REVIEW ARTICLE

Current Controversies in the Management of Patent Ductus Arteriosus in Preterm Infants

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Objective: Patent ductus arteriosus is very commonly seen in very low birth weight (VLBW) infants, affecting about one-third. The present review tries to identify the group of VLBW infants who need active intervention in day-to-day practice and to determine the mode of intervention, based on current published literatures.

Methods: We searched the Cochrane library, MEDLINE, EMBASE and CINAHL databases, and reference that of identified trials.

Results and Conclusions: Preterm infants with a birth weight of <800g are at risk of significant morbidity and mortality from PDA; it would be reasonable to treat them when symptomatic or if requiring positive pressure ventilator support. Those weighing >800g are unlikely to need treatment unless they are ventilator-dependent or show evidence of congestive heart failure.

Keywords: *Ibuprofen, Indomethacin, Low birth-weight infants, Patent ductus arteriosus.*

Patent ductus arteriosus (PDA) – persistence of the fetal ductus arteriosus – is the most common form of congenital cardiac abnormality in newborns, with a reported frequency of 31% in very low birth weight (VLBW) infants [1,2]. PDA is associated with significant hemodynamic abnormalities and has varying influence in pulmonary function. Incidence and severity of complications of PDA vary in different subgroups of the VLBW population. Therapeutic interventions for PDA have significant complications. If PDA is left untreated in preterm infants, there is a high likelihood of spontaneous closure. The purpose of this review is to assess current evidence to delineate the group of VLBW infants who need intervention and mode of intervention.

WHEN IS PDA CONSIDERED SIGNIFICANT?

Despite an obvious need, no specific clinical or echocardiographic criteria have been developed on which treatment of PDA could be based. Possibilities for assessing ductal significance include clinical and echocardiographic methods, and possibly biochemical markers.

Significant PDA may be indicated by clinical signs such as blood-stained endotracheal aspirates indicating pulmonary edema, bounding pulses with widened pulse pressure, hyperdynamic precordium and a continuous murmur on auscultation. Assessment is also assisted by a radiological finding of cardiomegaly and pulmonary congestion. However, all these signs have their own limitations, and studies have shown a poor correlation between physical signs and the presence of PDA in the first week of life [3].

Several echocardiographic findings are used as surrogate markers of ductal significance [4]. Although this approach has limitations such as inter- and intra-observer variations in measurement, a bedside functional echocardiography gives valuable information in assessing ductal significance. The commonly used echocardiographic markers are: a left atrium to aortic root dimension ratio of more than 1:1.4, a ductal diameter of more than 1.4 mm/kg body weight, left ventricular enlargement, and diastolic flow reversal [5]. However, there are no strict criteria or scoring systems to assess the significance of ducts and that is another area of potential research. Published evidence indicates that B-type natriuretic peptide (BNP) and N-terminal Pro-BNP could be used as a potential biochemical marker in assessing the severity of ductal shunt [6].

WHEN DOES PDA REQUIRE INTERVENTION?

The main argument in favor of treating PDA is effect on various organ systems due to altered hemodyanamics. Left-to-right shunting increases with the postnatal decrease in pulmonary vascular resistance, leading to a compensatory increase in cardiac output and a widening of the pulse pressure. The flow pattern in the aorta changes with the development of diastolic steal. Retrograde diastolic flow may develop in the cerebral circulation, the descending aorta, and renal and

mesenteric blood vessels. This hemodyanamic effect is presumed to cause significant morbidities in cardiovascular and other organ systems in preterm infants [7-14].

The main argument against active intervention in PDA is significant adverse effects related to both medical and surgical treatments. None of the treatment trials were designed to determine these effects, so clinicians have had to rely on information from prophylactic treatment trials to reach a conclusion on this issue. Prophylactic trials using indomethacin showed transient alteration in renal function and urine output, though this is less of a concern with ibuprofen. Indomethacin by itself does not appear to increase the incidence of other neonatal morbidities such as necrotizing enterocolitis (NEC), gut perforation, retinopathy of prematurity (ROP), chronic lung disease (CLD) or cerebral white matter injury [15]. However, an increased incidence of gut perforation has been observed with concurrent use of indomethacin and steroids [12,16]. Although the cerebral vasoconstrictive effect of indomethacin has been a concern for clinicians, long-term follow up of infants who received indomethacin prophylactically shows a decrease in the incidence of periventicular leukomalacia (PVL) without any adverse neurodevelopmental effect at 18 months of age [17,18].

Surgical ligation of PDA is associated with its own set of morbidities, with the potential for serious implications for long-term outcome. The immediate morbidities associated with ligation are pneumothorax, chylothorax, infection, vocal cord paralysis, need for thoracotomy, and the post-ligation need for ionotropic support [19]. Surgical ligation of PDA has been linked to long-term adverse neurodevelopmental outcome, though it is unclear whether this is caused by the surgery itself or the anaesthesia [20,21]. Evidence for a causal relationship between ligation and development of CLD is clearer [22].

The second major argument against intervention is that PDA is a physiological event in preterm infants and no benefit is derived from its closure. If left untreated, the natural history of PDA is 'likely closure'. Ductus arteriosus (DA) provides a pulmonary-to-systemic circulatory diversion during fetal life, when pulmonary blood flow is minimal and pulmonary vascular resistance (PVR) is high [8,23]. Premature DA closure in fetal life results in a cascade of events, eventually leading to pulmonary hypertension in the newborn with possible right ventricular failure in a range of severities. Immediately after birth, PVR decreases rapidly due to lung expansion and an increase in partial pressure of oxygen, with an accompanying five-fold decrease in pulmonary artery pressure and a 7- to 10-fold increase in pulmonary blood flow [8,23]. In term infants without lung disease, a functional closure of the DA can be documented using echocardiography by age of 3 days. Even with the presence of significant lung disease, DA usually closes within 5 days in preterm infants (>30 wk gestation) [8].

Trials aimed at closing the PDA provide us with the information needed to improve our judgment in terms of overall morbidity and efficacy of therapy. Closure should result in a reduction in the incidence of PDA-related morbidities. A review by Knight, *et al.* [9] examined three groups – prophylactic, pre-symptomatic and symptomatic therapy – and showed either a reduction in the incidence of PDA or symptomatic PDA. However, there were no intergroup differences regarding death, CLD, ROP or NEC [5,9,15,17,18,24].

To Treat or Not to Treat?

After going through the evidence, physicians are left with two opposing schools of thought - one advocating treatment and the other advocating no treatment. However, infants with a birth weight <800 g are at risk of significant morbidity and mortality from PDA and the natural course in this group is uncertain. In this group, it would be reasonable to treat PDA when the infant is symptomatic and on mechanical ventilation. Such high-risk infants can be identified by echocardiography at 24-30 hours of age, and those having a large PDA can be treated with cyclooxygenase (COX) inhibitors [25]. Infants with a small-to-moderate PDA could be managed conservatively and if required, treatment could be deferred for 7-14 days, to allow spontaneous PDA closure [25,26]. Infants weighing >800g are unlikely to need treatment unless they are ventilator-dependent and show evidence of congestive heart failure or renal failure. In these cases, it is reasonable to leave the decision to treat at the clinician's discretion [26].

Our own unpublished audit shows that infants born at 23-25 wk gestation with no antenatal steroid exposure are at the highest risk of PDA-related morbidities. These infants would benefit from prophylactic low-dose indomethacin treatment for prevention of intraventricular hemorrhage (IVH) [27]. However, a targeted neonatal echocardiographic examination prior to treatment is preferable to exclude duct-dependent congenital heart disease and significant right-to-left shunt across the duct.

MANAGEMENT STRATEGIES

Clinicians have five management options for dealing with PDA in preterm infants: (1) prophylactic pharmacologic treatment (COX inhibitors), (2) pre-symptomatic

pharmacologic treatment of PDA, (3) conservative management, (4) pharmacological closure of the PDA, and (5) surgical ligation.

Prophylactic Pharmacotherapy

Prophylactic pharmacotherapy is the practice of administering COX inhibitors (indomethacin or ibuprofen) to preterm infants within the first 24h of life irrespective of the diagnosis of PDA. Dose and interval of indomethacin is 0.1mg/kg at 12h intervals or 0.2 mg/kg at 24h intervals [28]. In the majority of studies, 3 doses were used starting at 6-12h of age. Ment, *et al*. [29] and Cower, *et al*. [29] used 5 and 6 doses, respectively. With ibuprofen, most studies used 3 doses starting from 2 to 6 h of age (1st dose was 10 mg/kg, followed by the 2nd and 3rd doses of 5 mg/kg at 24h intervals) [29].

Meta-analyses and systematic reviews of randomized controlled trials (RCTs) that examined the prophylactic use of COX Inhibitors for PDA in preterm infants showed a number of short-term benefits, including reductions in later symptomatic PDA, rate of severe IVH and the need for surgical ligation. However, there was no evidence to suggest that it improved the rate of disability-free survival, and did not routinely recommend it in the management of PDA in preterm infants.

Pre-symptomatic Pharmacologic Treatment of PDA

Studies that have looked into the pre-symptomatic treatment of PDA have not demonstrated any advantage in terms of death, ROP, NEC or bronchopulmonary dysplasia (BPD) [30]. An overall small reduction in the number of days on supplemental oxygen, especially in infants weighing <1000 g at birth has been reported [31]. However, as a whole, randomized trials have shown no benefit in respiratory outcome when the ductus were treated at a pre-symptomatic stage or when infants with a birth weight <1000 g were treated early. There was a significant (RR 0.38, 95% CI 0.26-0.55) reduction in the subsequent need to treat PDA. The overall experience gained from the prophylactic indomethacin group suggest that there is not enough evidence to support presymptomatic treatment [24]. However, this practice may have a role in infants born within 23-25 wk of gestation, given the high incidence of PDA requiring treatment in this group. This possibility requires further investigation [32].

Conservative Management

This includes fluid restriction to <130 mL/kg/d in preterm infants of more than 4 days of age, high positive end-expiratory pressure and low inspiratory time (0.35s) [32]. In a prospective study involving 30 infants of <30 wk gestational age and a mean (SD) birth weight of 994 g (600-1484 g), conservative management achieved PDA closure in all infants. Conservative treatment has the obvious advantage of being devoid of side effects of medication or surgical ligation. Therefore, it is reasonable to employ conservative PDA management in preterm infants as the initial management step. However, infants born at 23 to 25 wk gestation were found to have a lower likelihood of spontaneous PDA closure and a higher risk of treatment failure with ibuprofen. In this subgroup of infants with significant PDA, treatment with a COX inhibitor would be acceptable to most clinicians after 48-72 h of life [32].

Pharmacological Closure

Pharmacological treatment of PDA is the mainstay of treatment if conservative measures fail. To date, indomethacin, ibuprofen and mefenamic acid have been used; of which indomethacin and ibuprofen have been extensively studied.

Indomethacin is of proven efficacy in the management of PDA [33], though availability of indomethacin is now limited. In a large collaborative study of 3559 infants, clinically significant PDA was detected in 421 infants, all of whom were randomized to receive indomethacin or placebo. Functional closure of PDA was achieved within 48 hours in 79% of the indomethacin group compared to 28% in the control group. Relapse occurred in 33% of responders; many of these relapses did not require further treatment [5]. Clinically reproducible side effects of indomethacin treatment include transient renal impairment, gastrointestinal (GI) hemorrhage and focal GI perforation. It also reduces prostaglandin-dependent blood flow to the kidneys, GI tract and brain. Indomethacin interferes with platelet adhesion and therefore thrombocytopenia is considered a contraindication for its use. However, the clinical significance of this undesirable effect is unclear.

Most clinicians use short-course regimens (≤3 doses) of indomethacin to treat PDA. Reviews of randomized or quasi-randomized trials have shown no benefit with prolonged regimens (≥4 doses) in terms of PDA treatment failure, CLD, IVH and mortality. A prolonged course has been shown to increase the incidence of NEC [34]. Doses of indomethacin are lower when used for the prevention of IVH (0.1mg/kg/dose intravenously at 6-12h of postnatal age and at 24h intervals for 2 additional doses) [34].

Due to concerns about the adverse effects of indomethacin, other COX inhibitors have been investigated. Ibuprofen has received the most attention [30]. Two preparations are available: ibuprofen lysine and ibuprofen THAM. Use of the THAM preparation has

been associated with increased risk of NEC, and has shown a high frequency of adverse respiratory, renal and GI events [35]. In view of the side effects, the original trial was stopped after 135 enrolments and further use of the THAM preparation has been discouraged. Review of 8 RCTs by Wyllie involving 509 infants found no difference between ibuprofen and indomethacin for the primary outcome measure of failure to close the PDA [30]. Ibuprofen has fewer adverse effects on kidney function, but may be associated with increased risk of pulmonary complications, including CLD and rarely pulmonary hypertension. Available data support the use of either drug for the treatment of PDA [36]. A randomized pilot study by Cherif, *et al*. [37] with 64 VLBW infants has shown that oral ibuprofen is as good as intravenous ibuprofen in terms of ductal closure, and is associated with fewer side effects [36]. However, use of oral indomethacin or ibuprofen is confined to countries where availability or cost prohibits the use of the intravenous preparation [37]. Larger studies are needed to confirm the safety and efficacy of oral use compared to parenteral preparation.

There is recent interest in the use of the non-selective COX inhibitor (peroxidase sites) paracetamol as an alternative to established COX inhibitors; four cohort studies involving 29 individual cases have been published. Dosage was 60 mg/kg/d for 2-7 days. Most cases were extremely low birth weight (ELBW) infants with a background history of either failure with or contraindications to COX inhibitors. Closure was observed in 20/29 cases with first course, with eventual closure observed in 27/29 cases. The pharmacokinetics of paracetamol in ELBW infants is not clearly established and its safety, especially with a high unauthorized dose, is not documented [38]. The primary question of whether paracetamol results in PDA closure beyond the natural history of this phenomenon has not yet been answered. Therefore, its use should be limited to large RCTs to prove its efficacy and safety.

Surgical Ligation

Surgical ligation is contemplated only when pharmacological closure is ineffective or is contraindicated in a preterm infant who is hemodynamically unstable due to PDA. A study in preterm infants (23-28 wk gestation) reported that compared to drug treatment alone, primary surgery was associated with increased incidence of neurodevelop-mental impairment (NDI) (adjusted OR 1.79) and BPD (adjusted OR 2.19). Secondary surgical closure (indomethacin treatment followed by ligation) was associated with increased odds for NDI (OR 1.53) and CLD (OR 3.1), but decreased adjusted odds for death [39].

To date, no RCT has compared surgical ligation and multiple courses of indomethacin for persistent PDA in preterm infants. A study of 61 VLBW infants has shown that a second and third course of indomethacin was associated with good results in terms of PDA closure. However, a third course of indomethacin may be associated with an increased risk of PVL compared to surgical ligation after a failed second course of indomethacin for persistent PDA [37].

NOVEL TREATMENT APPROACHES

A novel approach by Sperandio, *et al*. [40] of escalating the dose of indomethacin stepwise every 12h to reach a maximum single dose of 1mg/kg has shown an overall closure rate of 98.5%. Adverse effects were comparable to initial non-responders. Study results were limited due to the retrospective nature of the study and lack of long-term follow up.

Endoscopic and catheter closure: Video-assisted thoracic surgery on PDA is a recognized and effective alternative to traditional surgery, but it requires further study [41]. Experience with transcatheter management of PDA in VLBW infants is limited and currently inadequate for implementation in routine practice.

RESEARCH ISSUES

The most compelling question in the management of significant PDA in preterm infants is the outcome of untreated or conservatively managed infants with a birth weight <800 g compared to outcome with pharmacological and/or surgical closure. An RCT to address this issue will be difficult to design, and will likely face sample size and ethical issues. However, based on current experience and published evidence, such a study would be relevant and worth addressing in the near future. Computer-based decision aids to incorporate parental preferences into the treatment of PDA also merit further attention [42]. Most of the other issues are related to optimal intervention, complications and long-term outcome in preterm infants treated for PDA. These issues can be summarized as follows:

- Echocardiogram-assisted individualized dosing regimens of a COX-inhibitor for pharmacological closure of PDA
- The impact of multiple courses of indomethacin/ COX-inhibitors for pharmacological closure of PDA on long-term outcome in <1000g birth weight infants compared to surgical or video-assisted ligations
- The impact of multiple courses of indomethacin on long-term neurological outcome in preterm infants with PDA

- The long-term outcome of infants with significant PDA who are treated with video-assisted ductal ligation.

CONCLUSION

Infants with a birth weight of <800g are at risk of significant morbidity and mortality from PDA, and it would be reasonable to treat the PDA in such infants when they are clinically symptomatic and require positive pressure ventilatory support. However, infants born at a gestational age of 23-25 wk without antenatal steroid exposure are at a higher risk of PDA-related morbidities and would benefit from prophylactic low-dose indomethacin for prevention of IVH. Preterm infants with a birth weight >800g are unlikely to need treatment for PDA unless they are ventilator-dependent and showing evidence of congestive heart failure or renal impairment.

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