Patent ductus arteriosus: to treat or not to treat?

William E Benitz

ABSTRACT
Persistent patentity of the ductus arteriosus in the preterm infant is associated with numerous morbidities, including higher rates of bronchopulmonary dysplasia and increased mortality. These strong associations have led to widespread use of cyclooxygenase inhibitors and surgical ligation to achieve ductal closure in the expectation that closing the ductus will reduce these complications. Each of these interventions has its own associated adverse effects. Neither individual randomised controlled trials nor meta-analyses of those trials have been able to demonstrate long-term benefits of these treatments despite their efficacy in inducing ductal closure and reducing the need for ductal ligation. Despite the potential shortcomings of those trials, they provide substantial cumulative evidence that early, routine treatment to close a persistently patent ductus arteriosus in preterm infants does not improve outcomes and should therefore be abandoned. Future trials of these interventions for patent ductus management should address different questions. Persistence of ductal patency should be considered a sign of rather than a direct cause of the several morbidities with which it is clearly associated. Practitioners should tolerate ductal patency and learn to manage its causes and consequences rather than focusing on achievement of ductal closure.

In his seminal 1958 report that a patent ductus arteriosus (PDA) murmur is heard more frequently and for a longer time in preterm infants, Burnard also associated delayed ductal closure with respiratory disease:

In premature babies, . . . there was a clear connexion with dyspnoea, and the murmur was not heard unless respiratory distress was present.1

Other morbidities, including more severe respiratory distress syndrome (RDS), prolonged assisted ventilation, pulmonary haemorrhage, bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), renal impairment, intraventricular haemorrhage (IVH), periventricular leukomalacia, cerebral palsy and death, were soon found to be more prevalent in preterm infants with persistent PDA.2 Excessive mortality among infants with PDA persists to the present time.3 The strength of these associations, coupled with increasing awareness of the disordered haemodynamics of a large left-to-right shunt into the low resistance pulmonary circulation, led to the hypothesis that prolonged ductal patency had a causal role in these morbidities.

Reports of surgical ligation of the ductus in preterm infants in the early 1970s were followed by numerous confirmations that ligation could be accomplished without excessive perioperative mortality. Descriptions of induced ductal closure by non-steroidal anti-inflammatory drugs by Friedman et al4 and Heymann et al5 in 1976 were followed by numerous studies confirming that indomethacin and ibuprofen effect ductal constriction and closure, particularly during the first week after birth. These successes were followed by widespread adoption of aggressive measures to ensure early ductal closure in preterm infants.

Treatments to achieve ductal closure have a number of associated morbidities. In contrast to the anticipated prompt respiratory improvement, surgical ligation is often associated with impaired left ventricular systolic function, sometimes resulting in circulatory and respiratory collapse requiring marked escalation in intensive care support.6 In a randomised controlled trial, prophylactic ligation increased the risk of bronchopulmonary dysplasia.7 Surgical ligation is also associated with diaphragmatic paresis,8 life-long paresis of the left vocal cord9 and late development of scoliosis.10 Randomised trials of early indomethacin demonstrated prolongation of ventilator support,11 worse oxygenation and increased surfactant requirements,12 and requirements for higher mean airway pressures13 and inspired oxygen concentrations.13 14 Treatment with indomethacin has been associated with spontaneous intestinal perforation,15 impaired renal function16 and altered cerebrovascular autoregulation.17 Similar effects have been seen with ibuprofen,18 although adverse effects may be less frequent. Downstream effects of early exposure to cyclooxygenase (COX) inhibitors on definitive ductal closure have not been fully explored. Intervention to close a PDA is not entirely benign.

Excluding trials such as those comparing indomethacin with ibuprofen or short with long courses of indomethacin, in which ductal closure was achieved equally in both treatment groups, 49 randomised controlled trials of PDA closure in preterm infants, including nearly 5000 subjects, have been published.2 Although nearly all of these trials were primarily designed to assess effects on ductal patency or IVH, all reported data on one or more secondary outcomes. Neither individual trials nor meta-analyses have demonstrated long-term benefits of measures to close the PDA. Cochrane reviews of prophylactic surgical ligation,19 indomethacin20 or ibuprofen21 of PDA treatment with indomethacin22 or ibuprofen,23 or of surgical versus medical PDA closure24 all found that benefits were limited to ductal closure, fewer ductal ligations, and – with prophylactic indomethacin – less IVH (IVH > grade II) and periventricular leukomalacia.20 These neuroimaging effects were not associated with better neurodevelopmental outcomes. Other meta-analyses were also unable to identify beneficial effects, irrespective of whether the criteria for study inclusion were permissive or rigorous (as in the Cochrane analyses) or how trials were grouped for meta-analysis (by treatment, timing, era before or after surfactant, or other aspects of trial design).2 25 CIs for effects on the most important outcomes (death, BPD, death or BPD, NEC, developmental delay, neurosensory impairment, and death or neurosensory impairment) include 1 (no effect) and are narrow (reflecting a low probability that the effect size deviates much from 1). This is not an absence of evidence for a benefit from early, routine ductal closure, but rather substantial evidence for an absence of benefit.

This conclusion has three important implications. First, routine treatment to induce early closure of a persistent PDA in preterm infants should be abandoned, because it does not help these babies. Second, more similar clinical...
trials are not needed, and may be inappropria- 
tate, because addition of another tri-
也可能move the pooled CI away from the point estimate of no effect only if it 
enrows many subjects and demonstrates a sub-
tantial effect. If yet another trial must be con-
ducted to convince those who believe that routine treat-
ment with COX inhibitors followed by liga-
tion when COX inhibitors fail is the current standard regimen, it should be 
designed to demonstrate non-inferiority of avoiding those measures, in the con-
text of standardised approaches to other relevant aspects of care, such as fluid 
management, respiratory care and transfusion guidelines. Third, the concept 
that a PDA is, in itself, harmful to pre-
term infants should be set aside. If that 
were so, closing the ductus, which was 
consistently achieved in the reported tri-
als, should reduce harmful effects, but it 
does not. Delayed ductal closure in preterm infants must be a reflection of 
some underlying process, such as a sys-
temic inflammatory response, that both 
delays ductal closure and produces the various morbidities that unquestionably 
are covariant with PDA.

If closing the ductus is not helpful, 
what are we to do with these babies? The observation that a particular class of treatments (intervention to close the 
PDA) fails to improve outcomes does not 
mean that no treatment is useful or 
necessary, or that the PDA can simply be 
ignored. Other treatments may improve 
outcomes without inducing ductal clo-
sure. These might fall into two broad 
categories. First, insight into why the 
ductus remains open in some preterm 
infants must be a reflection of 
some underlying process, such as a sys-
temic inflammatory response, that both 
delays ductal closure and produces the various morbidities that unquestionably 
are covariant with PDA.

Several conclusions should not be 
drawn from the negative meta-analyses. 
It would be wrong to conclude that there 
are no very low birthweight infants 
who might benefit from ductal closure. 
Unfortunately, we do not know pre-
cisely how to identify them or when or 
how to treat them. Because the available 
data come from trials of early interven-
tions, typically before age 10–14 days, 
and many control infants received ‘back 
up’ or ‘rescue’ treatment later in their 
course, it is quite plausible that infants 
with a persistent PDA in the third or 
fourth week after birth may benefit 
ductal closure. Those with signs of 
congestive heart failure, pulmonary con-
gestion or renal ischaemia are obvious 
candidates, but empiric data to inform 
treatment criteria are lacking. Retrograde 
diastolic flow in the descending aorta is 
associated with an increased risk of NEC 
in term infants with congenital heart 
disease. 

This haemodynamic distur-
bance has been demonstrated in preterm 
infants with PDA, but its relationship to 
risk of NEC in preterm infants remains 
hypothetical. Development of echocar-
diographic, clinical or laboratory criteria 
for either early or delayed intervention 
is an important goal, and progress is 
being made in this area.

If we are to avoid repeating the errors of the past, 
it will be essential to complete the full 
sequence of investigations, demonstrat-
ing that new criteria predict continued 
ductal patency, correlate with adverse 
outcomes and identify a cohort in which 
those outcomes can be ameliorated or 
averted by closing the ductus. Until 
the results of such work are available, 
however, management of these infants 
will have to be guided by clinical judge-
ment, informed, as much as possible, by 
pathophysiology rather than direct evi-
dence. Nonetheless, a more conservative 
approach in which intervention to close 
the ductus is deferred until the third or 
fourth week after birth will intrinsi-
cally reduce the proportion of infants 
who receive treatment, since spontane-
ous ductal closure will occur in a large 
proportion of infants (especially those 
weighing >1000 g at birth). 

Finally, data gathered from preterm infants 
have no bearing on management of term 
infants with a persistent PDA, particu-
larly in the context of congenital heart 
disease or other syndromic anomalies. 
Use of COX inhibitors or ligation in 
those infants must be guided by experi-
ence in infants with similar diagnoses.

There is still a great deal to be learned 
about the natural history of ductal clo-
sure in preterm infants, but it is time to 
reassess our long-held conviction that a 
persistent ductus is a source of rather than a 
sign of trouble for these infants. As we 
learn to live with patency of the ductus, 
we can hope to learn how best to man-
ge both its causes and consequences. 

Much hard work lies ahead. Until that 
work is done, we are well advised to 
follow the example of Clyman and 
colleagues in moving incrementally 
towards less aggressive, more conserva-
tive approaches to management of the 
PDA in preterm infants.

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