, is historic and includes a small number of infants. Kaapa et al., in 1983, randomized 27 preterm infants to either indomethacin (n = 13) or control (n = 14). The total duration of mechanical ventilation and oxygen exposure was significantly shorter in the indomethacin group [6]. Furthermore, Gerhardt and Bancalari, in 1980, found improved lung compliance in ten infants after surgical ligation of PDA [7]. Harris et al., in 1982, found that BPD occurred more frequently in infants with PDA and that early ductal closure decreased BPD incidence [8].

On the other hand, among 252 infants with GA ≤28 weeks, Brooks et al. found no significant differences in the incidence of CLD, CLD or death, NEC, IVH, duration of oxygen, or hospital stay between infants without PDA (n = 154), infants with PDA closed after medical treatment (n = 65), and infants with significant PDA after medical treatment (n = 33) [9]. Furthermore, Schmidt et al. described a similar incidence of BPD among 1202 infants (500–999) grams randomized to either control or prophylactic indomethacin despite difference in the incidence of PDA between the two groups, i.e., 24% in the indomethacin group versus 50% in the control group [2]. Additionally, the PDA-TOLERATE trial by Clyman et al. found no differences between infants randomized to early PDA treatment at 6–14 days of life versus infants with conservative treatment of PDA in the incidence of necrotizing enterocolitis (16% vs. 19%), BPD (49% vs. 53%), BPD or death (58% vs. 57%), or death (19% vs 10%) [4]. In a pooled analysis of randomized controlled trials for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of PDA, Sankar et al. found that NSAIDs showed higher protection against ducal opening as well as intraventricular hemorrhage greater than grade 2; however, there was no association with the development of any other neonatal morbidity including BPD, NEC, or death [10]. These data overwhelmingly indicate lack of evidence for PDA as a contributing factor to neonatal morbidity including BPD, NEC, or mortality and brings into question the need for early or aggressive treatment of all PDA cases.

5. So which PDA to target for treatment?

Multiple criteria have been used to try to identify hemodynamically significant PDA (HsPDA). These include GA, chronological age, need for respiratory or hemodynamic support, and echocardiographic findings. While the purpose of such classification was to identify which PDA is associated with potential complications and thus requires treatment, data presented in the previous section indicate the presence of a poor association between HsPDA according to different criteria and neonatal morbidity and the difficulty trying to identify which PDA to treat. However, certain factors continue to be used clinically to identify which PDA to target either for treatment or for study. These can be classified into clinical criteria and echocardiographic findings. Clinical findings include infants <26 weeks of GA, especially in the first week of life; need for inotropic support; need for moderate-to-high respiratory support, especially in intubated and ventilated neonates; pulmonary edema and/or hemorrhage; or evidence of impaired tissue perfusion as indicated by oliguria, elevated creatinine, or feeding intolerance.

Echocardiographic criteria are related to either ductal size (diameter) or shunt pattern, evidence of volume overload, pulmonary overflow, or systemic/tissue hypoperfusion. In extremely premature neonates, a PDA diameter of ≥1.5 mm or a PDA/left pulmonary artery diameter ratio of ≥0.5 and a growing or pulsatile shunt pattern indicate an HsPDA. Evidence of systemic overcirculation is indicated by a left atrium/aortic ratio of ≥1.4 or left ventricular output of >300 mL/kg/min. Increased pulmonary arterial flow is indicated by a left pulmonary artery end diastolic velocity of >20 cm/s. Retrograde blood flow in the descending aorta, low antegrade flow in systole or diastole, and absent/reversed end-diastolic flow in end organs (middle cerebral, superior mesenteric, or renal arteries) signify tissue hypoperfusion and steal syndrome [11].

Multiple other factors have been implicated as markers for an HsPDA, including phase photoplethysmography differences (Pleth variability index); platelet count; nucleated red blood cell count; biochemical markers including CRP, natriuretic peptides, Troponin T, and carbon monoxide; and cerebral pulsed-wave Doppler assessment and near-infrared spectroscopy [12]. In our clinical practice, PDA is targeted for medical treatment in infants who continue to require significant respiratory support after the first week of life and have HsPDA according to the above-mentioned criteria.

6. Which medication to use?

NSAIDs including indomethacin and ibuprofen have been used successfully for the treatment of PDA, while emerging evidence indicates the potency of acetaminophen as an effective alternative agent. Both indomethacin and ibuprofen are nonselective COX inhibitors that work through inhibition of the production of prostaglandins from free arachidonic acid. Acetaminophen shows downstream effects at the POX site that prevents conversion of PGG2 to PGH2. All three medications ultimately result in a decrease in PGE2, PGI2, and thromboxane, and, finally, constriction and closure of PDA [13].

The increased use of acetaminophen in the treatment of PDA is related to the lower incidence of gastrointestinal and renal complications. Multiple trials have compared either indomethacin or ibuprofen to acetaminophen for the treatment of PDA. Multiple limitations including a low number of infants enrolled, lack of standardization of PDA diagnosis, variable GA, and age at treatment as well as route of administration preclude generalization of the data. Nonetheless, pooled analysis of all randomized trials indicate comparable effectiveness of acetaminophen to either ibuprofen or indomethacin with lower incidence of gastrointestinal bleeding and comparable risks of neonatal morbidities including death, IVH, BPD, ROP, or NEC [13]. However, data regarding the efficacy of acetaminophen indicated a relationship with time of use and GA of the infants treated. Acetaminophen seems to be most appropriate as the first-line treatment for PDA in the first week of life secondary to its comparable effectiveness to ibuprofen and indomethacin associated with a lower risk profile. However, there is limited evidence to suggest the use of acetaminophen in infants who failed initial treatment with NSAIDs. Furthermore, acetaminophen seems to be more effective among more mature preterm infants and less so in ELBW infants. Additionally, lack of a protective effect against IVH precludes its use for prophylaxis in ELBW infants.

Secondary analysis of the PDA-Tolerate trial suggests an explanation for the comparable efficacy of acetaminophen in the first week of life, as many of the PDA cases would have closed spontaneously. As infants were only treated after the first week of life and thus excluded infants who would have had a spontaneous PDA closure, acetaminophen was less effective than indomethacin in closing a PDA in either the early treatment group (27% vs. 63%) or the conservative treatment group (40% vs. 60%). The study has its own limitations in the low number of infants treated and that the fact that the trial was not powered to examine this secondary analysis [4]. Further studies are needed to clearly identify comparable efficacy of acetaminophen in HsPDA.

7. Is there a role for PDA ligation?

Multiple studies have evaluated the risks/benefits of PDA ligation as compared to either medical treatment alone or conservative management. Unfortunately, randomized controlled trials included a small number of infants and were carried out more than 30 years ago; thus, the results are not relevant to current neonatal practices. Most of the current reports comparing the outcome of PDA ligation to medical treatment include retrospective, observational, or Epoch studies.. PDA ligation has been associated with a higher likelihood of chronic lung disease or BPD [14–16], neurodevelopmental impairment, and retinopathy of prematurity (16, 17) but improved mortality [14–17]. The diversion of competing outcomes of improved mortality but worsening morbidity raises the possibility that neonatal morbidity associated with PDA ligation is related to improved survival in otherwise complicated, ill neonates rather than the ligation itself, versus a selection bias where unstable ill neonates with a higher mortality rate never made it to PDA ligation, thus explaining lower mortality in patients who underwent surgical ligation. Furthermore, the main indication for PDA ligation is persistent need for mechanical ventilation at a later age of life, thus including babies who are already at a higher risk for BPD, ROP, and NDI who have survived the initial critical period associated with a higher mortality [18]. Weisz et al. evaluated in their cohort of 754 extremely premature infants the effect of PDA ligation versus medical management and controlled for not only antenatal and early perinatal risk factors but also later neonatal factors including need for, and duration of, mechanical ventilation, sepsis, and NEC. Similar to other studies, PDA ligation was associated with increased incidence of BPD, NDI, and ROP and improved survival; however, after controlling for neonatal factors including mechanical ventilation, PDA was no longer associated with either BPD, ROP, or NDI [17]. The increased morbidity associated with PDA could very well be secondary to either surgical or anesthesia complications, side effects of the procedure itself, or postoperative instability. Further randomized controlled trials are clearly needed to examine the effect of PDA ligation on later morbidities in ELBW infants. However, with changing national trends, especially in the USA and Canada, toward conservative management of PDA and away from both medical and surgical treatment of PDA [19,20], finding enough subjects to enroll might become a challenge. While there remains a role for PDA ligation in persistent hemodynamically significant PDA who are either not eligible for medical therapy secondary to NEC or renal impairment or are resistant to it, the selection of such babies remains a challenging controversy. Early conservative or prophylactic ligation of PDA, although clearly not indicated, might contribute to higher morbidity or mortality.

Possible complications related to PDA ligation include surgical and anesthesia complications, postoperative hemodynamic instability including hypotension and shock, vocal cord paresis/paralysis, GERD, and need for prolonged intubation and mechanical ventilation. These possible complications have led to a rise in the nonsurgical, transcatheter approach to PDA ligation. Apalodimas et al. reported on their experience of this approach and how they have switched to transcatheter ligation of PDA and completely away from surgical ligation between 2014 and 2018 [21]. However, this approach remains limited in practice by need for expertize and the practicality of infant weight.

In conclusion, the approach and management of PDA continue to be an important debated issue. Despite that, some specific rules apply:

1. There is currently no evidence to support prophylaxis or treatment of non-hemodynamically significant PDA.
2. Diagnosis of hemodynamically significant PDA requires both echocardiographic findings and clinical symptoms.
3. Acetaminophen seems to be as effective as NSAID in closing PDA and associated with fewer complications in the first week of life; however, it does not seem to be effective for prophylactic closure of PDA or as rescue treatment.
4. While PDA ligation has been associated with increased morbidity including BPD, ROP, and NDI, this association might be related to selection or confounding biases.
5. Non-surgical transcatheter PDA closure is an evolving, expanding new approach to persistent PDA in preterm neonates, which requires further evaluation.

References

[1] Clyman RI. Patent ductus arteriosus, its treatments, and the risks of pulmonary morbidity. Semin Perinatol 2018;42(4):235–42.
[2] Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts R, Saroj S, et al. Long term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344(26).

[3] Semberova J, Sirc J, Miletin J, Kucera J, Berka I, Sebkova S, et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. Pediatrics 2017 Aug;140(2):1–8.
[4] Clyman RI, Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson S, 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 Feb;205:41–8.
[5] Bancalari E. Changes in the pathogenesis and prevention of chronic lung disease of prematurity. Am J Perinatol 2001;18(1).
[6] Kääpä P, Lanning P, Koivisto M. Early closure of patent ductus arteriosus with indomethacin in preterm infants with idiopathic respiratory distress syndrome. Acta Paediatr Scand 1983 Mar;72(2):179–84.
[7] Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate 1980;38(1–2):96–105.
[8] Harris JP, Merritt TA, Alexson CG, Longfield L, Manning JA. Parenteral indomethacin for closure of the patent ductus arteriosus. Clinical experience with 67 preterm infants. Am J Dis Child 1982 Nov;136(11):1005–8.
[9] Brooks JM1, Travadi JN, Patole SK, Doherty DA, Simmer K. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. Arch Dis Child Fetal Neonatal Ed 2005 May;90(3):F235–9.
[10] Sankar MN, Bhombal S, Benitz WE. PDA: to treat or not to treat. Congenit Heart Dis 2019 Jan;14(1):46–51.
[11] Shepherd JL, Noori S. What is a hemodynamically significant PDA in preterm infants? Congenit Heart Dis 2019 Jan;14(1):21–6.
[12] Kluckow M, Lemmers. Hemodynamic assessment of the patent ductus arteriosus: beyond ultrasound. Semin Fetal Neonatal Med 2018 Aug;23(4):239–44.
[13] Jasani B, Weisz DE, McNamara PJ. Evidence-based use of acetaminophen for hemodynamically significant ductus arteriosus in preterm infants. Semin Perinatol 2018 Jun;42(4):243–52.
[14] 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.
[15] Mirea L1, Sankaran K, Seshia M, Ohlsson A, Allen AC, Aziz K, et al. Treatment of patent ductus arteriosus and neonatal mortality/morbidities: adjustment for treatment selection bias. J Pediatr 2012;161:689–94.
[16] Madan JC, Kendrick D, Hagadorn JI, Frantz 3rd ID. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. Pediatrics 2009;123:674–81.
[17] Weisz DE, Mirea L, Rosenberg E, Jang M, Ly L, Church PT. Association of patent ductus arteriosus ligation with death or neurodevelopmental impairment among extremely preterm infants. JAMA Pediatr 2017;171:443–9.
[18] Weisza Dany E, Giesingera Regan E. Surgical management of a patent ductus arteriosus: is this still an option? Semin Fetal Neonatal Med 2018;23:255–66.
[19] Hagadorn JI, Brownell EA, Trzaski JM, Johnson KR, Lainwala S, Campbell BT, et al. Trends and variation in management and outcomes of very low-birthweight infants with patent ductus arteriosus. Pediatr Res 2016 Dec;80(6):785–92.
[20] Reese J, Scott TA, Patrick SW. Changing patterns of patent ductus arteriosus surgical ligation in the United States. Semin Perinatol 2018 Jun;42(4):253–61.
[21] Apalodimas L, Waller Iii BR, Philip R, Crawford Cunningham J, Sathanandam S. A comprehensive program for preterm infants with patent ductus arteriosus. Congenit Heart Dis 2019 Jan;14(1):90–4.