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Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all?

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Abstract

Although a moderate-size PDA needs to be closed by the time a child is 1–2 years old, there is great uncertainty about whether it needs to be closed during the neonatal period. While 95% of neonatologists believe that a moderate-size PDA should be closed if it persists in infants (born before 28 weeks) who still require mechanical ventilation, the number that treat a PDA when it occurs in infants that do not require mechanical ventilation varies widely. Both the high likelihood of spontaneous ductus closure and the absence of RCTs, specifically addressing the risks and benefits of neonatal ductus closure, adds to the current uncertainty. New information suggests that early pharmacologic treatment has several important short-term benefits for the preterm newborn. On the other hand, ductus ligation, while eliminating the detrimental effects of a PDA on lung development, may create its own set of morbidities that counteract many of the benefits derived from ductus closure.

Introduction

Numerous studies have demonstrated that a prolonged, persistent left-to-right shunt through a patent ductus arteriosus (PDA) shortens the life span of animals and humans (1–6). The long-term morbidities that are associated with a PDA (subacute bacterial endocarditis and irreversible pulmonary hypertension) can usually be avoided if the ductus is closed within the first two years after birth. Although a PDA needs to be closed by the time a child is 1–2 years old, there is great uncertainty about whether a persistent PDA needs to be closed during the neonatal period (7–9).

In newborn infants, a persistent PDA increases pulmonary hyperemia and edema, and decreases renal, mesenteric and cerebral perfusion. Pharmacologic and surgical treatments can eliminate these hemodynamic aberrations. On the other hand, there is a high likelihood

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that the ductus will close spontaneously (without any specific treatment) during the neonatal period. Therefore, early treatment runs the risk of exposing infants to drugs or procedures they might not need.

Incidence of spontaneous ductus closure

Pulsed Doppler echocardiographic assessments of full term infants indicate that functional closure of the ductus arteriosus occurs in almost 50% of the infants by 24 hours, in 90% by 48 hours, and in all by 72 hours after birth (Table 1). The rate of ductus closure is delayed in preterm infants; however, essentially all healthy preterm infants (and 90% of those with respiratory distress syndrome), who are ≥30 weeks gestation, will close their ductus by the fourth day after birth. Preterm infants of less than 30 weeks gestation, with severe respiratory distress, have a 65% incidence of persistent ductus patency beyond the fourth day of life. Even among these infants, spontaneous closure can occur during the neonatal period (Table 1). Sixty-seven percent of infants, weighing between 1000 and 1500 grams at birth, will spontaneously close their ductus by seven days after birth (94% will close prior to hospital discharge) (10). Among VLBW (≤ 1500 grams) infants that still have a persistent PDA at the time of hospital discharge, 86% will spontaneously close their PDA by the end of the first year (the rest will still have a persistent PDA or will require coil occlusion during the first year) (11). On the other hand, spontaneous ductus closure during the neonatal period only occurs in 30-to-35% of infants weighing <1000 grams at birth (10, 12) (Table 1). For infants ≤27 weeks (or weighing <1000 grams), with a persistent PDA at the time of hospital discharge, 75% will spontaneously close their PDA and 25% will require coil occlusion by the end of the first year (13).

Several perinatal and postnatal events can alter the incidence of spontaneous ductus closure: infants who are small for gestational age (14–16), develop late onset septicemia (17) or receive excessive fluid administration during the first days of life (18) are more likely to develop a clinically symptomatic PDA in the neonatal period. Furosemide administration and phototherapy also have been reported to increase the incidence of PDA (19, 20); however, more recent studies have not found this to be the case (21, 22). Administration of exogenous surfactant can alter the presentation of a PDA. Surfactant has no effect on the contractile behavior of the ductus; rather, it alters pulmonary vascular resistance and leads to an earlier clinical presentation of the left-to-right shunt in animals (23, 24) and humans (25–28). In one single center study, lowering the “tolerable” range of oxygen saturations led to an increased incidence of PDA in preterm infants (29). On the other hand, no change in the incidence of PDA was detected in a recent, large, multicenter trial after the “tolerable” range of oxygen saturations was lowered (30). Several perinatal factors increase the likelihood that the ductus will close spontaneously: non-Caucasian infants and infants who receive antenatal glucocorticoids are significantly more likely to close their ductus in the neonatal period (31–33).

Surgical and pharmacologic treatment options for closing the PDA during the newborn period

Surgical Ligation

Surgical ligation produces definitive ductus arteriosus closure, however, it is associated with its own set of morbidities: thoracotomy, pneumothorax, chylothorax, scoliosis and infection (34). The incidence of unilateral vocal cord paralysis (which increases the requirements for tube feedings, respiratory support and hospital stay) has been reported to be as high as 67% in infants with birthweights ≤1000 grams, following PDA ligation (35, 36). Approximately 25–30% of infants with birthweights ≤1000 grams will require inotropic support for

profound hypotension during the postoperative period (37). In addition, neonatal transport to another facility may be required if surgical expertise is not readily available.

Early surgical ligation has recently been shown to be an independent risk factor for the development of bronchopulmonary dysplasia (38, 39). Early surgical ligation increases the expression of genes involved with pulmonary inflammation and decreases the expression of pulmonary epithelial sodium channels (that are critical for alveolar water clearance) (40). These changes may contribute to the lack of improvement in pulmonary mechanics after PDA ligation. In addition, early surgical ligation impedes lung growth (41–43). These findings raise the possibility that ductus ligation, while eliminating the detrimental effects of a PDA on lung development, may create its own set of problems that counteract many of the benefits derived from ductus closure (38, 39).

Indomethacin and Ibuprofen

Inhibition of prostaglandin synthesis with nonselective inhibitors of cyclooxygenase-1 and -2 (e.g., indomethacin and ibuprofen) appears to be an effective alternative to surgical ligation (44). In most intensive care nurseries, indomethacin and ibuprofen have replaced surgery as the preferred therapy for closing a persistent PDA. However, both have been associated with several potential adverse effects in the newborn. Indomethacin produces significant reductions in renal (45, 46), mesenteric (47, 48), and cerebral blood flow (49–54). Indomethacin also reduces cerebral oxygenation (54, 55). Alterations in creatinine clearance and oliguria (that are minimally responsive to dopamine or furosemide therapy (56, 57)) are common problems with the initial doses of indomethacin. Renal function returns towards normal after the initial doses of indomethacin or after drug discontinuation (58). Some of indomethacin's actions on these organ systems may not be due to its inhibition of prostaglandin synthesis (59–61).

Although indomethacin produces significant physiologic alterations, none of the controlled, randomized trials that have examined the relationship between indomethacin and neonatal morbidity have found an increase in the incidence of necrotizing enterocolitis, gastrointestinal perforation, ROP, chronic lung disease, or cerebral white matter injury following indomethacin treatment (62). Although indomethacin, by itself, has not been shown to increase the incidence of gastrointestinal perforations, the combination of indomethacin *and* postnatal steroids, administered simultaneously, has been shown to increase the incidence of gastrointestinal perforations/necrotizing enterocolitis (63, 64).

Indomethacin's cerebral vasoconstrictive effects are frequently cited as a concern for neonatologists (53, 65); however, a Cochrane systematic review found that indomethacin prophylaxis is more likely to decrease rather than increase the incidence of periventricular leukomalacia (62). Although there is no evidence that prophylactic indomethacin has any beneficial or adverse effects on neurodevelopmental outcome at 18 months (66), there is evidence that there may be long term benefits at 4.5 and 8 years (67–69).

Ibuprofen, another nonselective cyclooxygenase inhibitor, has been shown to close the ductus in animals (70) and preterm infants. It appears to be as effective as indomethacin in producing PDA closure in very low birthweight infants (at least in infants with a mean gestational age of 28 weeks) (71). In contrast with indomethacin, ibuprofen does not appear to affect mesenteric blood flow (46, 59, 61) and has less of an effect on renal perfusion, oliguria (46, 59, 61), and cerebral blood flow (54, 61, 72, 73). Animal studies suggest that ibuprofen may have some cytoprotective effects in the intestinal tract (74). Although individual studies have not found ibuprofen to be superior to indomethacin in the prevention of NEC, a recent meta-analysis suggests that ibuprofen may be associated with a lower incidence of NEC than indomethacin (71). On the other hand, ibuprofen does not appear to

have the same intracranial hemorrhage sparing effects that are seen with indomethacin. The optimal age-appropriate dosing schedule for ibuprofen is still under consideration (75). Ibuprofen's effects on total and free serum bilirubin concentrations (76, 77) raise concerns about the safety of some of the higher dose options.

PDA and Neonatal Morbidity: To treat or not to treat

At this time, clear evidence is lacking for or against many of the current approaches to a PDA in the newborn period (7, 78, 79). Although indomethacin and ibuprofen have been shown to be effective in producing ductus closure (44), the long-term benefits of ductus closure on chronic lung disease, necrotizing enterocolitis or survival have yet to be established (78, 80–83). Published randomized controlled trials (RCTs) provide only a limited amount of information to help guide current PDA treatment choices. Unfortunately, most PDA-related RCTs were not designed to address the question of whether or not a symptomatic PDA should be treated during the neonatal period; they were designed, instead, to assess the relationship between "timing" of treatment ("early" or "late") and efficiency of PDA closure. Therefore, the published RCTs are only useful for examining the effects of short-term exposures (between 2–6 days) to a PDA. RCTs that examined preterm infants, whose PDA first became symptomatic when they were several days old, found that "early" PDA closure did not alter the incidence of serious neonatal morbidities, like BPD, NEC or ROP, when compared with an approach that "delayed" PDA closure by 2–6 days (80). On the other hand, using indomethacin as a "prophylactic" treatment (i.e., starting treatment within 12 hours of birth) appeared to have some benefits compared with delaying treatment until "early" PDA symptoms appeared (usually 2–3 days after birth). These "prophylactic" treatment RCTs (and their meta-analysis) demonstrate that indomethacin prophylaxis decreases the incidence of 1) severe early pulmonary hemorrhage, 2) severe grades of IVH, 3) the risk of developing a symptomatic PDA, and 4) the risk that indomethacin treatment will fail to close the PDA and that surgical ligation will be needed (62, 66, 84–88).

The postnatal age when indomethacin treatment is initiated plays an important role in determining its ability to close the PDA. Even when indomethacin concentrations are maintained in the "desired" range, the drug's ability to produce ductus closure remains inversely proportional to the postnatal age at the time of treatment (45, 89–91). With advancing postnatal age, dilator prostaglandins play less of a role in maintaining ductus patency and other factors become more responsible for its persistent patency (33, 92–95). As a result, indomethacin becomes less effective in producing PDA closure as postnatal age increases (89).

Although a "prophylactic" treatment approach has several important short-term benefits, it results in over-treatment of infants that might close their ductus spontaneously and never need treatment (see above). Sixty-seven percent of infants with birthweights >1000 grams will spontaneously close their ductus by 7 days of age, and 94% will close their ductus by the time of discharge (10, 12). At this time, less than 30% of neonatologists in the United States use indomethacin "prophylactically", despite its short-term benefits (96). Early echocardiographic measurements may be able to identify infants who are likely to ultimately develop cardiopulmonary compromise from their PDA. If this proves to be true, it would enable us to give early/prophylactic treatment to a more targeted population (97–100).

Although most infants with birthweights >1000 grams tolerate the presence of a PDA, while awaiting spontaneous closure, infants with birthweights ≤1000 grams are much less likely to do so. Sixty percent of infants with birthweights ≤1000 grams will develop significant symptoms (pulmonary edema, hypotension, renal impairment, or need for persistent or escalating respiratory support) that will affect their neonatal hospitalization (10, 12).

Unfortunately, there is little information about the consequences of long-term exposure to a persistent, symptomatic, moderate-to-large left-to-right PDA shunt in infants ≤1000 grams. Only one small RCT performed almost 30 years ago, was designed to examine the effects of a *persistent* symptomatic PDA on neonatal pulmonary morbidity in infants with birth weights ≤1000 grams (101). The investigators found that surgical closure of the PDA, when signs of congestive failure developed, decreased the need for prolonged ventilatory support (compared with infants that were *not allowed* to have their PDA ligated) (101). Whether these findings are still applicable in the setting of modern neonatal treatment (e.g., antenatal glucocorticoids, surfactant replacement therapies, "gentle" ventilation, etc) has become a matter of controversy among neonatologists (102). The role of a persistent PDA in the development of necrotizing enterocolitis is even more controversial since there are no clinical trials that have addressed this issue.

These uncertainties have resulted in several areas of controversy regarding PDA management: 1) whether or not to use indomethacin prophylaxis, 2) when to treat a moderate-to-large PDA, and 3) whether or not enteral feeding should be stopped in the presence of a PDA or during treatment of a PDA (7, 78, 79, 81, 103). At this time, 95% of American neonatologists believe that a moderate-to-large PDA should be treated if it persists in infants born before 28 weeks who still require mechanical ventilation (96). The number of neonatologists that treat a persistent PDA when it occurs in infants that do not require mechanical ventilation varies significantly (Table 2). Marked differences in the willingness of neonatologists to feed infants in the presence of a PDA account for much of the variation in the rates of indomethacin use and PDA ligation. It is interesting to note that 70% of US neonatologists believe that enteral feeding needs to be stopped in the presence of a PDA. In contrast, non-US neonatologists have exactly the opposite opinion: 70% believe that enteral feeding should continue in the presence of a PDA (96).

The controversy about treatment really focuses on infants born before 28 weeks gestation, or with birthweights ≤1000 grams, since only 30% will close their PDA spontaneously and 60% will develop significant PDA-related symptoms that affect their hospitalization (10, 12). Recently a cohort-controlled study was reported that compared a "conservative" approach with a more "aggressive" approach for treatment of infants that failed to close their PDA after indomethacin treatment (13). The "aggressive" approach used early surgical ligation (within 2 days) when the infant's PDA failed to close after indomethacin treatment. The "conservative" approach continued feedings in the presence of a PDA and only ligated the PDA if cardiopulmonary compromise (persistent inotrope-dependent hypotension and/or persistent or escalating respiratory support) developed. There were no significant differences in the rates of BPD, sepsis, ROP, neurologic injury or mortality between the two groups. The risk for NEC was significantly less in the conservatively treated infants, even though they received enteral feedings in the presence of a PDA.

Despite the investigators' desire to avoid ligation in infants treated with the "conservative" approach, 70% of the infants born before 28 weeks gestation ultimately met ligation criteria (persistent hypotension and/or escalating respiratory support) and were ligated during the neonatal period. The likelihood that infants would meet ligation criteria was inversely related to their gestational age: 80% of infants born at 24–25 weeks gestation met ligation criteria, compared with 56% of those born at 26–27 weeks, and 14% of those born at 28–29 weeks. Although most of the conservatively treated immature infants ultimately were ligated, there was a significantly longer delay before the ligation was performed (compared with infants ligated during the "aggressive" approach period). The delay in ligation may be beneficial since accumulating evidence suggests that several of the morbidities associated with ligation (hypotension and need for inotropic support (37, 104), vocal cord paralysis

(35), and bronchopulmonary dysplasia (38, 105)) are significantly reduced when ligation is delayed.

Approximately 30% of the “conservatively” treated infants, that were born before 28 weeks gestation, did not develop cardiopulmonary compromise from their PDA and were not ligated prior to hospital discharge. Eighty percent of these infants ultimately closed their PDA spontaneously, despite initial indomethacin failure (13). Further investigations will be needed to determine which infants are most likely to benefit from surgical ligation and which infants might best be left untreated when pharmacologic approaches are no longer an option.

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Table 1

Rates of spontaneous ductus arteriosus closure (%)

A. Gestation	Closed on day 4	Closed on day 7	Closed at discharge
Full term	100	100	100
≥30 weeks	90	98	98
27–28 weeks	22	36	na
25–26 weeks	20	32	na
24 weeks	8	13	na
B. Birthweight			
1000–1500 grams	35	67	94
<1000 grams	21	34	na

Data from the following sources: (10, 12, 27, 106, 107). NA, no data available.

Table 2

What criteria do neonatologists use to determine whether or not to treat a moderate-to-large PDA with indomethacin/ibuprofen or surgery.

Number of neonatologists willing to use Indomethacin/Ibuprofen or surgical ligation to close a *moderate-to-large PDA* when infants have one of the following conditions (%)		
Infant's condition:	**Treatment Options**	
	Indomethacin/Ibuprofen*	**Surgical Ligation+**
Any infant < 900 grams and < 28 weeks: regardless of whether they need any respiratory support	36	9
Infants < 900 grams and < 28 weeks: who require NCPAP for respiratory support	73	37
Infants < 900 grams and < 28 weeks: who require mechanical ventilation (IMV, HFOV, etc)	96	91
Infants < 900 grams and < 28 weeks: who require mechanical ventilation (IMV, HFOV, etc) and require inotropes for hypotension	99	99

Board certified neonatologists registered with the American Academy of Pediatrics were surveyed in December 2010 (n = 755 responses).

A moderate-to-large PDA is defined as having holodiastolic retrograde flow in the descending aorta.

*Exact question: *In infants that are < 900 grams and < 28 weeks gestation, I use indomethacin or ibuprofen to treat a moderate-to-large PDA under the following circumstances*…

+Exact question: *In infants that are < 900 grams and < 28 weeks gestation, I would ligate a moderate-to-large PDA if it has not responded to indomethacin or ibuprofen (or if indomethacin or ibuprofen is contraindicated) under the following circumstances*…