Preterm patent ductus arteriosus: are we any closer to knowing when to treat?

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Abstract
Debate about the importance of the preterm patent ductus arteriosus (PDA) remains unresolved. Ultrasound studies of PDA have suggested that the haemodynamic impact may be much earlier after birth than previously thought but we still don’t know when to treat a 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 which test treatment against almost never treating. Observations of very early postnatal haemodynamic significance suggest 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.

Keywords ductus arteriosus; echocardiography; ibuprofen; indomethacin; infant premature; systemic blood flow

Introduction
It is a universal truth that the weaker the evidence about a particular issue in medicine, the more opinion around it will swing. Such has been the fate of the preterm persistent ductus arteriosus (PDA) which has swung from being viewed as a cause of most adverse outcomes in preterm neonatology, to being proposed as an innocent physiological bystander. The former view results from observational studies that have consistently associated persistent PDA shunting with a range of adverse outcomes including necrotising enterocolitis (NEC), peri/intraventricular haemorrhage (P/IVH), chronic lung disease (CLD) and death. There are two limitations to these studies, firstly the co-linearity between each of these outcomes, persistent PDA and immaturity. This strong cross association confounds the interpretation of the statistical analyses. The second limitation is the range of ways in which PDA has been defined using a menagerie of clinical and, latterly, echocardiographic criteria. This inconsistency limits generalizability.

If PDA causes these adverse outcomes then treating PDA should reduce the incidence of those outcomes. The “innocent bystander” view has derived from amalgamations of randomised trials which show little evidence of consistent effect of treating PDA on outcomes. With the exception of prophylactic treatment, these trials are historically and methodologically diverse but conclusions are drawn to the effect that ‘if treating makes no difference to outcomes then preterm PDA may not be patholog-ical’. It would be my opinion that we need to be careful with such conclusions less they be taken as fact. Lack of evidence of effect is not the same as evidence of lack of effect. While the ‘innocent bystander’ conclusion is valid, there are other explanations of this paradox that are equally valid. Specifically whether we’ve really understood what’s going wrong?

Ultrasound and the ductus
Normal ductal physiology
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, Figure 1. In most term babies, functional closure occurs by 24 hours of age. Intimal ischaemia and then necrosis results from the continued intense constriction of the muscular wall and the ductus eventually evolves into the ligamentum arteriosum. Ultrasound studies have resulted in a shift in thinking about the preterm ductus. 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 1960’s. While this may have been true in the late 1960’s, it’s not true now and, indeed, the reverse may be the case e.g. early left to right shunting may cause more haemodynamic pathology in the early hours of circulatory transition than a few days later, even if the volume of the shunt does increase.

Early preterm ductal behaviour
The ductus does just one active thing which is to constrict and close after birth. At all preterm gestations there is great variation in this constriction, from those with minimal constriction to those where the constriction is much as would be seen in a well term baby. Figure 2 shows ductal colour Doppler diameter at 5 hours 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. In babies where the ductal constriction fails, there is potential for a large shunt which will remove blood from the systemic circulation and load it into the pulmonary circulation.

Using superior vena cava (SVC) flow as a surrogate measure of systemic blood flow, we showed a significant negative relationship between duct diameter and SVC flow at 5 hours of age but this relationship was not significant on the subsequent studies at 12, 24 and 48 hours. This has not been a consistent finding in the literature, Groves et al found a similar relationship at 5 hours in univariate analysis which became insignificant on multivariate analysis. However what pointers there are suggest that, if ductal shunting has a negative relationship of systemic blood flow, it does so very early after birth. 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. This early low systemic blood flow is associated with the development of intraventricular haemorrhage and later necrotising enterocolitis.
While the heart can compensate for effective loss of blood from the systemic circulation, the overload of the pulmonary circulation is passive, inevitable and only limited by the resistance of the vasculature. The immediate clinical risk of this seems to be pulmonary haemorrhage (a misnomer because it’s not blood but haemorrhagic pulmonary oedema). In one study, twelve of 126 very preterm babies developed pulmonary haemorrhage at a mean age of 36 hours. At the time of haemorrhage, 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. PDA features consistently as a risk factor for chronic lung disease but treatment of the PDA, including prophylactic treatment, makes no difference to incidence of chronic lung disease.

**Treatment of the preterm ductus arteriosus**

So should we be treating PDA in preterm babies? Systematic review of the literature shows that there is no clear evidence of effect on long term outcomes of treating PDA. Laughon and Bose proposed that the reason for the lack of effect might be that the patency of the preterm ductus was a physiological phenomenon. Benitz reviewed the data with a similar message suggesting that most preterm babies cope very well with a ductal 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 where the PDAs are genuinely left alone. Such trials have still not happened, so not treating ducts at all has not been systematically tested in the modern era of neonatology.

If you are going to treat, what to treat with?

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 less negative effect on renal and cerebral blood flow and also possibly less gastrointestinal side effects. These effects are mainly transient, so it’s unclear whether this difference matters to the baby. The Cochrane review on ibuprofen shows an increased risk of necrotising enterocolitis after indomethacin use compared to ibuprofen but this probably needs interpreting with caution because the analysis combined trials of oral and IV for both medications and indomethacin doesn’t increase the risk of NEC in trials where it is compared with placebo. It appears that both drugs are acceptable therapy and choice is often determined by non-clinical factors such as cost or availability. Ibuprofen is usually given as three doses, 24 hours apart, of 10 mg/kg, 5 mg/kg and 5 mg/kg, though there is some pharmacokinetic data that this dose should be increased after day 5. There is also one early treatment trial which suggests 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. 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 IV ibuprofen (expensive). It therefore seems reasonable to consider oral ibuprofen if there is some feed tolerance.

There are several suggested regimens for indomethacin but three doses, 24 hours apart, of 0.2 mg/kg, 0.1 mg/kg and 0.1 mg/kg seems as effective as longer courses and may have less side effects. Not continuing 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.

The studies in the Cochrane review suggest that about 75% of PDAs will close with these drugs, though more recent trials of intravenous vs oral ibuprofen are achieving closure rates between 60 and 70% with intravenous ibuprofen. 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’s probably worth repeating at least once. The role of surgery in babies where medical treatment has failed is more difficult (see below).

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

If you’re going to treat, when to treat?

This is the really difficult part. There are essentially three strategies that have been studied: 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 pre-symptomatic 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 defined 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 group who also get treated, Table 1. So in effect, most of the evidence in this area deals with earlier treatment of more babies vs later treatment of less babies rather than treatment vs no treatment.

Symptomatic treatment

Empirically, this approach exposes the least babies to the risks of treatment but treatment will be given later so this may increase the risks of the PDA for the babies. There is really only one significantly sized study which has explored this and that was published more than 25 years ago. The National Collaborative study had a complicated design which, as described above, meant 65% of babies initially given placebo received open label treatment 36–48 hours later. In a comparison which 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 that preceded this one in the late 1970’s early 1980s but this is pretty much it. It’s the clinical approach that is most commonly used but we don’t have any evidence to support it.

Pre-symptomatic treatment

The Cochrane review on this topic includes three studies, all published before 1990 and randomizing a grand total of 97 babies. The study of Mahony et al. would be classified by many now as a symptomatic strategy because enrolment depended on the development of a murmur, the other two studies used contrast echocardiography on day 3. The amalgamation of this 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 lead to two, probably more important, studies being excluded from the review. In 2001, Overmeire et al. 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. described an RCT of treatment within 72 hours 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 no differences were found in clinical outcomes.

So the available literature does not provide support for this approach although it must be highlighted in light of the above approaches.

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Table 1
discussion on physiology that day 3 may still be too late to make a difference, in other words, the damage may already be done.

**Prophylactic treatment**

This involves giving treatment prophylactically within the first 24 hours according to defined gestation or weight based criteria. Indomethacin is the best studied with 2872 babies randomised in 19 trials. Meta-analysis shows that prophylactic indomethacin reduces in 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 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 sub-group. The larger TIPP study followed babies until 18 months where one should be able to determine differences in major disability but it is an age where more subtle differences in function will be more difficult to differentiate. There is still some uncertainty about the effect of prophylactic Indomethacin on the incidence of pulmonary haemorrhage. The Cochrane review shows a trend to reduction which doesn’t quite reach significance (RR 0.84 CI 0.66-1.07). Eighty percent of the babies in this meta-analysis are from the TIPP trial and when babies in that trial were re-analysed on the basis of serious pulmonary haemorrhages, prophylactic indomethacin was associated with a 35% reduction in the risk of pulmonary haemorrhage over the first week. This was a post-hoc analysis but 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 haemorrhagic oedema (which it might affect).

There have been 6 RCTs of prophylactic ibuprofen enrolling 869 babies. 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.

So prophylactic indomethacin improves some short term outcome but without discernible effects on long term outcomes, prophylactic ibuprofen doesn’t have much impact on either. The reasons for this difference in effect are not clear.

**What’s the role of surgical ligation?**

While few centres would use surgical ligation as a first line treatment, it is still used in babies who fail to respond to medical treatment. There appears to be an international trend to a less aggressive approach to ductal ligation reflecting concerns that ligation of PDAs may do more harm than good. Several studies have shown acute, potentially detrimental, haemodynamic effects after duct ligation and, in another sub-analysis of the TIPP trial, babies who underwent surgical ligation had worse neurodevelopmental outcomes. Ligation rates within the New South Wales NICU network are about 10% in babies born before 27 weeks and 2% in babies born at 27–29 weeks. This issue needs a randomised trial. It is probably prudent to only consider ligation for babies who’ve failed at least two courses of medical treatment, who have echocardiographic evidence of a large duct and who have ongoing significant oxygen and ventilatory needs.

**How should I manage a PDA in 2014?**

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 largely elusive. Proposing the need for more trial PDA trials is really easy-one line at the end of an article. Getting these trials done is really hard.

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 retains an unphysiological state for the infant, which 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. Also because, it is the best studied, we have reasonable evidence of lack of harm. Whether reducing major IVH, PDA ligation and, probably, severe pulmonary haemorrhage is worthwhile is an open question but it’s been shown to do more than any other approach. We know almost nothing about the corollary of this which is no treatment. This is because no-one’s ever been game to try it in the context of a trial, we have no evidence of benefit but, more concerning, no evidence of lack of harm. If you don’t want to use prophylactic treatment and you’re not game to leave all your ducts 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.

**What next: very early ultrasound targeted treatment?**

For the reasons discussed above, we hypothesised that to make a difference with PDA treatment, treatment would have to be given early after birth. The problem with giving indomethacin to all babies is that, as shown in Figure 2, many babies are constricting their duct very nicely 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, babies born before 29 weeks had their duct assessed with cardiac ultrasound within the first 12 hours of life (ideally in the first 6 hours) and those with poorly constricting ducts (diameter above the median for population range data) were randomised in a double blind fashion to indomethacin or placebo while 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 hours of age were randomised, 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 haemorrhage (PH) (2% vs 21%, p = 0.004), a non-significant trend towards less periventricular/intraventricular haemorrhage (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 haemorrhage is consistent with mechanistic observations made about the relationship between early ductal shunting and pulmonary haemorrhage. We still don’t know enough about this very early targeted approach to recommend it clinically but there other trials in progress which are looking at this early ultrasound targeted approach. At least now the question being addressed is based on current understanding of the pathophysiology of the preterm ductus arteriosus. So in answer to the question posed in the title of this article, we are a bit closer to knowing when to treat but there’s a long way to go.

**FURTHER READING**


**Practice points**

- There is only limited evidence to support many current strategies for treating PDA in neonates
- Trial data suggests that very early treatment may be helpful in reducing some of the adverse consequences of PDA but there is no evidence of effect on longer term outcomes
- Patent ductus arteriosus in most preterm babies will close spontaneously in time, without treatment
- The increased availability of echocardiography may help to select babies who are most likely to benefit from treatment and so allow a tailored treatment which would minimise risks and maximise benefits to babies born prematurely