Received: 7 August 2018 | Accepted: 16 October 2018

DOI: 10.1111/chd.12708

SPECIAL ISSUE ARTICLE

WILEY Congenital Heart Disease

PDA: To treat or not to treat

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Abstract

Management of patent ductus arteriosus in extremely preterm infants remains a topic of debate. Treatment to produce ductal closure was widely practiced until the past decade, despite lack of evidence that it decreases morbidities or mortality. Meta-analyses of trials using nonsteroidal anti-inflammatory drugs have shown effectiveness in accelerating ductal closure, but no reduction in neonatal morbidities, regardless of agent used, indication, timing, gestational age, or route of administration. Surgical ligation closes the ductus but is associated with adverse effects. Recent experience with conservative approaches to treatment suggest improved neonatal outcomes and a high rate of spontaneous ductal closure after discharge. Careful postdischarge follow-up is important, however, because potential adverse effects of long-standing aortopulmonary shunts may be an indication for catheter-based ductal closure. Identification of extremely preterm infants at greatest risk of potential harm from a persistently patent ductus, who may benefit most from treatment are urgently needed.

KEYWORDS
bronchopulmonary dysplasia, indomethacin, patent ductus arteriosus, preterm

1 | INTRODUCTION

Patent ductus arteriosus (PDA) is a very common finding in extremely preterm infants less than 29 weeks of gestation. Persistent patency of the ductus arteriosus in preterm infants is unequivocally associated with increased morbidity and mortality. The prevailing opinion over the years was that closure of PDA would reduce the morbidity and mortality in extremely preterm infants. Numerous studies have outlined the use of medical and surgical treatment for ductal closure. While these studies have demonstrated effective closure of the ductus, the critical question remains whether medical or surgical closure of the PDA reduces morbidity and mortality. In this review, we will discuss the role of medical interventions to close the PDA in preterm infants. We will then address the association between treatments to close the PDA and outcomes and focus on the recent studies that explore the natural history of PDA in preterm infants.

2 | RANDOMIZED TRIALS OF TREATMENT TO ACHIEVE DUCTAL CLOSURE

Current medical treatments to promote PDA closure in preterm infants include use of prostaglandin synthase inhibitors, indomethacin and ibuprofen (cyclooxygenase inhibitors), and recently acetaminophen (peroxidase inhibitor), surgical ligation, and percutaneous placement of a vascular occluder. Although indomethacin and ibuprofen have been extensively studied in the preterm population and are effective in causing ductal closure, treatment is associated with significant renal and gastrointestinal side effects. Indomethacin causes a decrease in renal function by decreasing urine output and increase in serum creatinine levels. Indomethacin also decreases mesenteric perfusion and has been associated with spontaneous intestinal perforation with combined hydrocortisone use.[1] Ibuprofen causes fewer renal side effects compared to indomethacin, but has been shown to cause an increase in total and unbound serum

bilirubin levels, the clinical significance of which is unknown.[2] There have been reports of pulmonary hypertension with ibuprofen prophylaxis for PDA in preterm infants.[3] Antenatal exposure to indomethacin for tocolysis may impact the ability of the ductus to close spontaneously after birth in preterm infants and require surgical ligation.[4] Recent studies have suggested that acetaminophen may be effective in closing the ductus in preterm infants, but the drug is not approved by FDA for that specific use. There is no clear evidence that one pharmacologic agent is superior to the other in the treatment of PDA in preterm infants.[5]

Over the past few decades, there have been varied approaches with regards to timing of treatment of PDA. Some clinicians choose a prophylactic treatment approach, as studies have shown that prophylactic indomethacin treatment reduces the risk of severe intracranial hemorrhage and pulmonary hemorrhage, in addition to promoting closure of the PDA.[6] Since PDA closes spontaneously by the end of the first week in approximately 30% of even extremely preterm infants, other clinicians have questioned the use of prophylactic indomethacin therapy. Prior studies have also examined the effects of early symptomatic treatment versus late symptomatic treatment of PDA. Meta-analysis from randomized controlled trials (RCTs) of nonsteroidal antiinflammatory drugs (NSAID) treatment trials for PDA in preterm infants show that treatment is quite effective in causing closure of the ductus in preterm infants. The pooled odds ratio for persistent ductal patency after NSAID treatment based on 56 reports of RCTs involving 5747 patients was 0.23 [95% confidence interval (CI): 0.21-0.26] (Figure1).[7-15] Even though this meta-analysis included 4 different drugs administered by at least 2 different routes for three different categories of indications, as well as surgical ligation, subgrouping based on any of these variables showed equivalent results. Furthermore, limiting meta-analysis to trials performed after 1990 and including only those for which the mean gestational age of the subjects was less than 27 weeks (7 trials, 2008 subjects) yielded similar results. In some clinical trials, >50% of control subjects received open treatment, potentially compromising study validity. However, even if those trials were excluded, meta-analysis of the remaining 29 trials (4318 subjects) yielded the same results. Most of the RCTs of NSAID treatment enrolled subjects within the first 5 days after birth and only evaluated short-term PDA exposures, since the ductus closed spontaneously in many controls and was often treated in the remainder. Until recently, only a few small trials randomized subjects after 5 days of age; all were conducted before 1985 and few outcomes other than PDA closure and mortality were reported. Therefore, it was not possible to understand the natural course of a moderate to large PDA shunt or to assess potential benefits of later treatment in extremely preterm infants. The recently completed multicenter PDA-TOLERATE Trial (To Leave it Alone or Respond And Treat Early), which so far has been reported only in abstract form, attempted to address this important gap in information and knowledge. That exploratory RCT compared routine early treatment of moderate/large PDAs at the end of the first postnatal week to a conservative approach (which required prespecified respiratory and hemodynamic criteria before "rescue" treatment could be considered) enrolled 202 eligible extremely preterm infants ≤28 weeks of gestation. The early treatment approach decreased the duration of PDA exposure and the incidence of the primary outcome of combined "need for ligation or need for postdischarge PDA follow-up," but did not decrease the rates of surgical ligation or other morbidities (bronchopulmonary dysplasia [BPD], necrotizing enterocolitis [NEC], or retinopathy of prematurity [ROP]); subjects in the early treatment group had significantly higher rates of sepsis caused by organisms other than coagulase-negative *Staphylococci* (RR = 1.52) and death (RR = 1.79). Detection of effects of treatment on adverse outcomes may have been compromised by open treatment of 48% of the subjects assigned to the control group, reflecting an ongoing lack of equipoise regarding the benefits of PDA closure.

Based on the results of several randomized trials and meta-analyses, there is no evidence for short- or long-term benefits to close

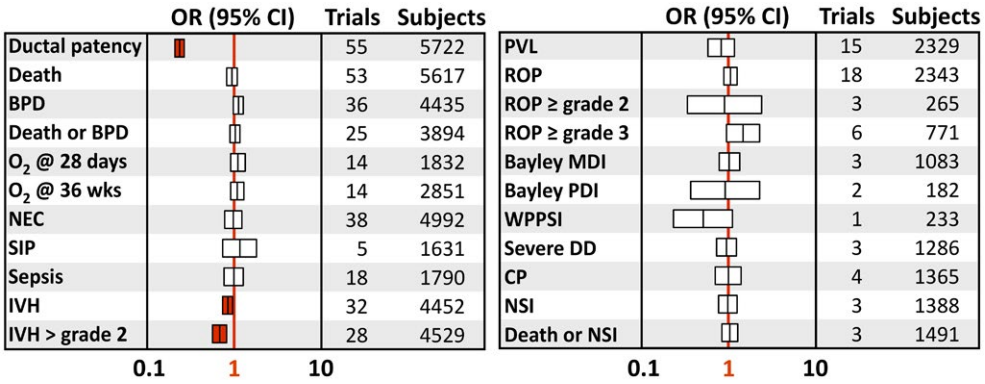

FIGURE 1 Pooled results of randomized controlled trials of NSAID therapy for persistent patent ductus arteriosus in preterm infants. Bars represent 95% confidence limits and the line at the midpoint of each bar denotes the point estimate of the pooled odds ratio. Bars for odds ratio significantly different from 1 are red (2-tailed $P < .05$). The numbers of trials (N) and subjects (n) for each outcome are shown at the right (N/n). Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; MDI, Mental Development Index; PDI, Psychomotor Development Index; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; DD, developmental delay; CP, cerebral palsy; NSI, neurosensory impairment

the PDA in preterm neonates.[16,17] The absence of demonstrable benefits from treatment cannot be discounted on the grounds that the trials are too old, included insufficient numbers of ELBW/ELGAN infants, or attributed to excessive open-label treatment of control subjects, as meta-analyses restricted to avoid those effects yield equivalent results. There is substantial evidence that PDA treatment at <1 day of age *is not* beneficial, *not* simply an absence of evidence that it *is*. Limited evidence indicates that PDA treatment at 2-3 or 7-10 days of age (vs 7-10 or 21 days of age, respectively) also is not beneficial. Later treatment to close the PDA (beyond 3 weeks of age) must be regarded as an untested and, therefore, unproven therapy. The role of selective early treatment remains to be determined. Thus, while there is evidence that medical interventions can close a ductus arteriosus, the question still remains, does intervention leading to closure of a ductus actually improve outcomes?

3 | SHORT-TERM EFFECTS OF TREATMENT ON RESPIRATORY SUPPORT

The effects of treatment to close the PDA on requirements for respiratory support in preterm infants have been studied in 35 randomized trials. A few small, early trials (3 trials, 81 subjects, 1978-1981) found that indomethacin-treated infants weaned off the ventilator and oxygen (O_2) support earlier compared to placebo-treated controls. In 22 trials, (2123 subjects) there was no difference in ventilator or O_2 use, and in 3 trials (134 subjects), there were no differences in blood gas measurements. Other trials (7 trials, 1324 subjects) showed higher O_2 requirements, longer use of ventilator support, and increase in surfactant use. Both indomethacin and ibuprofen have been associated with increase in O_2 requirements, and surgical ligation was linked to prolongation of mechanical ventilation.[7,18] For example, the RCT reported by Van Overmiere et al compared the early (day 3) vs late (day 7) indomethacin treatment for PDA in premature infants. Although the PDA closure rate was higher in the early treatment group, oxygen requirements and mean airway pressures among infants <28 weeks and the overall incidence of major morbidities (including mortality) was higher in the early treatment group. (23 vs 8%; $P = .017$).[19] The hypothesis that treatment to close the PDA is supported by many widely shared anecdotes, but not by controlled experiments. It remains possible that such benefits may accrue to carefully selected candidates for treatment, however.

4 | EXPERIENCE WITH NONINTERVENTIONAL STRATEGIES

Determining whether intervention to achieve closure of a ductus improves outcomes requires an understanding of the natural history of a PDA in the preterm neonate. Because of the widely held belief that treatment is beneficial, and therefore necessary, that natural history has been obscured by a lack of data on the trajectories of untreated preterm infants. Several recent studies, now including more than 1000 infants managed conservatively, have described the consequences of adoption of nonintervention strategies at individual centers.[20-27] With few exceptions, studies have not demonstrated an increased risk of morbidity or mortality in association with marked reduction or elimination of use of medical or surgical intervention to close the ductus. Kaempf reported increases in chronic lung disease and death after day 7 or chronic lung disease (as a combined outcome) following reduction in indomethacin use in a group of four affiliated nurseries,[28] but this observation has not been replicated. Another cohort study of conservative management in 178 patients between 23 and 26 weeks o gestational age compared patients from 2009 to 2011, when 64% of patients were treated with indomethacin and 82% underwent ligation, with a second epoch from 2012 to 2014 where medical symptomatic interventions such as fluid restriction and diuretic use were implemented.[25] None of the patients in the second epoch received any pharmacological or surgical interventions for the PDA. The authors found that nonintervention of the PDA did not result in increased morbidity or mortality; the nonintervention group had significantly shorter duration of O_2 use and a lower rate of O_2 use at 36 weeks of PMA. In a comparison of three cohorts, (1) a symptomatic treatment group (STG) when a hemodynamically significant PDA was present, (2) an early targeted treatment group (ETG) at 48 hours, and (3) a conservative treatment group, Letshwiti et al reported medical treatment of only 15% of patients and no ligations in the latter group, compared to ibuprofen treatment in 62% and 48% and ligation in 21% and 19% of the STG and ETG eras, respectively. While changes in respiratory management did occur during the study time period, they mainly occurred in a time that would not likely impact difference between the early targeted treatment and conservative management group. The authors found a significantly decreased risk for chronic lung disease in the conservative management group.[26] Semberova et al recently illustrated spontaneous ductal closure in the majority of preterm neonates prior to discharge, with incidence of PDA inversely related to gestational age, in a cohort of infants managed with a conservative approach. While the duration of ductal patency increased with decreasing gestational age, with a median age at ductal closure of 71 days in patients <26 weeks of GA, they identified no significantly increased risk of morbidities such as BPD or NEC (Figure 2).[27] These studies illustrate the concept that nonintervention does not appear to lead to increased morbidity or mortality.

Recent studies suggesting an association of increased morbidity and mortality with PDA ligation have caused concern among clinicians, likely contributing to an overall decrease in surgical ligations in extremely preterm infants.[29,30] These concerns are offset by a recent study of 308 patients with a hemodynamically significant patent ductus arteriosus (HSPDA) after medication treatment failure, which compared those who were ligated (n = 166) to those who were not (n = 142).[31] Infants in the nonligated group achieved ductal closure at a median age of 42 days, compared to 28 days in the ligated group. Even among these infants who had failed medical treatment, the PDA closed spontaneously in more than 85% before discharge. There were no differences in neurodevelopmental

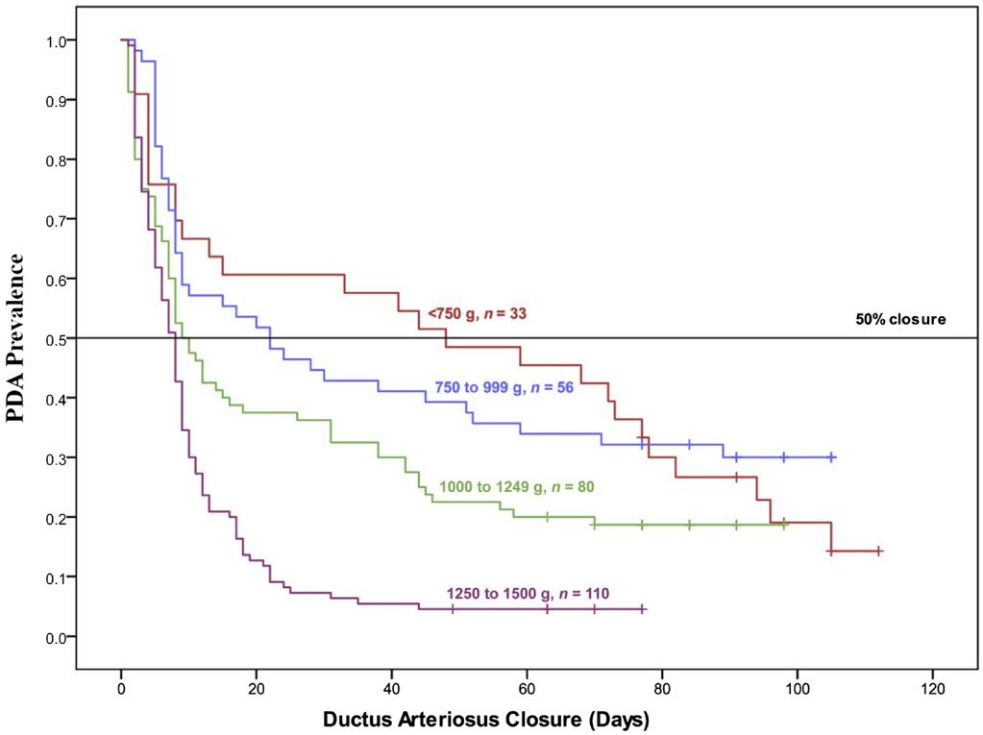

FIGURE 2 Prevalence of ductal patency stratified by GA over time in a cohort of 368 VLBW infants, 297 managed conservatively before hospital discharge. The horizontal line represents 50% closure. (Reproduced with permission from Semberova et al[27] Pediatrics, 2016:140: e20164258, Copyright ©2017, by the AAP)

outcomes at 18-24 months, chronic lung disease, or retinopathy of prematurity. However, nonligated patients had higher overall risk-adjusted mortality rates; they were more likely to die during the first 28 postnatal days, and the difference appeared to be attributable to much higher rates of death from sepsis or major brain injury. The authors speculate that the observed difference in adjusted mortality may reflect confounding by contraindication, such that infant with sepsis or major brain injury may have been deemed too unstable to be candidates for surgical ligation. Accordingly, this experience implies that no advantage is gained from late surgical ligation, despite the substantially longer period of exposure to PDA in the nonligated group.

5 | EVIDENCE FROM POPULATION SURVEYS

A retrospective study of 13 853 VLBW infants in the Pediatric Hospital Information System (PHIS) database found that use of interventions to close PDA decreased by 11% per year from 2005 to 2014.[32] This practice change was temporally associated with increases in unadjusted rates of bronchopulmonary dysplasia, periventricular leukomalacia, retinopathy of prematurity, and acute renal failure, but also with improved survival. Notably, increases in BPD and PVL in 2009 preceded declines in treatment rates in 2010 and did not correlate with further changes in treatment rates thereafter. Hospital-specific changes in PDA management did not correlate with hospital-specific changes in outcomes. These observations suggest that increases in morbidities may reflect increasing survival of extremely immature infants.

Data from another large national database of 61 520 infants born between 23 and 30 weeks gestation from 2006 to 2015 also demonstrated decrease in PDA interventions across all gestational age strata. Those trends were associated with decreasing mortality rates and no increase in morbidities (NEC, intraventricular hemorrhage, severe ROP), except for BPD, which increased only in the most immature infants (23-24 weeks of gestation). The rate of the combined outcome of BPD and mortality in those infants decreased, however. These authors noted that changes in practice, including the shift toward less PDA intervention, resulted in improvement in neonatal outcomes.[33] While the contribution of changing management of PDA to better outcomes is not certain, however, there is no clear evidence that nonintervention for a hemodynamically significant patent ductus leads to worse outcomes.

6 | CONCLUSIONS

Association does not equal causation; presence of a PDA does not mean that the PDA is the cause of necrotizing enterocolitis, BPD, or death, but may rather reflect guilt by association. There continues to be a lack of equipoise regarding ductal closure and benefits despite numerous studies, partly relating to significant treatment crossover among controls, due to inherent bias that a PDA leads to increased

morbidity and mortality. Available evidence strongly indicates that early, routine, and widespread treatment to close the PDA in preterm infants does not lead to better outcomes. However, there likely exists a cohort of patients who would benefit from intervention to close the ductus arteriosus, such as the most extremely preterm infants (≤26 weeks GA) or those with demonstrated severe hemodynamic disturbances, especially after the second or third postnatal week. Further research to delineate this cohort, with evidence-based risk stratification, could lead to studies that demonstrate benefits of intervention in a select subgroup of patients. Until this is better elucidated, it cannot be concluded that medical or surgical intervention to close the ductus arteriosus in a preterm neonate leads to improved outcomes.

DISCLOSURE STATEMENT

Drs. Sankar, Bhombal, and Benitz have no conflicts of interest or financial ties to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the data review and interpretation, manuscript preparation and revision, and approval of the final manuscript.

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How to cite this article: Sankar MN, Bhombal S, Benitz WE. PDA: To treat or not to treat. *Congenital Heart Disease*. 2019;14:46–51. https://doi.org/10.1111/chd.12708