A Pilot Randomized Controlled Trial of Early Targeted Patent Ductus Arteriosus Treatment Using a Risk Based Severity Score (The PDA RCT)

Afif EL-Khuffash, MD[1,2], Neidín Bussmann, MB[1], Colm R. Breatnach, PhD[1], Aisling Smith, MB[1], Elizabeth Tully, PhD[3], Joanna Griffin, PhD[4], Naomi McCallion, MD[1,2], John David Corcoran, MD[1,2], Elena Fernandez, MSc[5], Claudia Looi, BSc[5], Brian Cleary, PhD[5,6], Orla Franklin, MRCPCH[7], and Patrick J. McNamara, MD[8,9,10]

Objectives To evaluate the feasibility of recruiting preterm infants to a randomized controlled trial of patent ductus arteriosus (PDA) treatment based on a PDA severity score (PDAsc) and to characterize challenges in obtaining consent, compliance with the protocol, and PDA closure rates.

Study design This single-center, randomized control pilot study of 60 infants <29 weeks of gestation with a high PDAsc (≥5.0) at 36-48 hours of age receiving either ibuprofen or placebo intravenously. The study protocol did not allow for additional PDA therapy within the first 2 weeks. We reported the rate of consent, open label treatment, and PDA closure rates. The primary outcome was chronic lung disease or death.

Results We approached 83 families for enrollment with 73 (88%) providing consent; 13 infants had a PDAsc of <5; of the remaining infants, 30 were assigned ibuprofen and 30 received placebo. Eight infants received open label treatment in the first 2 weeks (12%). The overall PDA closure rate after treatment was 57% in the intervention group and 17% in the control group ($P < .01$). There was no difference in the primary clinical outcome (OR, 0.8; 95% CI, 0.3-2.1).

Conclusions Using a PDAsc for infant recruitment to a PDA treatment randomized controlled trial is feasible. There is a high rate of consent and relatively low rate of open-label PDA treatment. The overall PDA closure rate in the intervention arm was low placing the emphasis on devising more effective PDA closure strategies in future randomized controlled trials. *(J Pediatr 2021;229:127-34)*.

Trial Registration ISRCTN (13281214) and European Union Drug Regulating Authorities Clinical Trials Database (2015-004526-33).

The management of a patent ductus arteriosus (PDA) in premature infants, particularly those <29 weeks of gestation, remains a controversial topic in neonatal medicine. Randomized controlled trials, spanning several decades, have investigated PDA treatment but failed to demonstrate an improvement in either mortality or short-term morbidities, including chronic lung disease, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH), or long-term neurodisability.[1] Regardless, PDA remains a plausible contributor to these morbidities owing to its physiologic effects of pulmonary overcirculation and systemic hypoperfusion when shunt volume is high.

Failure of randomized controlled trials to demonstrate a beneficial effect resulting from PDA treatment stem from several important factors: (1) contamination of the control arm with open label PDA treatment, (2) lack of consistent demonstration that receipt of the randomized intervention to close the PDA modifies the hemodynamic significance of a PDA, and its impact on pulmonary overcirculation or systemic hypoperfusion, and (3) heterogeneity and lack of clarity in characterizing the hemodynamic significance and accurately identifying the "at-risk" population most likely to benefit from closure.[2] Many studies have used arbitrary cut-offs of clinical and echocardiography parameters, unrelated to important short- and long-term outcomes, with an over-reliance on PDA diameter to determine significance.[3]

A multicenter prospective observational study by our group devised a PDA severity score (PDAsc) between 36 and 48 hours of life incorporating markers of pulmonary overcirculation and left ventricular diastolic function to predict chronic lung disease or death before discharge.[4] We therefore designed a trial to randomize infants with a high PDAsc (≥5.0) to either early targeted treatment

IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
PDAsc	Patent ductus arteriosus severity score

From the [1]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland; [2]Department of Pediatrics, and [3]Department of Obstetrics & Gynecology, The Royal College of Surgeons in Ireland, Dublin, Ireland; [4]Department of Research & Academic Affairs, and [5]Department of Pharmacy, The Rotunda Hospital, Dublin, Ireland; [6]School of Pharmacy, Royal College of Surgeons in Ireland, Dublin, Ireland; [7]Department of Pediatric Cardiology, Our Lady's Children's Hospital Crumlin, Ireland; [8]Division of Neonatology, Stead Family Children's Hospital, Iowa City, IA; and Departments of [9]Pediatrics and [10]Cardiology, University of Iowa, Iowa City, IA

Funded by a Research Grant from the Temple Street Hospital Foundation (Grant Number: RPAC 16-03 to A.EL-K.). The National Children's Research Centre funded PhD fees associated with this project. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.10.024

with ibuprofen or placebo. In this pilot study, it was our aim to ascertain issues with recruiting infants and obtaining consent, compliance with the protocol, the rate of PDA closure, the rate (if any) of loss to follow-up, and the general feasibility and compliance of administering the intervention. We hypothesized that in preterm infants born <29 weeks of gestation, using a PDAsc to recruit infants into a PDA randomized controlled trial, where the primary outcome is the rate of chronic lung disease or death, is feasible and will result in a high recruitment rate.

Methods

This single-center, randomized, double-blind, 2 arm pilot study with a balanced (1:1) allocation was carried out in the level III neonatal intensive care unit of The Rotunda Hospital, Dublin, Ireland.

Participants

All infants born at <29 weeks of gestation with a PDA identified on comprehensive echocardiography between 36 and 48 hours of life were considered eligible. The PDA risk score was calculated based on the following formula: (Gestation in weeks × −1.304) + (PDA diameter in mm × 0.781) + (Left ventricular output in mL/kg/min × 0.008) + (maximum PDA velocity in m/s × −1.065) + (left ventricular a' wave *in cm/s* × −0.470) + 41, where 41 is the constant of the formula.[4]

Infants with a risk score of ≥5.0 were deemed to be at high risk for developing chronic lung disease or death and were randomized to either arm. Infants with a low-risk score (<5.0) were not randomized but followed to discharge in a similar fashion to randomized infants. Potentially eligible infants were excluded from the study if any of the following criteria were identified at screening: lethal congenital abnormality or obvious syndrome; suspected pulmonary hypoplasia; pulmonary hypertension defined as bidirectional shunting across the PDA; known or suspected NEC based on the Bell criteria; thrombocytopenia; a platelet count of <100 000/μL; impaired renal function with a creatinine of >100 μmol/L; oliguria of <1 mL/kg/h; culture-positive sepsis; congenital heart disease other than a PDA or a patent foramen ovale; active bleeding including grade ≥3 IVH or gastrointestinal hemorrhage.[5] A cranial ultrasound was performed before commencing treatment. IVH was defined and graded according to the Papile classification.[6]

Intervention and Study Procedures

Infants in the intervention arm received intravenous ibuprofen (Pedea 5 mg/1 mL; Recordati Rare Diseases, Lebanon, New Jersey) at an initial dose of 10 mg/kg (2 mL/kg), followed by 2 doses of 5 mg/kg (1 mL/kg) administered 24 hours apart. Treatment was given as an infusion over 15 minutes. Infants in the control group received an intravenous dose of placebo (normal saline), at an equivalent volume. After completion of the course, the PDA was assessed by echocardiography 24 hours after the last ibuprofen dose. If the PDA remained open (defined as any identifiable flow), then a second course of treatment (ibuprofen or placebo) was given.

The study protocol did not allow for additional PDA therapy for the first 2 weeks; however, the clinician responsible for the infant had the discretion to deviate from this protocol. Open-label treatment of a PDA beyond the first 2 weeks was at the discretion of the attending neonatologist. Paracetamol (15 mg/kg every 6 hours for 3 days followed by 10 mg/kg every 6 hours for 2 days) was permitted for open-label PDA treatment. The new onset of any of the exclusion criteria as listed above were considered as side effects of ibuprofen treatment if they occurred within 1-3 days of administration and necessitated discontinuation of the study medication and a return to standard care. In addition, concomitant treatment with gentamicin mandated the discontinuation of therapy owing to the increased risk of nephrotoxicity.

Echocardiography scans were performed at 3 time periods: 36-48 hours (echo 1 for enrollment); after first course of medication (echo 2 at 120 hours of age); and after second course of medication (echo 3 at day 8 of age). Evaluations were performed using the Vivid S6 (GE Medical, Milwaukee, Wisconsin) echocardiography system in accordance with recently published guidelines.[7] A comprehensive structural assessment was conducted to rule out congenital heart disease. The following measurements were obtained to facilitate the derivation of the PDAsc (methods detailed elsewhere): narrowest PDA diameter (mm) measured using 2-dimensional imaging at the pulmonary end; maximum shunt velocity across the PDA (in m/s); left ventricular output (in mL/kg/min); and tissue Doppler imaging of the lateral mitral valve annulus to measure left ventricular a' wave (late diastolic velocity).[8-10]

Outcome Assessment

We reported the number of infants approached, the rates of exclusion, consent in eligible infants, deviation from the study protocol, and the rate of PDA closure in both arms after the completion of the treatment course. The primary outcome was a composite of chronic lung disease and/or death before discharge. Chronic lung disease was defined as the need for oxygen supplementation at 36 weeks corrected gestational age.[11] The following secondary outcomes were recorded: pulmonary hemorrhage; surgical PDA ligation; culture positive sepsis; IVH status at 36 weeks corrected age; periventricular leukomalacia; NEC; retinopathy of prematurity requiring laser therapy; and days spent on invasive ventilation, continuous positive airway pressure, high-flow nasal cannula, and/or oxygen therapy.[5,6,12]

A sample of 30 infants per arm (a total of 60 infants) was planned for this pilot study. This study was not powered to demonstrate an absolute risk reduction in the primary clinical outcome in the intervention group. Based on our previous study, the projected rate of the composite primary outcome in infants with a PDAsc of ≥5.0 is 92%.[4] The sample

size of 60 infants is sufficient to demonstrate a significant difference in the primary outcome between the groups if the event rate is decreased from 90% (which is the anticipated rate in the control arm) to 55% in the intervention arm with a probability (power) of 80% based on a sample size of 24 per arm. The type I error probability associated with this test of this null hypothesis is 0.05. No interim analysis was conducted.

A computer-generated central randomization scheme was used to assign the infants to the 2 arms in a 1:1. Infants were stratified into 2 gestational age brackets of 23-26 weeks and 27-28 weeks. The study pharmacist received a file containing the sequence of treatment group assignments for the cohort from a statistician who was not otherwise involved in the study. Access to the file was restricted to selected pharmacy personnel and was both encrypted and password protected on the pharmacy server.

After randomization, the designated unblinded trial pharmacist prepared the trial drug or placebo and issued the syringe to the trial investigator team for administration. ibuprofen preparation is colorless, odorless, and indistinguishable from the saline preparation used for the placebo arm. Trial participants and their families, health care providers, data abstractors, echocardiographers, primary outcome assessors, and data analysts remained blind throughout to study to the randomized allocation.

Statistical Analyses

Continuous variables were presented as means (SD) or median (IQR) as appropriate. Dichotomous variables were presented as proportions and summarized in contingency tables. A χ^2 test (or a Fisher exact test as appropriate) was used for the primary analysis of the dichotomous primary and secondary outcomes. For continuous secondary outcomes, an independent samples t test was used to compare normally distributed data, and Wilcoxon rank-sum test was used for skewed data. Logistic regression analysis was conducted to examine the association between PDA presence on day 8 and other important predictor variable and the primary outcome (and its individual components) and reported as aORs with 95% CIs. All tests were 2 sided and a P value of <.05 was considered statistically significant. IBM SPSS (version 26; SPSS, Inc, Chicago, Illinois) was used for statistical analysis.

Results

Of 145 infants assessed for eligibility between April 2017 and January 2020, 62 met exclusion criteria; 83 families were approached for consent, 73 of whom agreed to participate in the study, giving a refusal rate of 12%. Infants underwent a comprehensive echocardiography assessment, of whom 13 infants had a PDA score of <5 (low risk) and were not randomized. The rate of chronic lung disease or death in the low-risk infants was 8% (1/13). The trial stopped after outcomes for the 60th infant were collected. Sixty infants had a risk score of ≥5.0 and underwent randomization; specifically, 30 infants were randomly assigned to receive ibuprofen (intervention arm) and 30 infants received placebo (control arm). In the intervention arm, 9 infants had early discontinuation of treatment (median, 1 dose [IQR, 0-2 doses]); 6 cases developed adverse events (severe IVH [n = 1], gram-negative sepsis [n = 2], thrombocytopenia [n = 1], pulmonary hypertension [n = 1], and spontaneous intestinal perforation [n = 1]) and 3 cases had commencement of a contraindicated concomitant medication (gentamicin). In the control arm 8 infants had early discontinuation of treatment (median, 1 dose [IQR, 0-2 doses]); 6 cases owing to adverse events (severe IVH [n = 2], culture positive sepsis [n = 2], NEC [n = 1], pulmonary hemorrhage [n = 1]) and 2 cases had commencement of a contraindicated concomitant medication (gentamicin). None of the infants were lost to follow-up. Eight infants (2 in the intervention arm and 6 in the control arm [13%]) received open-label treatment before the 2-week restriction period (median, day 8; range, days 6-12). In each case, open-label treatment was instituted by the attending neonatologist who was aware that this constituted a protocol deviation. The primary indication for this deviation was persistent need for invasive ventilation. Seven of those infants received paracetamol and 1 infant received ibuprofen. None of those interventions resulted in closure of the PDA. Outcome data were available for all recruited infants and analysis was conducted to include all infants (**Figure**).

Table I illustrates basic demographics and PDA characteristics in the 2 groups. Infants in the intervention arm had lower birthweight (830 ± 235 g vs 970 ± 217 g; P = .02), but there were no differences in any of the other clinical or PDA characteristics between the 2 groups (**Table I**). After the first course of treatment, PDA closure occurred in 16 infants (53%) in the intervention group and 3 infants (10%) in the control group (P < .01). A second course of treatment was administered for 10 infants in the intervention group (33%; median PDA diameter, 2.7 mm; IQR, 2.0-3.5 mm) and 19 infants in the control group (63%; median PDA diameter, 3.2 mm; IQR, 2.6-3.5 mm). The overall PDA closure rate by day 8 of age after completing the 2 treatment courses was 57% (n = 17) in the intervention group and 17% (n = 5) in the control group (P < .01).

The primary composite clinical outcome, its individual components, and the secondary outcomes are presented in **Table II**. There are no differences in the composite outcome of chronic lung disease or death, chronic lung disease, death, or any of the secondary outcomes between infants in the intervention group compared with the control group (**Table II**). One infant in the placebo arm received open-label ibuprofen treatment. This treatment did not result in PDA closure. There was no difference in the rate of open-label paracetamol treatment between the 2 groups. None of those treatments resulted in PDA closure.

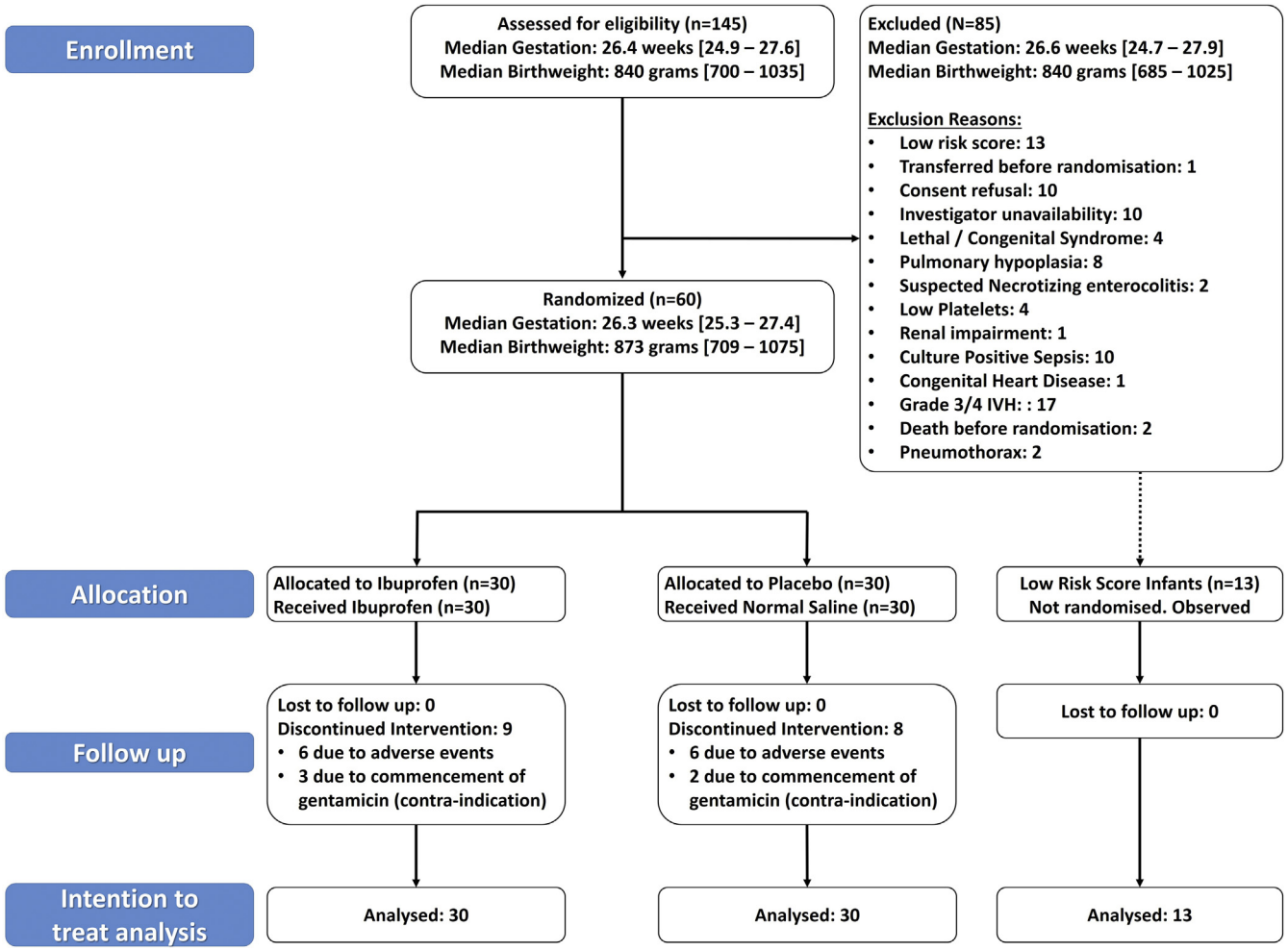

Figure. Study CONSORT flow diagram.

Table I. Baseline demographics and PDA characteristics

Characteristics	Ibuprofen (n = 30)	Placebo (n = 30)
Gestation (wk)	26.1 ± 1.4	26.3 ± 1.3
Birthweight (g)	830 ± 235	970 ± 217
Male sex	16 (53)	20 (67)
Cesarean delivery	20 (67)	17 (57)
Twin pregnancy	5 (17)	9 (30)
Cord pH	7.35 ± 0.09	7.33 ± 0.07
5-Minute Apgar score	8 [7-9]	8 [7-8]
Surfactant at delivery	25 (83)	30 (100)
Preeclampsia	6 (20)	4 (13)
Prolonged rupture of membrane	12 (40)	9 (30)
Fetal growth restriction	7 (23)	1 (3)
Magnesium sulphate administration	28 (93)	24 (80)
Antenatal steroid administration	29 (97)	24 (80)
PDA characteristics		
PDA risk score	7.4 [5.8-9.9]	7.1 [6.1-8.2]
PDA diameter (mm)	3.1 [2.7-3.5]	3.4 [2.9-3.7]
Left ventricular output (mL/kg/min)	208 [147-241]	205 [166-314]
PDA systolic velocity (m/s)	1.2 [0.5-1.7]	1.1 [−0.3 to 1.8]
Left ventricular a' wave (cm/s)	5.1 [3.9-5.9]	5.0 [4.2-6.7]

Data are mean ± SD, median [IQR], or count (%).

Logistic regression analysis of the entire cohort was conducted; predictor variables included PDA patency by day 8, gestational age, birthweight, male sex, and antenatal steroid administration. Persistent PDA patency by postnatal day 8 was independently associated with the composite primary outcome of chronic lung disease or death, and chronic lung disease. Gestational age was also an independent risk factor for composite primary outcome and death (Table III). There was no association between birthweight and any of the outcome variables.

Discussion

In this pilot randomized controlled trial of early PDA treatment based on a PDAsc, the rate of parental agreement to participate in this trial was high at 88%. This encouraging finding highlights the willingness of parents to enroll their high-risk premature infants to randomized trials in our institution. There was a relatively low rate of protocol deviations and open-label treatment of the PDA before the first 2 weeks of age as mandated by our study protocol (13%). Those

Table II. Clinical outcomes in the entire cohort

Outcomes	Ibuprofen (n = 30)	Placebo (n = 30)	OR (95% CI)	*P* value
Primary outcome				
Chronic lung disease or death	16 (53)	18 (60)	0.8 (0.3-2.1)	.80
Components of primary outcome				
Chronic lung disease in survivors	8 (36)	14 (54)	0.5 (0.2-1.6)	.26
Death	8 (28)	4 (13)	2.4 (0.6-8.9)	.33
Causes of death				
NEC	3 (37.5)	1 (25)	–	–
Respiratory failure	2 (25)	1 (25)	–	–
Sepsis	3 (37.5)	0	–	–
Pleural effusion	0	1 (25)	–	–
Severe IVH	0	1 (25)	–	–
Secondary outcomes				
Inotropes in the first week	2 (7)	2 (7)	1.0 (0.1-7.6)	1.00
Frusemide administration	21 (70)	18 (60)	1.6 (0.5-4.5)	.59
Median day of frusemide use	22 [16-39]	25 [19-33]	–	.75
Red cell transfusions	26 (87)	25 (83)	1.3 (0.3-5.4)	1.00
PDA treatment with paracetamol	5 (17)	10 (33)	0.4 (0.1-1.4)	.23
Median day of paracetamol treatment	15 [10-20]	12 [8-16]	–	.37
PDA ligation	6 (20)	6 (20)	1.0 (0.3-3.5)	1.00
Pulmonary hemorrhage	1 (3)	1 (3)	1.0 (0.1-16.8)	1.00
NEC	6 (20)	4 (13)	1.6 (0.4-6.5)	.73
Postnatal steroids	5 (17)	2 (7)	2.8 (0.5-15.7)	.42
Culture-proven sepsis	7 (23)	7 (23)	1.0 (0.3-3.3)	1.00
Retinopathy of prematurity requiring intervention	4 (13)	5 (17)	0.8 (0.2-3.2)	1.00
Grade III/IV IVH	1 (3)	1 (3)	1.0 (0.1-16.8)	1.00
Periventricular leukomalacia	4 (13)	0 (0)	–	.12
Ventilation days	3 [1-8]	3 [1-14]	–	.50
Continuous positive airway pressure days	38 [26-47]	34 [28-47]	–	.56
High-flow nasal cannula days	14 [9-25]	16 [8-22]	–	.88
Oxygen days	9 [1-20]	12 [2-26]	–	.66
Hospital days	87 [75-97]	87 [74-97]	–	.87

Data are presented as median [IQR], or count (%).
Chronic lung disease rates were assessed in survivors only.

Table III. Association between ductal patency by day 8 of age and the primary outcome

Independent variables	Dependent variables		
	Model 1: CLD/death	Model 2: CLD	Model 3: death
PDA at day 8 of age	5.8 (1.6-21.3)*	7.7 (1.9-30.1)*	0.3 (0.04-2.4)
Gestation	0.4 (0.2-0.8)*	0.7 (0.3-1.4)	0.2 (0.05-0.8)*
Birthweight	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.1)
Antenatal steroids	1.4 (0.6-3.6)	1.5 (0.6-3.9)	0.7 (0.2-2.7)
Male sex	4.0 (0.9-16.6)	4.4 (1.0-19.1)*	4.4 (0.6-34.4)

CLD, chronic lung disease or death.
Values are aOR (95% CI).
*Significant association between the independent and dependent variables.

findings suggest that there is a general acceptance to adhere to this study protocol; however, open-label treatment remains an important issue in PDA treatment trials. The rate of the clinical primary outcome in the thirteen infants with a PDAsc of <5 was low, providing some evidence that the PDAsc can accurately identify infants in whom the evolution of chronic lung disease or death is unlikely. However, the anticipated rate of chronic lung disease or death in the high-risk cohort who were enrolled in the randomized controlled trial (PDAsc ≥ 5.0) was lower than predicted (57% vs 90%). This relatively high anticipated incidence was derived from our previous observational study.

We observed a lower rate of the primary outcome than originally anticipated; this finding may be explained by our high exclusion rate of infants who would have been part of the original risk assessment in our previous observational study.[4] The risk score was potentially applied to a different population in the current trial owing to its stricter exclusion criteria. The low rate of spontaneous PDA closure in the control arm is evidence of the ability of the PDAsc score to discriminate shunts that are likely to be persistent. However, further work is required to improve the ability of the score to predict the evolution of chronic lung disease or death in this setting. The higher risk of chronic lung disease or death derived from the observational study may also stem from the exclusion reasons rather than the presence of the PDA. Given the relatively high enrollment rate of approached families and the relatively low rate of open-label treatment outside of the study protocol, a larger trial based on selection of high-risk infants may be a feasible approach to further address the association between a PDA and adverse outcomes.

We did not demonstrate any difference in the primary composite outcome of chronic lung disease or death, or its individual components between the 2 groups. Our findings are consistent with the results of most PDA treatment trials that concluded there was no difference in outcomes between infants who receive treatment vs placebo; however, our study was not powered to achieve this goal. Although the rate of death was twice as high in the intervention arm (28 vs 13%), the finding was not statistically significant and we noted that 3 of those deaths were due to sepsis and were not attributed to the intervention. This finding should not be acted on without validation in an adequately powered trial.

The overall rate of successful PDA closure in the intervention arm was only 57%; this was likely due in part to incomplete administration of the drug in one-third of the infants. The rate of adverse events were similar in both groups, highlighting the relatively common occurrence of adverse events in this high-risk population, irrespective of drug exposure. Recent evidence suggests that small for gestational age infants have a high clearance of the S-ibuprofen enantiomer, the pharmacologically active form of the drug in the racemic preparation of the medication used in this study.[13] We used Pedea, which is a racemic mixture of S (+) and R (−) enantiomers. Importantly, the inactive R-enantiomer remains inactive when administered intravenously, but is converted to the active form when given orally through liver metabolism which may explain the enhanced efficacy seen

in trials of oral ibuprofen.[14] Infants in the intervention group who failed ibuprofen treatment were of lower gestation and birthweight but had the highest rate of morbidities including the primary outcome and its components. This finding highlights the high rate of adverse outcomes seen in extremely premature infants. It was interesting to note that open-label treatment with paracetamol did not achieve ductal closure in any of the patients. This result may suggest that paracetamol is less effective for this purpose in higher risk infants and that prior reports of efficacy were contaminated by subjects with a lower risk profile.

Several carefully conducted metanalyses have failed to demonstrate an improvement in outcomes associated with PDA treatment in premature infants.[1,15] Although these data may support "leaving the PDA alone" or avoiding over-treatment, we suggest that it is important to consider the limitations of most PDA treatment trials, such as shortcomings in patient selection and risk stratification and the unpredictable efficacy of the studied treatment.[16] In addition, open-label treatment (in particular in the placebo arm) has contaminated most intervention trials.[17] These effects are coupled with a lack of comprehensive echocardiography data accurately capturing duration of ductal exposure and the magnitude of its physiologic impact in both the intervention and control groups. As a result, an appreciation of the true impact of chronic left to right shunt exposure has remained elusive.[14]

Quantification of the biological impact of a PDA on preterm health is challenging and requires the consideration of several elements, which include (1) PDA shunt volume assessment and its impact on the systemic and pulmonary circulations, (2) myocardial function evaluation, and (3) antenatal and perinatal characteristics that act as effect modifiers to either mitigate or exacerbate potential detrimental consequences of a shunt.[18-20] The PDA risk score, developed from prospectively collected data and used in this study, incorporates all 3 major elements, but further work is required to improve the ability of this score to predict chronic lung disease or death in an randomized controlled trial setting.[4] Unfortunately, ascertainment of risk does not assume responsiveness to treatment or a reduction in morbidity. Therefore, a lack of efficacy of ibuprofen therapy should not be interpreted as evidence of lack of PDA causality in terms of associated neonatal morbidities. The relationship between persistent PDA beyond day 7 and the primary outcome highlights the need to investigate treatment strategies with a high degree of efficacy in achieving PDA closure.

We acknowledge certain limitations of our study. The study was not designed or powered to identify a difference in the primary outcome between the groups; rather, it was meant to be a hypothesis-generating study attempting to identify better methodology for identifying high-risk patients and optimizing dosing regimens and treatment approaches aimed at achieving PDA closure.

In conclusion, in this small placebo-controlled trial of early ibuprofen treatment in preterm infants <29 weeks of gestation, selected based on an early PDA score, we found a high rate of enrollment to this trial coupled with a relatively low rate of open label PDA treatment outside the study protocol. Our findings indicate that this approach of enrolling high risk infants to PDA treatment trials is feasible. Further work is required to improve the ability of the PDA risk score to predict chronic lung disease/death in the randomized controlled trial setting. Future PDA treatment trials also should focus on appraising the efficacy of treatment regimens with a high success rate in achieving early PDA closure and shunt elimination compared with prolonged exposure to a hemodynamically significant shunt. ■

We thank Liam Dwyer, Research Assistant (Data Collection); Oliver Feeney, Research Assistant (Data Collection); Mandy Jackson, Sponsor Quality and Regulatory Affairs Manager (Trial Monitoring); Muiris Dowling, Sponsorship Officer (Trial Monitoring); Angela Farrelly, Clinical Trials Manager (Trial Monitoring); Royal College of Surgeons in Ireland, Trial Sponsor.

Submitted for publication Jun 23, 2020; last revision received Oct 10, 2020; accepted Oct 12, 2020.

Reprint requests: Afif EL-Khuffash, FRCPI, MD, DCE, Consultant Neonatologist, The Rotunda Hospital, Parnell Street, Dublin D01 P5W9, Ireland. E-mail: ; afifelkhuffash@rcsi.com; afif_faisal@hotmail.com

Data Statement

Data sharing statement available at www.jpeds.com.

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. Bussmann N, El-Khuffash A. What is the most efficacious oharmacological therapy for patent ductus arteriosus closure in premature infants? Ir Med J 2018;111:816.
3. Zonnenberg I, de Waal K. The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review. Acta Paediatr 2012;101:247-51.
4. 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.
5. Bell MJ. Neonatal necrotizing enterocolitis. N Engl J Med 1978;298:281-2.
6. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
7. de Boode WP, Singh Y, Gupta S, Austin T, Bohlin K, Dempsey E, et al. Recommendations for neonatologist performed echocardiography in Europe: consensus statement endorsed by European Society for Paediatric Research (ESPR) and European Society for Neonatology (ESN). Pediatr Res 2016;80:465-71.
8. Nestaas E, Schubert U, de Boode WP, El-Khuffash A, European Special Interest Group "Neonatologist Performed Echocardiography" (NPE). Tissue Doppler velocity imaging and event timings in neonates: a guide to image acquisition, measurement, interpretation, and reference values. Pediatr Res 2018;84:18-29.
9. van Laere D, van Overmeire B, Gupta S, El-Khuffash A, Savoia M, McNamara PJ, et al. Application of NPE in the assessment of a patent ductus arteriosus. Pediatr Res 2018;84:46-56.
10. El-Khuffash A, Schubert U, Levy PT, Nestaas E, de Boode WP, European Special Interest Group "Neonatologist Performed Echocardiography" (NPE). Deformation imaging and rotational mechanics in neonates: a guide to image acquisition, measurement, interpretation, and reference values. Pediatr Res 2018;84:30-45.

11. Bancalari E, Claure N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. Semin Perinatol 2006;30:164-70.
12. Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. Semin Neonatol 2000;5:3-16.
13. Engbers AGJ, Flint RB, Voller S, de Klerk JCA, Reiss IKM, Andriessen P, et al. Enantiomer specific pharmacokinetics of ibuprofen in preterm neonates with patent ductus arteriosus. Br J Clin Pharmacol 2020;86:2028-39.
14. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. JAMA 2018;319:1221-38.
15. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syste Rev 2020;1:CD004213.
16. El-Khuffash A, Levy PT, Gorenflo M, Frantz ID 3rd. The definition of a hemodynamically significant ductus arteriosus. Pediatr Res 2019;85:740-1.
17. Evans N. Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? Semin Fetal Neonatal Med 2015;20:272-7.
18. 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.
19. Sehgal A, McNamara PJ. Coronary artery perfusion and myocardial performance after patent ductus arteriosus ligation. J Thorac Cardiovasc Surg 2012;143:1271-8.
20. Kluckow M, Lemmers P. Hemodynamic assessment of the patent ductus arteriosus: beyond ultrasound. Semin Fetal Neonatal Med 2018;23:239-44.

50 Years Ago in *The Journal of Pediatrics*

Oral rehydration solution in children with cholera: proof of an important concept for child health

Nalin DR, Cash RA. Oral or nasogastric maintenance therapy in pediatric cholera patients. J Pediatr 1971;78:355-8.

After pioneering trials in adults,[1] Nalin and Cash reported on the use of oral rehydration solutions (ORS) in children with cholera. These children, from what is now Dhaka, Bangladesh, were dehydrated and losing water and electrolytes at a ferocious rate (~9 mL/kg/hour). After a 6-hour stabilization period with intravenous (IV) fluids, the children were then switched to oral or nasogastric ORS, titrated in amounts to match losses through diarrhea or vomitus. Eight of 12 children required no further IV fluids, and positive water-electrolyte balance was observed in all.

This understated but revolutionary proof of concept trial showed that "…pediatric cholera patients absorb the solution of glucose and electrolytes from their intestinal tracts in sufficient quantity to maintain positive fluid and electrolyte balance." The report led to the application of ORS in much more prevalent diarrheal diseases, including those caused by other bacteria and viruses. Many trials have shown ORS to be equivalent if not superior to IV fluids, including studies of children in the US.[2]

What are the other lessons 50 years on? ORS may be an important adjunct therapy for Ebola virus and Coronavirus disease 2019 infections,[3] and ORS use in the setting of IV shortage is not limited to resource-poor countries.[4] The development of oral rehydration therapy stands as a role model for science, highlighting the critical importance of support for research, field work, innovation, and global collaboration.[5]

Christopher P. Duggan, MD, MPH
Boston Children's Hospital and Harvard T.H. Chan School of Public Health
Boston, Massachusetts

Richard A. Cash, MD, MPH
Harvard T.H. Chan School of Public Health
Boston, Massachusetts

References

1. Nalin DR, Cash RA, Islam R, Molla M, Phillips RA. Oral maintenance therapy for cholera in adults. Lancet 1968;2:370-3.
2. Spandorfer PR, Alessandrini EA, Joffe MD, Localio R, Shaw KN. Oral versus intravenous rehydration of moderately dehydrated children: a randomized, controlled trial. Pediatrics 2005;115:295-301.
3. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol 2020;18:1663-72.
4. Patino A, Marsh R, Nilles E, Baugh C, Rouhani S, Kayden S. Facing the shortage of IV fluids—a hospital-based oral rehydration strategy. N Engl J Med 2018;378:1475-7.
5. Nalin DR, Cash RA. 50 years of oral rehydration therapy: the solution is still simple. Lancet 2018;392:536-8.