Title
Patent Ductus Arteriosus in Premature Infants: Clinical Trials and Equipoise

Authors
Liguori, Macrina B
Ali, Sanoj KM
Bussman, Neidín
et al.

Publication Date
2023-10-01

DOI
10.1016/j.jpeds.2023.113532

Peer reviewed

Patent Ductus Arteriosus in Premature Infants: Clinical Trials and Equipoise

Macrina B. Liguori, MD[1], Sanoj K. M. Ali, MD, FRACP[2], Neidín Bussman, MB[3], Tarah Colaizy, MD, MPH[4], Tim Hundscheid, MD[5], Nilkant Phad, PhD[6], Ronald Clyman, MD[7], Willem-Pieter de Boode, MD, PhD[5], Koert de Waal, MD[8], Afif El-Khuffash, MD[3], Samir Gupta, DM, MD, FRCPC, FRCPI[2,9], and Matthew Laughon, MD, MPH[1]

Persistent patency of the ductus arteriosus is common in premature infants, yet patent ductus arteriosus (PDA) management varies widely. In observational studies, PDA is associated with prolonged assisted ventilation, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy, renal impairment, and mortality.[1-7] These associations led many clinicians to treat a PDA in all preterm infants. However randomized controlled trials (RCTs) of PDA treatment have failed to demonstrate significant reductions in clinically important outcomes. As an example, prophylactic indomethacin trials (for reducing IVH) demonstrate that indomethacin reduces incidence of symptomatic PDA, need for ligation, and IVH, but has no effect on BPD, NEC, long-term neurodevelopmental impairment (NDI) or death.[1,8] Thus, it is unclear if PDA is part of the causal pathway for development of these morbidities.

One of the explanations for the lack of effect from PDA treatment is that there is no standardized definition of a hemodynamically significant PDA (hsPDA). This may lead to a wide range of "symptomatic" PDA included in the trials, including PDAs that would likely close on their own without intervention.[9-11] If trials enriched their populations with PDAs with greater hemodynamic effects, there may be greater clinical benefit to treatment of the PDA. Current "gold standard" definitions of hemodynamic significance are based on echocardiographic measures including PDA diameter ≥1.5 mm, left atrium: aortic root ratio ≥1.4:1, and other flow and velocity parameters.[12,13] As these measurements alone do not provide detail on end organ effect, several scoring systems have been proposed to incorporate both echocardiographic and clinical criteria in the definition of hsPDA.[10,14] Other research has focused on biomarkers such as natriuretic peptides[12,13] or incorporation of novel technologies such as near infrared spectroscopy.[15] A standardized definition of hsPDA is one way to narrow the population of trial participants to discover if there is a cohort of preterm infants at high risk of morbidity without PDA treatment. This, in combination with a consensus on clinically relevant outcome measures, would allow for better cross comparison between RCTs.

Management of PDA varies widely in clinical practice. Some sites and clinicians aggressively manage PDAs, administering prophylactic indomethacin (to reduce IVH, with the added effect of reducing hsPDA), frequently screening for PDA, and administering medications to close the PDA. Other sites and clinicians are conservative and do not even look for PDA with echocardiograms and essentially ignore it. These clinicians note that while incidence of PDA is higher with lower gestational age and birth weight, spontaneous closure still occurs at some point.[9,16-20] Indeed, the neonatal field has become more conservative over time, with decreasing rates of PDA diagnosis, medical treatment, and ligation over the past decade.[11,21] This leads to challenges in conducting trials because of lack of clinician equipoise, with providers often practicing in the extremes of either aggressive treatment or no treatment whatsoever, unwilling to have their patients randomized to either arm of a trial.

Well-designed trials to evaluate the long-term impact of PDA interventions are needed. Despite years of rigorous study, the optimal method and timing of ductal closure or other management of PDA in preterm neonates remains unclear. At its most basic interpretation, equipoise refers to the point at which "there is insufficient scientific evidence to clearly state the superiority of an intervention" and is often considered to be an ethical prerequisite to conducting RCTs.[22] When interpreted on the individual level, equipoise is highly problematic for the clinician scientist who, in their role as a physician, has a duty to offer treatment recommendations and preferences to patients, but as an investigator must be equally confident of study treatment options.

BPD	Bronchopulmonary dysplasia
hsPDA	Hemodynamically significant patent ductus arteriosus
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NRN	Neonatal Research Network
NSAIDs	Nonsteroidal anti-inflammatory drugs
PDA	Patent ductus arteriosus
RCTs	Randomized controlled trials

From the [1]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Division of Neonatology, Sidra Medicine, Ar-Rayyan, Doha, Qatar; [3]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland; [4]Department of Pediatrics, University of Iowa, Iowa City, IA; [5]Division of Neonatology, Department of Perinatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands; [6]Department of Neonatology, John Hunter Children's Hospital and University of Newcastle, Newcastle, New South Wales, Australia; [7]Department of Pediatrics and Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA; [8]Department of Neonatology, John Hunter Children's Hospital, University of Newcastle, Newcastle, New South Wales, Australia; and [9]Department of Neonatology, Durham University, Durham, United Kingdom

https://doi.org/10.1016/j.jpeds.2023.113532

Clinical equipoise addresses this challenge by stating that as long as "an honest, professional disagreement exists amongst expert clinicians," it may be considered ethical to enroll patients in RCTs.[23] While clinical equipoise has become ingrained in the culture of clinical research, equipoise is not synonymous with ethical. For example, some treatments may have immediate benefits that preclude physicians from achieving equipoise, yet RCTs to evaluate long-term outcomes may still be ethical.[23]

The symposium, *PDA in Premature Infants: Clinical Trials and Equipoise (https://www.med.unc.edu/pediatrics/npm/research/laughon-research/research_symposium/)*, was convened to discuss novel approaches to the challenges that face PDA trials amongst the leaders of recent clinical trials. A planning team led by neonatologists at The University of North Carolina at Chapel Hill recruited an international faculty comprised of active trialists, and symposium participants were recruited via faculty recommendations and an open invitation to 2 professional neonatal networks. In addition, the planning team conducted a literature review to identify additional symposium participants. Approximately 100 researchers, trialists, and neonatologists joined a three-hour virtual session of presentations and discussion. This manuscript reviews the symposium presentations, discusses key findings related to clinical equipoise from the PDA trials, and provides design recommendations to inform clinical equipoise in future PDA trials.

Background

PDA Management Strategies

Current PDA treatment approaches include prophylactic treatment (for IVH),[8] screening and administering indomethacin, ibuprofen or acetaminophen,[24-27] and surgical ligation or cardiac catheterization with placement of a PDA occluder[28-31] or some combination of the above. Management approaches also include an expectant management/nonintervention/conservative approach, with clinicians not routinely obtaining echocardiograms and not administering medications or referring for ligation or cardiac catheterization.[32,33]

Symposium Summary and Discussion

The symposium panelists represented 6 PDA trials conducted across the US, United Kingdom, Ireland, Belgium, the Netherlands, Denmark, and Australia. They included 2 completed trials, 2 pilot trials assessing feasibility of a larger trial, and 2 ongoing trials. The trials included early ibuprofen treatment vs conservative management with delayed treatment of the PDA (PDA-TOLERATE),[34] early treatment vs expectant management of PDA in preterm infants (BeNeDuctus),[35] outcome after selective early treatment for closure of PDA in preterm babies (Baby-OSCAR),[36] the PDA RCT,[37] Neonatal Research Network Management of the PDA Trial (NRN PDA Trial),[38] and Randomized, Placebo-Controlled Pilot Trial Of Early Targeted Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in preterm infants with a PDA (Pilot Trial of Early Targeted NSAIDs).[39]

The panelists reviewed their trial designs, outcomes, and challenges faced in trial design and implementation (**Table**). There was consensus that management of PDA is an ideal topic for clinical equipoise given the lack of evidence to support any 1 management strategy, yet all research groups had experienced challenges from lack of equipoise at individual centers. For some, this meant extending study timelines and adding additional provider education to gather momentum in enrollment while others focused on taking a more pragmatic approach to study design.

Panelists agreed that a major problem complicating the design of all prior PDA RCTs is knowing which infants to enroll into the trial. Though PDA has been associated with increased morbidity in the preterm population, it remains unclear which preterm infants, if any, may have reduced morbidity following PDA treatment. Thus, a challenge for modern trials is selection of the ideal patient population. Prior PDA trials experienced high levels of open label treatment and contemporary RCTs have aimed to minimize this. There have also been refusals to enroll in studies due to concern that some infants were "too sick" to randomize to placebo. Yet another challenge to PDA RCT design is the lack of agreed upon outcomes to be measured. Finally, the panelists shared external challenges ranging from poor parental understanding to COVID-19 pandemic related research postponements.

Despite these challenges, each trial had unique approaches to help answer the questions remaining in PDA management. The PDA RCT and the Pilot Trial Of Early Targeted NSAIDs were pilot trials to assess feasibility of recruitment and adherence to the experimental protocol. In an effort to exclude infants who experience early spontaneous closure of PDA,[17,43] PDA-TOLERATE enrolled patients between 5 and 7 days postnatal age. Other trials focused on early targeted intervention within the first 72 hours, which has the potential to create a greater difference in time of PDA exposure in treatment and nontreatment groups. The NRN PDA Trial takes a pragmatic approach, allowing enrollment anywhere from 48 hours to 21 days of life. All 6 studies required an echocardiogram for enrollment, and the majority used criteria of PDA size >1.5 mm in diameter for patient inclusion. In addition to PDA diameter, a few of the trials used other echocardiographic criteria. The PDA RCT created a scoring system based on echocardiographic criteria that demonstrated promise in identifying and excluding low-risk PDAs.[37] Half of the studies used a placebo, whereas the other half randomized the control group to expectant management per unit standards, essentially an "open label" design. The BeNeDuctus trial proposed that an unblinded trial design without placebo use helps to limit open label treatment in the expectant management group, as the presence of PDA is truly viewed as an epiphenomenon in that study group.[44] However, the Pilot Trial of Early Targeted NSAIDs was also able to demonstrate

Table. Summary of symposium trials, their objectives, and unique challenges faced

Trial information	Objective	Key challenges to future trials and clinical equipoise
Early treatment vs delayed conservative treatment of the patent ductus arteriosus (PDA-TOLERATE) ClinicalTrials.gov identifier: NCT01958320 (2013 – 2017) Multicenter, International n = 202 Randomized Parallel assignment Single masking P: < 28 weeks GA and moderate/large PDA present at 5-7 days after birth and requiring nasal continuous positive airway pressure or invasive respiratory support at the time of enrollment I: NSAID (indomethacin, ibuprofen, or acetaminophen) used as SOC treatment. C: Following randomization, infants are not to be treated with medications used to produce PDA closure unless they develop rescue criteria at a later point in time. O: Number of infants who undergo in-hospital PDA ligation or who have an open ductus at the time of discharge requiring outpatient cardiology monitoring.	To determine whether prolonged exposure to a moderate/large PDA shunt increases neonatal morbidity.[34] Since early spontaneous PDA closure often confounded the interpretation of trial results in prior PDA treatment RCTs where infants were enrolled in the first days after birth,[40] the PDA-TOLERATE trial enrolled infants who still had a moderate/large PDA at 7 days since they were much more likely to have a prolonged persistent PDA if left untreated.	Only 48% of infants screened for the trial were eligible (Prior to 7 days, 10% had died and 42% had spontaneous ductus constriction). Although the incidence of moderate/large PDA at 7 days was 48% in the entire study population, incidence at individual study centers was quite variable (50%-92% among infants <26 weeks; 22%-79% among those 26-27 weeks). Twenty-two percent of parents refused enrollment, lack of investigator equipoise led to nonenrollment in 18% of eligible infants. Failure of the study drugs to constrict the PDA, and use of off-label rescue treatment (48% of control group) minimized the difference in duration of PDA exposure between the early and nontreatment arms, which biased the results toward the null hypothesis. Although early treatment infants were enrolled and received PDA treatment at 8 days, not all constricted their PDA. As a result, moderate/large PDA shunts persisted among infants in the early treatment arm until a median age of 16 days. Similar delays in ductus closure after early drug treatment have affected other recent PDA treatment RCTs.[37,39,41]
Expectant management vs early ibuprofen treatment of PDA in Preterm Infants (BeNeDuctus) ClinicalTrials.gov identifier NCT02884219 (2016-2020) Multisite, The Netherlands, Belgium, and Denmark n = 273 Randomized Parallel assignment No masking (Open label) P: Extreme preterm infants <28 weeks GA at 24-72 hours of life with an echocardiographic confirmed PDA with a transductal diameter of ≥1.5 mm. I: Ibuprofen used as SOC treatment according to local protocol C: Expectant management O: Composite outcome of mortality and/or NEC (Bell stage IIa or higher) and/or moderate/severe BPD at a PMA of 36 weeks	The hypothesis is that expectant management is noninferior (defined as significant absolute risk difference <10% for the primary outcome) to early pharmacological treatment with ibuprofen. While other PDA RCTs are mainly blinded and placebo-controlled, this trial was designed as an unblinded nonplacebo-controlled trial to randomize the clinician's treatment approach. The goal was to minimize the chance of "open label" treatment in the expectant management group. In the expectant management group the PDA was considered as an epiphenomenon and therefore not treated or re-evaluated apart from a blinded echocardiography on a postnatal age of 7 days if feasible. In the early pharmacological treatment group, the PDA was considered the causal factor of neonatal morbidity and mortality and therefore treated with ibuprofen, re-evaluated after a full course, and given subsequent treatment if needed.	Two hundred seventy-three infants were randomized, of which 136 were randomized to expectant management. Only 1 patient (0.7%) received "open label" treatment and no surgical ligation was performed in the expectant management group prior to discharge home in comparison to a median percentage of around 50% in previous RCTs. The findings show that it is feasible to randomize the treatment intention of the medical team rather than to perform a placebo-controlled trial, which allows for a true nonintervention cohort.
Baby-OSCAR Trial: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies ISRCTN84264977 (2015-2019) Thirty-two centers in the United Kingdom n = 653 Randomized Parallel assignment Masked P: Extremely preterm babies (23 0/7-28 6/7 gestation) with PDA identified by echocardiography, using diagnostic criteria of diameter >1.5 mm, with pulsatile or growing PulseWave Doppler flow pattern. I: IV ibuprofen within 72 hours of birth. C: Matched placebo (0.9% normal saline) O: Death or moderate/severe BPD at 36 weeks PMA. Secondary outcomes included components of primary outcome, complications of prematurity, safety of intervention and long-term outcomes of survival without severe neurodevelopmental disability and respiratory morbidity at 2 years corrected age with health economic evaluation.[36]	The hypothesis is that early targeted treatment of hsPDA with ibuprofen within 72 hours of birth improves short- and long-term health and economic outcomes in ELGANs. This was a pragmatic trial that focused on addressing deficiencies identified in previous RCT's such as small size of trials, limited inclusion of ELGANs who are at highest risk of complications from PDA, and lack of long-term follow-up. Open label treatment of study infants was limited by using strict clinical and echocardiographic criteria. The study also performed long-term neurodevelopmental and respiratory follow-up including a health economic evaluation.	Recruitment ceased prematurely after enrolling 90% of the planned 730 infants due to intrinsic and extrinsic reasons. These included problems with availability of IV Ibuprofen, changing clinical practice with increased use of noninvasive respiratory support, new therapies and competing trials in similar GA group, and the pandemic mandating a temporary halt in non-COVID-19 related research in the United Kingdom .

(*continued*)

Table. Continued

Trial information	Objective	Key challenges to future trials and clinical equipoise
THE PDA RCT ISRCTN13281214 (2016-2020) Single center, Ireland n = 60 Randomized Parallel assignment Masked P: Infants age <29 weeks GA with PDA identified on echocardiography between 36 and 48 hours of life. I: IV ibuprofen administered as a 3-dose course, which may be repeated once. C: Matched placebo (0.9% saline), which may also be repeated once. O: Chronic lung disease defined as the need for oxygen at 36 weeks PMA and/or death before discharge. Secondary outcome measures of neonatal morbidity (see trial listing).	The hypothesis is that, in preterm infants born less than 29 week's gestation, using a PDAsc to recruit infants into a PDA RCT, where the primary outcome is the rate of BPD/death, is feasible and will result in a high recruitment rate.[37]	The trial was highly feasible, as reflected in the high recruitment rate (88%) and relatively low protocol deviation and open label treatment in the first week of the trial (13%). Despite higher PDA closure rates in the intervention vs control arms (57% vs 17%), there was no difference in the primary outcome (BPD/Death), its individual components, or secondary outcomes. On subgroup analysis, infants in the intervention arm with PDA closure following treatment had a lower rate of BPD/Death (29%) vs those in the intervention arm who failed to achieve PDA closure (85%) and those in the placebo group (60%, all $P < .05$).[42] The low rate of the primary composite outcome in those infants with a PDAsc < 5 confirms the score can identify those infants who do not require treatment. This study, and the post hoc analysis, highlight that a causal link between PDA and neonatal morbidities cannot be assessed solely by treatment assignment; consideration must be given to whether the desired effect of treatment (shunt elimination) was achieved.
Management of the PDA Trial ClinicalTrials.gov identifier: NCT03456336 (2018-Ongoing) 16 centers in The United States n = 1116 (estimated) Randomized Parallel assignment No Masking (Open label) P: Any infant 48 hours to 21 days of life, born at 22 0/7 to 28 6/7 gestations, with symptomatic PDA as defined by modified McNamara criteria with clinical and echocardiographic criteria. I: Indomethacin or ibuprofen per local site usual care dosing and schedule. The choice of NSAID will be left to the center; however, infants may only receive one or the other. C: Infants assigned to the expectant management group will receive indomethacin or ibuprofen if cardiopulmonary compromise occurs. O: Death or BPD at 36 weeks PMA. Secondary outcome measures of morbidity (see trial listing)	The hypothesis is that in premature infants with a symptomatic PDA, expectant management reduces death or BPD by 10% (from 50% to 40%) when compared to active treatment. The NRN PDA trial is unique in its highly pragmatic approach. The study does not mandate screening echocardiograms (though echocardiograms are needed to meet study eligibility), and treatment drug choices are not mandated. Therefore, the likelihood of an infant having a screening echocardiogram for symptomatic PDA is dependent on unit standard or individual neonatologist preference. Similarly, treatment in the active management group choice (ibuprofen or indomethacin) is by clinician preference. Expectant management plans are entirely the clinician's decision. Actively managed infants may receive ligation or transcatheter closure of the PDA at the team's discretion if pharmacologic therapy is unsuccessful. Expectantly managed infants may have their PDA closed if cardiopulmonary compromise develops.	Recruitment began in 2018 and estimated enrollment will be 1116 infants. Prior review of the NRN database anticipated recruitment of 240 infants per year; current annual enrollment is ~126 infants. Apart from delays due to the pandemic, the slow enrollment has mostly been due to lack of equipoise. At the time of study development, most providers were concerned about the risks of "withholding" treatment for infants who needed it, whereas the current major concern is treating infants who do not need therapy.
Randomized placebo-controlled pilot trial of early targeted NSAIDs in preterm infants with a patent ductus arteriosus ACTRN12616000195459 (2018-2020) Two centers in Australia n = 72 Randomized Parallel assignment Masked P: Preterm infants <29 weeks GA with a PDA diameter >1.5 mm and <72 hours after birth. I: NSAIDs (IV ibuprofen or indomethacin, dependent on site), which may be repeated once. C: Matched placebo. Infants in either group may receive 1 course of paracetamol or ligation if meeting agreed upon clinical criteria. O: Recruitment rate and incidence of open-label treatment. Secondary clinical outcomes included chronic lung disease or death.	The main aim was to test feasibility of the study protocol regarding enrollment rate and avoidance of open label therapy. Infants in both groups were offered supportive care rather than "no" care, which was a deliberate strategy to reassure parents and clinicians that PDA directed therapy, was still available.	Fifty-four percent of approached parents consented to the study. The main barrier to obtaining consent and enrollment was difficulty creating a true understanding of the aim of the trial to parents. Most participating clinicians found PDA management easier when the decision about starting NSAIDs was left to a study protocol and a randomization process. Open label NSAID treatment rates were low, suggesting equipoise was present during the study period and limitation of open label treatment is feasible. PDA closure at day 10 was higher in the NSAID vs control group (74% vs 30%) but no differences in secondary clinical outcomes were found. Even though the pilot had few protocol violations and reasonable recruitment rates, there are questions about feasibility of a large trial with an estimated sample size of over 600 infants with a PDA.

PDA, patent ductus arteriosus; *PDAsc*, patent ductus arteriosus score; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *GA*, gestational age; *SOC*, standard of care; *PMA*, postmenstrual age; *NEC*, necrotizing enterocolitis; *RCT*, randomized controlled trials; *BPD*, Bronchopulmonary dysplasia; *ELGANs*, extremely low gestational age newborns.

low rates of open label treatment within a placebo group.[27] With regard to choice of therapy, all the trials used NSAIDs (indomethacin or ibuprofen) in the treatment group, with only the PDA-TOLERATE and the NRN PDA trial allowing the use of paracetamol/acetaminophen. Most of the studies mandated intravenous dosing of the experimental drug, except for the NRN PDA trial, which did not mandate treatment dose or schedule, and the BeNeDuctus Trial, which allowed enteral ibuprofen use and dosage per local protocol.

The primary endpoint of PDA-TOLERATE, The NRN PDA Trial, and Baby-OSCAR is death or BPD at 36 weeks postmenstrual age. The BeNeDuctus trial had a broader composite primary outcome of NEC, moderate to severe BPD, or death at 36 weeks postmenstrual age. The Pilot Trial of Early Targeted NSAIDs and The PDA RCT were pilot trials with primary outcomes of patient recruitment, rates of PDA closure, and open label treatment. Secondary outcomes for all trials included other measures of neonatal morbidities. Three studies (The Baby-OSCAR trial, BeNeDuctus Trial, and the NRN PDA Trial) were designed to investigate neurodevelopmental impairment at 2 years of age, and the Baby-OSCAR and BeNeDuctus include a cost-effectiveness analysis of health services used up to 2 years of age.[36,38,44]

The increasing availability of echocardiography has differentiated modern PDA trials from the past, however assessing the true hemodynamic significance of the PDA remains elusive. Scoring systems such as the staging criteria from McNamara et al have been developed as a more specific measure of hemodynamic impact from a PDA.[14] Another scoring system, the patent ductus arteriosus score (PDAsc), developed by El-Khuffash et al incorporates GA and 4 echocardiographic variables to create a weighted risk score and is promising in its ability to stratify infant risk of BPD/Death.[42] However, even when hemodynamic significance can be well defined, major questions remain about the effect of other patient characteristics (eg gestational age, birthweight, and level of respiratory support) and/or duration of exposure to a hsPDA on outcomes. Numerous observational studies support a link between prolonged PDA exposure and increased morbidity and mortality.[45-49] Yet, RCTs have failed to demonstrate any benefit of pharmacologic therapies for PDA in reducing the risk of BPD/Death.[24,34,37] The incidence of treatment failure in the interventional arm, and spontaneous closure and open-label treatment in the control arm are often cited as cause for concern in the interpretation of PDA trial results, as they reduce the differences in exposure to hemodynamic effects of the PDA. These questions have led to post-hoc analyses. In PDA-TOLERATE and Early Ibuprofen Treatment of PDA in preterm infants (TRIO-CAPI), post hoc analyses found associations with prolonged PDA exposure and BPD/death only in those infants with prolonged (≥10 days) tracheal intubation.[50,51] The PDA RCT found an association between higher rates of BPD/death and ineffective shunt closure (PDA patency beyond 8 days of age).[52] However, more is needed to enhance prospective identification of infants at highest risk for BPD/death and address the issue of poor treatment efficacy. Future trials need to evaluate optimal use of current therapies to maximize probability of successful early shunt elimination, consider more efficacious therapies such as catheter-based PDA occluders, minimize open label treatment within control subjects, monitor duration and magnitude of shunt exposure, and consider adverse effects of medical therapy.[53]

Recruitment and enrollment for PDA trials is challenged by lack of clinician equipoise. As an example, in the meeting of the Australian and New Zealand Neonatal Network it was revealed that the PDA is no longer in the top 3 of proposed hemodynamic research agenda items. In an analysis of PDA-TOLERATE, centers with a primary approach of watchful waiting prior to the study were more likely to enroll patients and avoid "rescue" treatment. This finding fosters some hope for the future of PDA trials, as the overall trends in PDA management have swung toward the conservative approach.[11,21] Indeed, in the BeNeDuctus trial and Pilot Trial of Early Targeted NSAIDs, rates of open label treatment of PDA were only 0.7% and 2.7%, respectively,[27,35] a great improvement from prior trials such as PDA-TOLERATE in which 48% of expectantly managed infants received open label rescue therapy.[34] However, a 2020 international survey of neonatologists demonstrated a lack of national guidelines, heterogenous methods of screening and management of PDA, and widely varied responses to statements regarding clinical equipoise, even amongst those neonatologists who had been involved in prior PDA research.[54]

Equipoise is essential for conducting clinical trials. A lack of equipoise may result in the differential recruitment of patients based on the opinion of the physician, rather than trial design. While offering trial participation may result in moral distress if an individual physician does not have equipoise, failing to offer enrollment to eligible patients is a disservice to both the families that desire the opportunity to be in clinical trials and the medical community at large by compromising the study population and skewing results of the trial itself. Since parental consent is a requisite for trial entry, infants excluded from the trial may have a different demographic composition than the infants who are eventually enrolled. This was seen in the PDA-TOLERATE trial where a greater number of non-White infants were treated outside the study due to lack of physician equipoise.[53] Infants treated outside the trial not only represented a different demographic as those enrolled, but also demonstrated significantly different outcomes compared with those enrolled in the trial,[53] raising the question of how trial outcomes would have varied if all eligible infants had been enrolled. Prior perinatal trials, such as the WHO ACTION trials of antenatal corticosteroid use in low-resource settings, have succeeded in emphasizing clinical equipoise to encourage investigation of existing knowledge gaps.[55,56] Similarly, the field of pediatric critical care has appealed to physicians for equipoise in topics where current therapies are driven by adult

data.[57-60] The procedural pain in premature infants trial succeeded in attaining clinical equipoise between experimental and control groups by emphasizing the potential for harm associated with morphine use, despite its known analgesic properties, and ultimately demonstrated that adjunctive pain management strategies were safer for nonventilated infants.[61]

PDA trials are also subject to enrollment challenges from lack of parental understanding and consent, as was seen in the pilot trial by de Waal et al.[39] It can be much easier to explain a trial with a new promising treatment, compared with re-examining a treatment that has been common practice for over 5 decades. In PDA-TOLERATE, centers with unit protocols for both treatment and nontreatment had the highest rates of parental acceptance. Parents want to know what will happen to their infant if they choose not to enroll in the study. In contrast with units where the choice of treating or not treating a PDA was left to the preference of the on-call neonatologist, having a predefined treatment option for infants who did not enroll in the study (eg, "in our unit all babies who have PDAs at 7 days are treated with indomethacin" or "in our unit we just monitor infants with a PDA and only treat the PDA if signs of heart failure occur," etc.), gave parents firm options to choose between. It helped the person trying to obtain consent draw clear distinctions between what would happen to infants who entered the study and those who did not and helped parents think through why they might or might not want to join the study. In the Baby-OSCAR trial, parental education was provided through multiple outlets including banners, pamphlets, and podcasts.[36]

Conclusions

PDA management varies widely in daily clinical practice. Randomized trials of management of the PDA are essential to inform practice. Lack of clinician equipoise is a major barrier to enrollment, and centers and clinicians may need to be reminded or educated about equipoise prior to their participation in studies. Though the symposium panelists each had their own approaches to PDA trial design, all agreed that (if located at a participating center and caring for an eligible patient) they would be willing and eager to enroll that patient in any of the discussed trials. Any RCT requires substantial work regarding study design from the study team and, at a minimum, local investigational review board approval. Once a trial has been agreed upon at a site, clinical practitioners at the extremes of PDA management should note that the views of their opposing view colleagues are worthy of consideration and suspend their individual approach for a particular patient in order to allow the randomization process to decide. With this outlook for the future of PDA trials, there is hope that RCTs will be well designed, well received, and able to advance our understanding of the role of PDA and its management in neonatal morbidity. ■

Data Statement

Data sharing statement available at www.jpeds.com.

Declaration of Competing Interest

No specific funding support was utilized to host this symposium.

The authors have no conflicts of interest to disclose.

Special thanks to Dr. Aisling Smith for her presentation of The PDA RCT in the symposium; Joseph Hatch with UNC Children's Research Institute and UNC School of Medicine IT in their assistance with setup and technical support of the symposium; Laurie Stockton, research manager, for organizing the symposium, arranging Continuing Medical Education credit, and support throughout manuscript production; and Grace Fulton for manuscript formatting.

Submitted for publication Oct 28, 2022; last revision received May 24, 2023; accepted May 30, 2023.

Reprint requests: Macrina B. Liguori, MD, Pediatrics, UNC Hospitals, CB 7596, Chapel Hill, NC 27599. E-mail: macrina.liguori@unchealth.unc.edu

References

1. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010;30:241-52.
2. Siassi B, Emmanouilides GC, Cleveland RJ, Hirose F. Patent ductus arteriosus complicating prolonged assisted ventilation in respiratory distress syndrome. J Pediatr 1969;74:11-9.
3. Kitterman JA, Edmunds LH, Gregory GA, Heymann MA, Tooley WH, Rudolph AM. Patent ducts arteriosus in premature infants. Incidence, relation to pulmonary disease and management. N Engl J Med 1972;287:473-7.
4. Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr 2000;137:68-72.
5. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. Pediatrics 1999;104:1345-50.
6. Ryder RW, Shelton JD, Guinan ME. Necrotizing enterocolitis: a prospective multicenter investigation. Am J Epidemiol 1980;112:113-23.
7. Drougia A, Giapros V, Krallis N, Theocharis P, Nikaki A, Tzoufi M, et al. Incidence and risk factors for cerebral palsy in infants with perinatal problems: a 15-year review. Early Hum Dev 2007;83:541-7.
8. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966-72.
9. Reese J, Laughon MM. The patent ductus arteriosus problem: infants who still need treatment. J Pediatr 2015;167:954-6.
10. El-Khuffash A, Weisz DE, McNamara PJ. Reflections of the changes in patent ductus arteriosus management during the last 10 years. Arch Dis Child Fetal Neonatal Ed 2016;101:F474-8.
11. Runte KE, Flyer JN, Edwards EM, Soll RF, Horbar JD, Yeager SB. Variation of patent ductus arteriosus treatment in very low birth weight infants. Pediatrics 2021;148:e2021052874.
12. Mitra S, Rønnestad A, Holmstrøm H. Management of patent ductus arteriosus in preterm infants–where do we stand? Congenit Heart Dis 2013;8:500-12.
13. Perez KM, Laughon MM. What is new for patent ductus arteriosus management in premature infants in 2015? Curr Opin Pediatr 2015;27:158-64.
14. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal Ed 2007;92:F424-7.

15. Patra A, Thakkar PS, Makhoul M, Bada HS. Objective assessment of physiologic alterations associated with hemodynamically significant patent ductus arteriosus in extremely premature neonates. Front Pediatr 2021;9:648584.
16. Sung SI, Chang YS, Kim J, Choi JH, Ahn SY, Park WS. Natural evolution of ductus arteriosus with noninterventional conservative management in extremely preterm infants born at 23-28 weeks of gestation. PLoS One 2019;14:e0212256.
17. Nemerofsky SL, Parravicini E, Bateman D, Kleinman C, Polin RA, Lorenz JM. The ductus arteriosus rarely requires treatment in infants > 1000 grams. Am J Perinatol 2008;25:661-6.
18. Herrman K, Bose C, Lewis K, Laughon M. Spontaneous closure of the patent ductus arteriosus in very low birth weight infants following discharge from the neonatal unit. Arch Dis Child Fetal Neonatal Ed 2009;94:F48-50.
19. Yum SK, Moon C-J, Youn Y-A, Lee JY, Sung IK. Echocardiographic assessment of patent ductus arteriosus in very low birthweight infants over time: prospective observational study. J Matern Fetal Neonatal Med 2018;31:164-72.
20. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000;106:659-71.
21. Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN. Changes in the diagnosis and management of patent ductus arteriosus from 2006 to 2015 in United States neonatal intensive care units. J Pediatr 2017;189:105-12.
22. Garcia J, Elbourne D, Snowdon C. Equipoise: a case study of the views of clinicians involved in two neonatal trials. Clin Trials 2004;1:170-8.
23. Joffe S, Miller FG. Equipoise: asking the right questions for clinical trial design. Nat Rev Clin Oncol 2012;9:230-5.
24. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 2014;99:F99-104.
25. Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. J Pediatr 1983;102:895-906.
26. Van Overmeire B, Van de Broek H, Van Laer P, Weyler J, Vanhaesebrouck P. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. J Pediatr 2001;138:205-11.
27. de Waal K, Phad N, Stubbs M, Chen Y, Kluckow M. A double blind, randomised controlled pilot trial of early pharmacological treatment versus supportive management in preterm infants with a patent ductus arteriosus. J Paediatr Child Health 2019;55(S1):119.
28. Ting JY, Resende M, More K, Nicholls D, Weisz DE, El-Khuffash A, et al. Predictors of respiratory instability in neonates undergoing patient ductus arteriosus ligation after the introduction of targeted milrinone treatment. J Thorac Cardiovasc Surg 2016;152:498-504.
29. Othman HF, Linfield DT, Mohamed MA, Aly H. Ligation of patent ductus arteriosus in very low birth weight premature infants. Pediatr Neonatol 2020;61:399-405.
30. Weisz DE, Mirea L, Rosenberg E, Jang M, Ly L, Church PT, et al. Association of patent ductus arteriosus ligation with death or neurodevelopmental impairment among extremely preterm infants. JAMA Pediatr 2017;171:443-9.
31. Rodríguez Ogando A, Planelles Asensio I, de la Blanca ARS, Ballesteros Tejerizo F, Sánchez Luna M, Gil Jaurena JM, et al. Surgical ligation versus percutaneous closure of patent ductus arteriosus in very low-weight preterm infants: which are the real benefits of the percutaneous approach? Pediatr Cardiol 2018;39:398-410.
32. Smith A, McNamara PJ, El-Khuffash AF. Non-pharmacological management of a hemodynamically significant patent ductus arteriosus. Semin Fetal Neonatal Med 2018;23:245-9.
33. de Waal K, Prasad R, Kluckow M. Patent ductus arteriosus management and the drift towards therapeutic nihilism - what is the evidence? Semin Fetal Neonatal Med 2021;26:101219.
34. Clyman RI, Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson S, et al. PDA-TOLERATE trial: an exploratory randomized controlled trial of treatment of moderate-to-large patent ductus arteriosus at 1 Week of age. J Pediatr 2019;205:41-8.e6.
35. Hundscheid T, Onland W, Kooi EMW, Vijlbrief DC, de Vries WB, Dijkman KP, et al. Expectant management or early ibuprofen for patent ductus arteriosus. N Engl J Med 2023;388:980-90. https://doi.org/10.1056/NEJMoa2207418
36. Gupta S, Juszczak E, Hardy P, Subhedar N, Wyllie J, Kelsall W, et al. Study protocol: baby-OSCAR trial: outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies, a multicentre, masked, randomised placebo-controlled parallel group trial. BMC Pediatr 2021;21:100.
37. El-Khuffash A, Bussmann N, Breatnach CR, Smith A, Tully E, Griffin J, et al. A pilot randomized controlled trial of early targeted patent ductus arteriosus treatment using a risk based severity score (the PDA RCT). J Pediatr 2021;229:127-33.
38. Management of the PDA trial - full text view - ClinicalTrials.gov [internet]. Accessed February 21, 2023. https://clinicaltrials.gov/ct2/show/NCT03456336
39. de Waal K, Phad N, Stubbs M, Chen Y, Kluckow M. A randomized placebo-controlled pilot trial of early targeted nonsteroidal anti-inflammatory drugs in preterm infants with a patent ductus arteriosus. J Pediatr 2021;228:82-6.e2.
40. Sosenko IRS, Fajardo MF, Claure N, Bancalari E. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. J Pediatr 2012;160:929-35.e1.
41. Sung SI, Lee MH, Ahn SY, Chang YS, Park WS. Effect of nonintervention vs oral ibuprofen in patent ductus arteriosus in preterm infants: a randomized clinical trial. JAMA Pediatr 2020;174:755-63.
42. El-Khuffash A, James AT, Corcoran JD, Dicker P, Franklin O, Elsayed YN, et al. A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. J Pediatr 2015;167:1354-61.e2.
43. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics 2006;117:1113-21.
44. Hundscheid T, Donders R, Onland W, Kooi EMW, Vijlbrief DC, de Vries WB, et al. Multi-centre, randomised non-inferiority trial of early treatment versus expectant management of patent ductus arteriosus in preterm infants (the BeNeDuctus trial): statistical analysis plan. Trials 2021;22:627.
45. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr 2015;166:1488-92.
46. Sellmer A, Bjerre JV, Schmidt MR, McNamara PJ, Hjortdal VE, Høst B, et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. Arch Dis Child Fetal Neonatal Ed 2013;98:F505-10.
47. Clyman RI, Hills NK. The effect of prolonged tracheal intubation on the association between patent ductus arteriosus and bronchopulmonary dysplasia (grades 2 and 3). J Perinatol 2020;40:1358-65.
48. Mirza H, Garcia J, McKinley G, Hubbard L, Sensing W, Schneider J, et al. Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants. J Perinatol 2019;39:1648-55.
49. Clyman RI, Hills NK, Liebowitz M, Johng S. Relationship between duration of infant exposure to a moderate-to-large patent ductus arteriosus shunt and the risk of developing bronchopulmonary dysplasia or death before 36 weeks. Am J Perinatol 2020;37:216-23.
50. Clyman RI, Kaempf J, Liebowitz M, Erdeve O, Bulbul A, Håkansson S, et al. Prolonged tracheal intubation and the association between patent ductus arteriosus and bronchopulmonary dysplasia: a secondary analysis of the PDA-TOLERATE trial. J Pediatr 2021;229:283-8.e2.
51. Clyman RI, Hills NK, Cambonie G, Debillon T, Ligi I, Gascoin G, et al. Patent ductus arteriosus, tracheal ventilation, and the risk of bronchopulmonary dysplasia. Pediatr Res 2022;91:652-8.
52. Bussmann N, Smith A, Breatnach CR, McCallion N, Cleary B, Franklin O, et al. Patent ductus arteriosus shunt elimination results in a reduction in adverse outcomes: a post hoc analysis of the PDA RCT cohort. J Perinatol 2021;41:1134-41.

53. Liebowitz M, Katheria A, Sauberan J, Singh J, Nelson K, Hassinger DC, et al. Lack of equipoise in the PDA-TOLERATE trial: a comparison of eligible infants enrolled in the trial and those treated outside the trial. J Pediatr 2019;213:222-6.e2.
54. Hundscheid T, El-Khuffash A, McNamara PJ, de Boode WP. Survey highlighting the lack of consensus on diagnosis and treatment of patent ductus arteriosus in prematurity. Eur J Pediatr 2022;181:2459-68.
55. Vogel JP, Oladapo OT, Pileggi-Castro C, Adejuyigbe EA, Althabe F, Ariff S, et al. Antenatal corticosteroids for women at risk of imminent preterm birth in low-resource countries: the case for equipoise and the need for efficacy trials. BMJ Glob Health 2017;2:e000398.
56. WHO ACTION Trials Collaborators. The World Health Organization ACTION-I (Antenatal CorTicosteroids for Improving Outcomes in preterm Newborns) Trial: a multi-country, multi-centre, two-arm, parallel, double-blind, placebo-controlled, individually randomized trial of antenatal corticosteroids for women at risk of imminent birth in the early preterm period in hospitals in low-resource countries. Trials 2019;20:507.
57. Baltagi SA, Jaquiss RDB. Commentary: comparison of management strategies for the neonate with symptomatic tetralogy of Fallot and weight <2.5 kg-jogging towards equipoise? J Thorac Cardiovasc Surg 2022;163:208-9.
58. Hill KD, Kannankeril PJ. Perioperative corticosteroids in children undergoing congenital heart surgery: five decades of clinical equipoise. World J Pediatr Congenit Heart Surg 2018;9:294-6.
59. Mills KI, Albert BD, Bechard LJ, Duggan CP, Kaza A, Rakoff-Nahoum S, et al. Stress ulcer prophylaxis versus placebo-a blinded randomized control trial to evaluate the safety of two strategies in critically ill infants with congenital heart disease (SUPPRESS-CHD). Trials 2020;21:590.
60. Oishi P, Fineman JR. Equipoise and acumen in pediatric acute respiratory distress syndrome research. Am J Respir Crit Care Med 2020;201:1326-7.
61. Soffer OD, Cornelissen L, Cummings C, Berde C. Morphine compared to placebo for procedural pain in preterm infants: safety, efficacy and equipoise. J Perinatol 2019;39:1428-31.