PART A: EVIDENCE-BASED ANSWER AND SUMMARY
The ductus arteriosus (DA) is an important structure in fetal life. The DA connects the pulmonary artery to the aorta and serves to shunt blood away from the lungs into the umbilical placental circulation where gas exchange takes place. At birth, closure of the DA is an essential part of postnatal adaptation. Closure of the DA is initiated by an increase in oxygen and changes in pulmonary and systemic blood pressure (1). In full-term newborns, the DA routinely closes within one to five days after delivery (2). In preterm infants, failure of DA closure after birth can be associated with an increased incidence of chronic lung disease (CLD), intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC). Clinicians may choose to treat the patent DA (PDA) in an attempt to minimize the risk of these complications. However, although there is a statistical association between PDA and these complications, no formal causal relationship has been demonstrated. Prostaglandin inhibition – using indomethacin or ibuprofen – is the standard strategy to close the DA. Surgical closure of the DA is an alternative option.

Experimental studies in the clinically relevant chronically ventilated preterm baboon model of CLD have provided some insights into the physiological effects and hemodynamic consequences of a pathological DA, the reversibility of these effects on ductal closure and the relationship of these changes to important neonatal morbidities. Although the PDA results in diminished cardiac function and increases ventilatory requirements, surgical ligation on day 6 has no effect on lung histology (3). Conversely, early indomethacin treatment versus placebo improves pulmonary mechanics and minimizes lung injury by limiting pulmonary blood flow and the consequences of increased pulmonary/systemic blood flow (4). A moderate PDA shunt also limits the increase in postprandial mesenteric blood flow velocity and may contribute to feeding intolerance (5).

In the clinical setting, two strategies are usually used to close the DA to avoid PDA-associated complications: prophylactic (within 24 h of life, whether the DA is patent or not) and therapeutic (within seven days of life to infants who display clinical symptoms or echocardiographic signs of PDA) closure of a PDA. When pharmacological therapy fails, surgical ligation of the PDA is often proposed. The effectiveness and safety of these strategies have been evaluated in meta-analyses.

Prophylactic closure of a PDA in preterm infants
Prophylactic indomethacin results in favourable intermediate outcomes such as reduction of significant PDA, need for surgical ligation, severe IVH and serious pulmonary hemorrhage (6). No evidence of short-term gastrointestinal or renal adverse effects was detected. There was no significant difference between indomethacin and control groups with respect to the important long-term outcome of death, CLD or severe neurosensory impairment. The lack of long-term neurosensory benefit despite the reduction in rate of severe IVH is intriguing, and potential explanations can only be speculative. A potential neurotoxicity effect of the drug cannot be excluded.

Four trials (7) evaluated the effect of ibuprofen in 672 premature infants born at less than 34 weeks’ gestational age. Ibuprofen significantly decreased the incidence of a PDA on day 3, the need for rescue treatment with cyclooxygenase inhibitors and the need for subsequent surgical ligation. Ibuprofen significantly increased the serum creatinine levels and decreased urine output. Ibuprofen did not significantly alter mortality, or the incidence of grade 3/4 IVH, CLD, NEC, gastrointestinal hemorrhage, intestinal perforation or the time to reach full feeds.

The DA had closed spontaneously by day 3 in up to 60% of infants in the control group compared with 8% to 27% of infants in the treatment group (7). This result suggests that the prophylactic approach unnecessarily exposes a large proportion of infants to a drug that has concerning side effects without conferring any important long-term benefits on outcome.

Treatment of a PDA in preterm infants
Clyman (8) conducted a systematic review comparing four indomethacin treatment strategies according to timing: prophylactic, early symptomatic (two to three days of life),
Evidence for Clinicians

late symptomatic (seven to 10 days of life) and later symptomatic (two to six days after late treatment). Unfortunately, only one trial did not use backup treatment. In this review, all three of the other treatment strategies prevented the development of a symptomatic PDA or the need for backup treatment. Surgical ligation, pulmonary morbidity and NEC were less likely to occur with early treatment than with late treatment.

Another systematic review (9) evaluated the effectiveness and safety of ibuprofen compared with placebo or no intervention for closing a PDA in preterm infants, and the efficacy of ibuprofen versus indomethacin for closing a PDA. Only the placebo study did not fulfill the entry criteria. Eleven studies comparing ibuprofen versus indomethacin were identified and these included 620 patients. The main findings show no statistically significant difference between ibuprofen and indomethacin in failure of ductal closure, mortality, surgical ligation, duration of ventilation, IVH, periventricular leukomalacia, NEC, time to full enteral feeds, retinopathy of prematurity (ROP), sepsis, duration of hospital stay or gastrointestinal bleed, or CLD at 36 weeks of age. The incidence of decreased urine output was lower in the ibuprofen group compared with the indomethacin group. Oxygen dependency at 28 days was statistically significantly more likely to occur in the ibuprofen group. The main methodological weakness was the failure to mask clinicians to the study drug because the dosing schedule (ibuprofen or indomethacin) was different. The authors concluded that ibuprofen does not confer any benefit over indomethacin for the treatment of a PDA and that indomethacin should remain the drug of choice.

Surgical closure of a PDA
Routine surgical ligation of a PDA refractory to medical treatment is widely practiced (10-12) even though there is no evidence that surgical ligation of a hemodynamically significant PDA is associated with improved long-term outcomes in preterm infants. One study (13) suggested that a PDA is less likely to close with indomethacin if the PDA is associated with a large left atrium/aorta ratio on echocardiography and that surgical ligation may be the better option. However, surgery can be associated with significant short- and long-term complications including pneumothorax, hemodynamic instability, intraoperative bleeding, phrenic nerve palsy, wound infection and vocal cord paralysis (10,12,14-16).

A randomized trial (17) comparing prophylactic ligation versus standard treatment without indomethacin showed a reduced incidence of NEC with surgical ligation. There were no statistically significant differences in mortality, severe IVH, CLD and ROP. A recent meta-analysis (18) concluded that based on current evidence, the high rate of spontaneous closure, availability of medical therapies, and the potential short- and long-term complications of surgical ligation, the use of prophylactic surgical therapy is not indicated (18).

The evidence for therapeutic ligation versus indomethacin for symptomatic PDA has also recently been reviewed (19). The only trial addressing this question found no statistically significant difference between surgical closure and indomethacin treatment in mortality, CLD, NEC, sepsis or IVH. In the surgical group, there was a statistically significant decrease in failure of PDA closure but an increase in the incidence of pneumothorax and stage III and IV ROP compared with the indomethacin group (20).

Evaluated studies were conducted in the past 20 years or more, and may not be representative of today's patient population. A more recent analysis of the Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP) (21) suggests that PDA ligation may be associated with increased risks of BPD, severe ROP and neurosensory impairment in extremely low birth weight infants (21).

Summary
In preterm infants, a PDA can be associated with an increased incidence of CLD, IVH and NEC. Prophylactic PDA closure with indomethacin or ibuprofen reduces the incidence of significant PDA and need for surgical ligation; indomethacin also reduces the risk of severe IVH (without affecting long-term neurodevelopmental outcome) and serious pulmonary hemorrhage. Sixty per cent of PDAs close spontaneously. Treatment of a PDA before 10 days of age reduces the development of a symptomatic PDA or the need for backup treatment. There is no evidence to indicate that ibuprofen is superior to indomethacin. Surgical ligation, pulmonary morbidity and NEC are less likely to occur with early treatment (before seven days) compared with late treatment (seven to 10 days). Surgical ligation is efficient in closing the DA, but associated with complications. The current evidence indicates the need for trials assessing clinically relevant outcome measures to determine if and when closure of a PDA is indicated.

PART B: CLINICAL COMMENTARY
Prophylactic DA closure
Despite numerous trials, the controversy regarding prevention of a PDA remains. The main limitation of the trials is the clinical relevance of outcome measures. Among the primary outcomes (ie, DA closure at day 3 of life, need for rescue treatment and need for surgical ligation), only the need for surgical ligation may be clinically relevant. However, the benefit of avoiding surgical ligation may depend on institution-related factors such as the incidence of postoperative complications, waiting time and the need for transfer to another facility with surgical capacity (10,14,22). The indications for ligating a DA vary among centres and within centres, and may skew this outcome measure. The number needed to treat to avoid surgical ligation was 25, indicating that prophylactic treatment exposes a large proportion of premature infants to a drug with some side effects, without conferring important long-term benefits. This is particularly important given that up to 60% of premature infants in the placebo group closed their DA.
spontaneously (7). In some instances, inducing early DA closure might be deleterious, as suggested by the occurrence of pulmonary hypertension in three infants within 1 h after ibuprofen administration (23,24). These observations highlight the physiological importance of the DA in premature infants with residual respiratory disease and remaining high pulmonary vascular resistance.

Similarly, the importance of markers used to assess the potential side effects of ibuprofen can be questioned. A decrease in urine output or an increase of plasma creatinine level may be without short- and long-term consequences for the baby if transient and reversible.

An association between PDA and various complications including CLD, IVH and NEC is often reported. Whether a PDA is responsible for these complications is unclear. Both medical and surgical interventions to close the DA can be associated with additional morbidity (10,14,22). More recent reports (25) also suggest the early (day 0 to day 3 of life) use of prophylactic indomethacin as an independent risk factor for spontaneous intestinal perforation in very premature infants. In the light of results of systematic reviews, the question of whether prophylactic closure of a PDA is indicated becomes legitimate. If the PDA directly contributes to morbidity, then closure should result in a reduced incidence of the morbidity. Current systematic reviews evaluating the potential benefit of prophylactic PDA closure indicate otherwise. While prophylactic ibuprofen decreases the incidence of PDA, there is no statistically significant difference in the incidence of the complications associated with PDA (26).

Long-term outcome results for ibuprofen prophylaxis are not yet available. The importance of assessing clinically relevant end points and the long-term effects of prophylactic PDA treatment is highlighted by the TIPP trial. The TIPP trial, which is the largest randomized controlled trial on indomethacin prophylaxis to date, showed a significant decrease in the incidence of severe IVH (a clinically relevant outcome), but this did not result in a clinically relevant (improved survival without neurosensory impairment) long-term benefit (27) or in an economic benefit (28). Unfortunately, it remains impossible to determine whether the association between neurodevelopmental outcome and DA treatment reflects increased ductal disease, the need for escalation of therapeutic interventions, complications of treatment or comorbidities.

Despite a lack of randomized trials supporting these strategies, a current tendency in neonatal intensive care units is early extubation and the use of nasal continuous positive airway pressure after surfactant therapy to reduce respiratory morbidity (29). This practice may induce a higher risk of severe pulmonary hemorrhage in preterm infants with PDA. A recent analysis from the TIPP trial (30) suggests that serious pulmonary hemorrhage worsens long-term outcome and that prophylactic indomethacin reduces the rate of early serious pulmonary hemorrhage, mainly through its action on the PDA. Although prophylactic indomethacin is less effective in preventing serious pulmonary hemorrhages that occur after the first week of life, the current tendency toward early extubation may fuel the discussion regarding prophylactic PDA closure in this patient population.

Treatment of a PDA

With regard to prophylactic PDA closure, the clinical relevance of the outcome measures can be questioned. For the primary outcome – DA closure after one or three doses of the study drug (mostly given during the first week of life) – it is unknown whether the presence of a PDA beyond this age has any adverse effects. The significance of reopening of a DA is also unknown. If asymptomatic, a PDA can be tolerated and may not need subsequent intervention. The indication for surgical closure of a PDA may vary between centres. Thus, the decision to treat a PDA (either pharmacologically or surgically) needs to be based on objective and reliable markers of adverse effects due to a PDA (31).

Current trials of treatment of the DA do not consider illness severity and heterogeneity of the clinical presentation. In addition, they do not satisfactorily address anatomic closure or standardization of the hemodynamic significance. Recently developed algorithms combining clinical and echocardiographic criteria (32) or biological markers (such as B-type natriuretic peptide (33) or troponin T levels (34)) may be useful to guide treatment decisions.

Perspectives

The current evidence indicates the need for trials assessing clinically relevant outcome measures to determine if and when therapeutic closure of a PDA is indicated. Thus, implications for research include the following: to determine the natural history of a PDA in premature infants stratified by gestational age or birth weight, and to identify objective and reliable markers to assess or predict PDA-induced complications. In parallel, improvements in our understanding of the basic mechanisms regulating DA tone, oxygen sensitivity of the premature DA, and ductal tissue remodelling, as well as the design of miniaturized devices (35) and/or noninvasive procedures (36), may lead to new, safer and efficient therapeutic strategies to modulate DA patency (37-39). Additional improvements could come from specific targeting of pharmacological therapies to the ductal tissue to avoid systemic adverse effects (40).

Summary

Prophylactic closure of a PDA in preterm infants remains controversial because of the lack of an unambiguous cause-and-effect relationship between neonatal complications and PDA, and the potential adverse effects of medical and surgical treatments for DA closure. The lack of an objective and reliable marker to predict PDA-associated complications adds another degree of uncertainty regarding whether to treat a PDA. Studies identifying clinical, echocardiographic, biological and genetic markers to reliably predict PDA-associated complications are urgently warranted. In the meantime, practice will continue to rely on local history and infrastructure (access to echocardiography and surgery) and, therefore, will remain inconsistent among centres.
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REFERENCES