Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist?

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Ibuprofen
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Summary
How to manage the preterm patent ductus arteriosus (PDA) remains a conundrum. On the one hand, physiology and statistical association with adverse outcomes suggest that it is pathological. On the other hand, clinical trials of treatment strategies have failed to show any long-term benefit. Ultrasound studies of PDA have suggested that the haemodynamic impact may be much earlier after birth than previously thought (in the first hours); however, we still do not know when to treat PDA. Studies that have tested symptomatic or pre-symptomatic treatment are mainly historical and have not tested the effect of no treatment. Prophylactic treatment is the best-studied regimen but improvements in some short-term outcomes do not translate to any difference in longer-term outcomes. Neonatologists have been reluctant to engage in trials that test treatment against almost never treating. Observations of very early postnatal haemodynamic significance suggest that targeting treatment on the basis of the early postnatal constrictive response of the duct may optimize benefits. A pilot trial of this strategy showed reduction in the incidence of pulmonary haemorrhage but more trials of this strategy are needed.

1. Introduction

A conundrum is defined as an intricate and difficult puzzle; how we should manage the preterm patent ductus arteriosus (PDA) is indeed a conundrum. On the one hand, there is evidence that the preterm PDA can be pathological. First, haemodynamic studies show that the PDA facilitates shunting of large volumes of blood from the systemic to the pulmonary circulation, draining blood from the former and overloading blood into the latter. Second, observational studies that have consistently associated persistent PDA shunting with a range of adverse outcomes including necrotizing enterocolitis (NEC), peri/intraventricular haemorrhage (P/IVH), chronic lung disease (CLD) and death [1–3]. Interpretation of these studies is limited by the co-linearity between each of these outcomes, persistent PDA and immaturity, and also by the wide range of ways in which PDA has been defined using a menagerie of clinical and, latterly, echocardiographic criteria [4].

On the other hand, since PDA is causing these adverse outcomes then treating it should reduce the incidence of those outcomes. Yet amalgamations of the results of randomized trials show little evidence of consistent effect of treating PDA on outcomes [5–8]. However, again there are limitations in that, with the exception of prophylactic treatment, these trials are historically and methodologically diverse.

A purist interpretation of this conundrum would be that if treating makes no difference to outcomes then preterm PDA may not be pathological. However, lack of evidence of effect is not the same as evidence of lack of effect, and the other interpretation could be that we have not understood the natural history of the pathology of the PDA or what happens when we try to treat PDA medically. In other words, in many babies the treatment may not be doing what we want it to do.

Systematic review is important for defining the limitations of our understanding, but it is less useful for defining whether the right treatment questions have been asked in the right way. For that, you have to study the babies and their ducts with the goal of understanding what is pathological and what is not pathological about their behaviour. Good treatment strategies still depend on accurate diagnosis and an understanding of the natural history of the pathophysiology.

2. Cardiac ultrasound and the ductus

Cardiac ultrasound has been pivotal to the development of our understanding about the ductus. Ultrasound allows direct imaging...
of the ductus, assessment of constriction, the shunt direction and velocity, and the disturbance to blood flow patterns in the great vessels either side of the ductus (Fig. 1).

2.1. Normal ductal physiology

In most term babies, functional closure occurs by 24 h of age [9]. Intimal ischemia and then necrosis result from the continued intense constriction of the muscular wall and the ductus eventually evolves into the ligamentum arteriosum that we all have where our ductus arteriosus used to be.

Ultrasound studies have resulted in a shift in thinking about the preterm ductus but dogma in medicine is not easy to change. There has been a long-held view that early postnatal ductal shunting is not important and that pathological ductal shunting evolves after a few days. This thinking has been the premise of many of the clinical trials, and it evolved from studies that were done in the late 1960s [10]. Whereas this may have been true in the late 1960s, it is not true now and, indeed, the reverse may be true, as early left-to-right shunting may cause more hemodynamic pathology in the early hours of circulatory transition than a few days later, even if the volume of the shunt does increase.

2.2. Early preterm ductal behaviour

The ductus does just one active thing in its postnatal life. It constricts and closes. Otherwise it is just a passive conduit for blood with flow direction determined by the pressures at either end. At all preterm gestations, there is great variation in the degree of constriction during the early postnatal hours. This varies from those with minimal constriction to those where the constriction is much as would be seen in a well term baby [2]. Figure 2 shows ductal color Doppler diameter at 5 h of age plotted against gestation in 124 babies born before 30 weeks. In most babies, the shunt is pure left-to-right or bidirectional with a dominant left-to-right component, showing that pulmonary pressures are usually sub-systemic even early after birth [2]. In babies where the ductal constriction fails, there is often a large shunt moving blood from the systemic circulation and loading it into the pulmonary circulation.

Using superior vena cava flow as a surrogate measure of systemic blood flow, we showed a significantly negative association between duct diameter and SVC flow at 5 h of age, but this association was not significant on the subsequent studies at 12, 24 and 48 h [11]. The strength of this association has not been a consistent finding in the literature; Groves et al. [12] found a similar association at 5 h in univariate analysis which became insignificant on multivariate analysis. However, existing evidence suggests that, if ductal shunting has a negative association with systemic blood flow, it does so very early after birth during this exquisitely vulnerable period of circulatory transition. After that time, in most cases, the heart seems to compensate well by increasing left ventricular output to maintain systemic blood flow in the face of this sump of blood back through the ductus. We showed a significant association between this early low systemic blood flow and development of intraventricular hemorrhage and later NEC, suggesting a possible mechanism by which PDA shunting might be part of the causation of these outcomes [11].

Whereas the heart can compensate for shunting of blood from the systemic circulation, the overload of the pulmonary circulation is passive, inevitable, and only limited by the resistance of the pulmonary vasculature. The early clinical risk of this seems to be pulmonary hemorrhage. The label ‘pulmonary hemorrhage’ is a misnomer because it is not blood but hemorrhagic pulmonary edema. In a serial hemodynamic study of 126 babies born before 30 weeks, 12 developed pulmonary hemorrhage at a mean age of 36 h [2]. Close to the time of hemorrhage, these babies had significantly higher estimated pulmonary blood flow and significantly larger ducts than the rest of the cohort, so again this clinical impact is happening early. The later role of increased pulmonary blood flow in development of ventilator dependency and chronic lung disease seems less certain and underlines the conundrum of PDA treatment. PDA features consistently as a significant risk factor for chronic lung disease but treatment of the PDA, including prophylactic treatment, makes no difference to incidence of chronic lung disease.

3. Treatment of the preterm ductus arteriosus

So should we be treating PDA in preterm babies? It has been apparent for many years from systematic review of the literature that there is no clear evidence of effect on long-term outcomes of treating PDA. The issue has been brought into sharper focus by several review articles, which have essentially re-worked the same studies and, perhaps not surprisingly, have failed to produce a clear answer. Laughon and Bose [5,6] proposed that the reason for the lack of effect might be that the patency of the preterm ductus was a
physiological phenomenon. Benitz [7,8] reviewed the data with a similar message suggesting that most preterm babies cope very well with a ducatal shunt and that it may be important in only a few. Both articles call for placebo-controlled trials of ductal treatment with an emphasis on a true control group, e.g. a group in which the PDAs are genuinely left alone. Such trials have yet to be performed.

3.1. If you are going to treat, what to treat?

This is the easy part. Both indomethacin and ibuprofen will close the majority of preterm patent ducts; they both have side-effects but ibuprofen seems to have fewer negative effects on renal and cerebral blood flow and also possibly fewer gastrointestinal side-effects [13]. These effects are mainly transient, so it is unclear whether this difference matters to the baby. The Cochrane review [13] on ibuprofen shows an increased risk of necrotizing enterocolitis after indomethacin use compared to ibuprofen. This probably needs interpreting with caution because it combined trials of oral and intravenous routes for both medications. Further, indomethacin does not increase the risk of NEC in trials when compared with placebo. It would be my opinion that both drugs are acceptable therapy and that choice is often determined by non-clinical factors such as cost or availability. Ibuprofen is usually given as three doses, 24 h apart, of 10 mg/kg, 5 mg/kg and 5 mg/kg, though there are some pharmacokinetic data indicating that this dose should be increased after day 5 [14]. There is one early treatment trial suggesting that doubling the dose of ibuprofen to 20 mg/kg, 10 mg/kg and 10 mg/kg achieves better closure rates with no difference in side-effects [15]. The numbers are too small to confirm safety but it seems reasonable to consider the higher dose if treating after day 5. There is now consistent evidence from several trials that oral ibuprofen (cheap) achieves better closure rates than intravenous ibuprofen (expensive) [16]. This is not yet standard care in Australia but it seems reasonable to consider oral ibuprofen if there is some feed tolerance or in more resource limited settings.

There are several suggested regimens for indomethacin but three doses at 24 h intervals, of 0.2 mg/kg, 0.1 mg/kg and 0.1 mg/kg seem as effective as longer courses [17] and may have fewer side-effects. Not continuing treatment in babies with a good constrictive response (assessed by ultrasound) to the first dose of indomethacin may allow further reductions in the duration of indomethacin treatment [18].

The studies in the Cochrane review suggest that about 75% of PDAs will close with both these drugs [13], though more recent trials of intravenous versus oral ibuprofen are achieving closure rates only between 60% and 70% with intravenous ibuprofen. Our clinical experience with ibuprofen is that we are not achieving closure rates as high as 75%. Audit of our first two years’ use of ibuprofen showed an early closure rate of 55%. Those that fail to close with one course are unlikely to respond to a second, but occasionally they do, particularly if they closed and then re-opened, so it is probably worth repeating at least once [19]. The role of surgery in babies in whom medical treatment has failed is more difficult and I discuss this in more detail below.

Paracetamol is emerging as a possible alternative to indomethacin and ibuprofen following a chance observation made by Hammerman et al. [20] in a baby with PDA who was given paracetamol for pain relief. More data are emerging on this topic. Dang et al. [21] randomized 160 babies born before 34 weeks to oral ibuprofen versus oral paracetamol in a non-blinded trial. Overall closure rates were similar at 79% vs 81% respectively with less gastrointestinal bleeding and less jaundice in the paracetamol group. Oncel et al. [22] randomized 90 babies born before 30 weeks and aged 48–96 h to oral ibuprofen or paracetamol. Closure rates were also similar at 77% vs 72% respectively. Although paracetamol seems to be an interesting alternative, there are not enough data yet to recommend it as standard care.

4. If you are going to treat, when to treat?

This is the really difficult part. There are essentially three strategies that have been studied. The first is to wait to see if the PDA becomes clinically apparent (e.g. murmur, bounding pulses or active praecordium) and/or symptomatic (e.g. respiratory deterioration or ventilator dependence) and then treat. Despite being probably the commonest strategy in clinical practice, the studies of this symptomatic approach are surprisingly limited. Second is a prophylactic treatment; these studies have used a range of diagnostic techniques, usually echocardiography, at a range of different postnatal ages, but usually about day 3, to select babies for treatment prior to the duct becoming clinically apparent. Third, and the best studied, is prophylactic treatment, which usually involves all babies within a definite weight or gestation range being treated shortly after birth without reference to the state of the ductus. It is a feature of all the clinical trials of PDA treatment that there is a high percentage of the control/placebo group who also receive treatment (Table 1 [23–35]). So the evidence in this area, in effect, tests earlier treatment of more babies versus later treatment of fewer babies as opposed to rigorously testing treatment versus no treatment.

4.1. Symptomatic treatment

Empirically, this approach exposes the fewest babies to the risks of treatment but treatment will be given later so this may

<table>
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<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
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<th>Control arm treatment</th>
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<td>2011</td>
<td>776</td>
<td>Yes</td>
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</table>

* Cochrane review.
increase the risks of the PDA for the babies. There is really only one significantly sized study that has explored this approach, published 27 years ago [27]. The National Collaborative study had a complicated design, which, as described above, meant that 65% of babies initially given placebo received open label treatment 36–48 h later. In a comparison that would be open to question by current standards, there were no differences in important clinical outcomes or eventual ductal closure, though the babies allocated to rescue surgery had more retinopathy and pneumothorax. There were a few smaller studies in the late 1970s and early 1980s preceding this, but little study otherwise. It is the clinical approach that is most widely used but we do not have any evidence to support it.

4.2. Pre-symptomatic treatment

The Cochrane review on this topic includes three studies, all published before 1990 and randomizing a total of 97 babies [36]. The study by Mahony et al. [28] would be classified by many now as a symptomatic strategy because enrollment depended on the development of a murmur, whereas the other two studies used contrast echocardiography on day 3. The amalgamation of these data showed less subsequent PDA and a reduction in duration of supplemental oxygen, but the authors wrap appropriate caution around the interpretation of the latter observation. The inclusion restrictions of this Cochrane review protocol led to two, probably more important, studies being excluded from the review. In 2001, Overmeire et al. [32] published a study comparing day 3 against day 7 treatment in babies with echocardiographically defined moderate or severe ductal shunting. Treatment was allocated on the basis of echocardiographic criteria on day 3. Early treatment was associated with more renal side-effects but without any evidence of respiratory advantage or any difference in other clinical outcomes. More recently, Aranda et al. [31] described a randomized controlled trial (RCT) of treatment within 72 h of life with ibuprofen or placebo with treatment based on echocardiographic criteria. Note the high rates of treatment in the control arms of all these studies (Table 1) and that no differences were found in clinical outcomes.

The available literature therefore does not provide support for this approach, although it must be highlighted in light of the above discussion on pathophysiology that day 3 may still be too late to make a difference – in other words, the damage may already be done.

4.3. Prophylactic treatment

This involves giving treatment prophylactically within the first 24 h according to defined gestation- or weight-based criteria. Indomethacin is the best studied with 2872 babies randomized in 19 trials [34]. Meta-analysis shows that prophylactic indomethacin reduces the incidence of later PDA treatment, PDA ligation, and major intraventricular haemorrhage (IVH), but does not affect mortality or long-term neurodevelopmental outcome. It is the last of these findings that has led many to argue, “Why prevent IVH if it doesn't improve neurodevelopment?” This appropriate question should probably be tempered by the observation that only one study has performed follow-up to school age, and that was in a subgroup [37]. The larger Trial of Indomethacin Prophylaxis in Preterms (TIPP) study [38] followed babies until 18 months, until which point one should be able to determine differences in major disability, but it is an age when more subtle differences in higher function will be more difficult to differentiate. There is still some uncertainty about the effect of prophylactic indomethacin on the incidence of pulmonary hemorrhage. The Cochrane review shows a trend to reduction which does not quite reach significance (relative risk: 0.84; 95% confidence interval: 0.66–1.07) [34]. Eighty percent of the babies in this meta-analysis are from the TIPP trial; when babies in that trial were re-analysed on the basis of serious pulmonary hemorrhages, prophylactic indomethacin was associated with a 35% reduction in the risk of pulmonary hemorrhage over the first week [39]. This was a post-hoc analysis but it highlighted some of the problems of ascertainment of outcomes in a large RCT, specifically differentiating minor bleeding resulting from upper airway trauma (which indomethacin is unlikely to affect) from serious hemorrhagic edema (which it might affect).

There have been six RCTs of prophylactic ibuprofen enrolling 869 babies [35]. Ibuprofen reduces the need for later treatment including ligation but does not affect other outcomes, particularly IVH. There is no longer term follow-up of these studies available at this time.

Thus, prophylactic indomethacin improves some short-term outcomes but without discernible effects on long-term outcomes, nor does prophylactic ibuprofen have much impact either. The reasons for this difference in effect are not clear.

5. What is the role of surgical ligation?

Although few centres would use surgical ligation as a first-line treatment, it is still used in babies who fail to respond to medical treatment and who continue to have medical conditions potentially attributable to the presence of a large PDA. There appears to be an international trend to a less aggressive approach to ductal ligation, reflecting concerns that ligation of PDA may do more harm than good [40]. Several studies have shown acute, potentially detrimental, hemodynamic effects after duct ligation [41,42] and, in another sub-analysis of the TIPP trial, babies who underwent surgical ligation had worse neurodevelopmental outcomes [43]. Ligation rates within the New South Wales NICU network are low at about 10% in babies born before 27 weeks and 2% in babies born at 27–29 weeks. This issue needs a randomized trial, but this may never happen. It is perhaps prudent to consider ligation only for babies who have failed at two courses of medical treatment, who have echocardiographic evidence of a large duct, and who have ongoing significant oxygen and ventilatory needs.

6. How should PDA be managed in 2015?

All this hand-wringing over the evidence is not particularly helpful to the practising 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. It could be argued that, if you were an evidence-based purist, then you should either never treat any PDA in any baby or you should use prophylactic indomethacin. It would be my opinion that the former should be applied with caution because it retains an unphysiological state that has not been proven to be safe. The latter could be supported on the basis that prophylactic indomethacin is the only approach that has been convincingly shown to have any effect on any outcome, and because it is the best studied and we have reasonable evidence of lack of harm. Whether it is worthwhile to reduce major IVH, PDA ligation and perhaps severe pulmonary hemorrhage is an open question, but it has been shown to do more
than any other approach. We know almost nothing about the consequences of never treating. This is because no-one has ever attempted it in the context of a trial; we have no evidence of benefit but, more concerningly, no evidence of lack of harm. If you do not want to use prophylactic treatment and do not wish to leave all your patients with PDA untreated, then the default should probably be to treat when the duct becomes clinically apparent in association with a probable respiratory effect, as, despite the lack of supporting evidence, there is probably the most clinical experience with this approach.

7. What next: very early ultrasound targeted treatment?

Few would argue about the need for more trials of PDA therapy, but in the real world, rightly or wrongly, many clinicians have difficulty accepting no treatment in individual babies with significant PDA. There have been proposals to compare conventional treatment of PDA after a few days, either symptomatically or presymptomatically, with a control group where the aim would be to treat when the duct becomes clinically apparent in association with the relationship between early ductal shunting and pulmonary hemorrhage is consistent with mechanistic observations made about the duct and pulmonary haemorrhage. The problem with giving indomethacin to all babies is that, as shown in Fig. 2, many babies are constricting their duct in the early postnatal period without any help. Based on this, we explored a selective approach to early treatment, essentially a refinement of prophylactic indomethacin, which is to give indomethacin targeted on the basis of early postnatal ductal constriction.

In the DETECT trial [33], babies born before 29 weeks had their duct assessed with cardiac ultrasound within the first 12 h of life (ideally in the first 6 h) and those with poorly constricting ducts (diameter above the median for population range data) were randomized in a double-blind fashion to indomethacin or placebo whereas those with well constricted ducts are not treated. The pilot phase of this trial has had to be stopped early due to removal of intravenous indomethacin from the Australian market, thus limiting the power of the findings. Prior to stopping the trial, 92 infants with a large PDA prior to 12 h of age were randomized, 44 to indomethacin and 48 to placebo. There was no difference in the main outcome of death or abnormal cranial ultrasound between the groups. Infants receiving early indomethacin had significantly less early pulmonary hemorrhage (2% vs 21%, P = 0.004), a non-significant trend towards less periventricular/intraventricular hemorrhage (PIVH) (4.5% vs 12.5%, P = 0.21) and were less likely to receive later open-label treatment for a PDA (20% vs 40%, P = 0.04). This study was inadequately powered to provide conclusive results but the reduction in pulmonary hemorrhage is consistent with mechanistic observations made about the relationship between early ductal shunting and pulmonary hemorrhage. We still do not know enough about this very early targeted approach to recommend it clinically, but there are other trials in progress looking at this early ultrasound targeted approach and we await the results with interest. At least now the question being addressed is based on current understanding of the pathophysiology of the preterm ductus arteriosus. I would propose that the clinical trial needed to solve this conundrum is one that compares very early (3–6 h of age) ultrasound targeted treatment with a control group in which PDA is truly never treated.

**Practice points**

- Preterm PDA is associated with a range of adverse outcomes, yet clinical trials of PDA treatment have failed to show reduced incidence of most of those outcomes.
- The hemodynamic impact of a PDA may be much earlier after birth than has been recognized in the design of those trials.
- High rates of open label treatment in the placebo arms of those trials mean that never treating PDA has not been rigorously tested.
- Both indomethacin and ibuprofen will close a PDA with comparable efficiency but ibuprofen has fewer side-effects.
- PDA closure rates are better with oral than with intravenous ibuprofen.
- We do not know when, or whether, to treat the preterm PDA.

**Conflict of interest statement**

None declared.

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**References**


