Condit *et al. BMC Nephrology* (2025) 26:138
https://doi.org/10.1186/s12882-025-04065-8

BMC Nephrology

RESEARCH Open Access

Association of patent ductus arteriosus treatment in extremely low gestational age neonates with two year kidney outcomes: a secondary analysis of the preterm erythropoietin neuroprotection trial (PENUT)

Paige E. Condit[1,6*], Ronnie Guillet[2], Dinushan Kaluarachchi[1], Russell L. Griffin[3], Shina Menon[4], David J. Askenazi[5] and Matthew W. Harer[1]

Abstract

Background Management of patent ductus arteriosus (PDA) is variable and includes expectant, medical, and procedural options. Both the hemodynamic effects of a PDA and its treatment put neonates at risk for acute kidney injury (AKI). Little is known about how different management approaches to a PDA, either conservative management or active management and either medical or surgical treatment, in preterm neonates impact kidney function over the longer term. The objective of this study is to evaluate rates of kidney dysfunction at two years of age in extremely low gestational age neonates (ELGANs) with treated compared to untreated PDAs.

Methods Secondary analysis of prospectively collected data from the PENUT trial. Kidney dysfunction defined by: eGFR < 90 mL/min/1.73 m^2, systolic or diastolic blood pressures (SBP or DBP) > 90th percentile, or proteinuria measured by albumin to creatinine ratio (ACR) > 30 mg/g. Between-group, variables were compared using chi-square or t-test statistics. General estimating equations and multivariable logistic regression was used to evaluate the association with outcomes.

Results Of 780 ELGANs, 261 (43%) were treated for PDA. Of those treated, 168 (64.4%) received pharmacologic treatment, 12 (4.6%) received surgical treatment, 57 (21.8%) received both, and 24 (9.2%) were listed as having a treated PDA without specification of management. After adjusting for confounding factors, those actively treated for a PDA were less likely to have SBP > 90th percentile at two years (29.5% treated vs. 34.3% control, adjusted OR 0.59, CI 0.36–0.99). The adjusted odds-ratios for differences in other 2-year kidney outcomes did not differ. Among those medically treated, indomethacin was used more commonly than either ibuprofen or acetaminophen.

*Correspondence:
Paige E. Condit
pcondit@wisc.edu

Full list of author information is available at the end of the article

Conclusions ELGANs receiving treatment for a PDA were less likely to have elevated SBP at two years. Prospective studies are needed to examine the effects of a hemodynamically significant PDA and its management on long-term kidney outcomes.

Keywords Hypertension, Chronic kidney disease, Kidney dysfunction, Acetaminophen, Indomethacin, Ibuprofen

Introduction

The ductus arteriosus is critical to fetal circulation, allowing for the most oxygenated blood to bypass the lungs and directly enter the systemic circulation. In term infants, it is typical for this vessel to constrict within 24 to 72 h after birth [1], but in extremely low gestational age neonates (ELGANs), approximately 66% have a persistently patent ductus arteriosus (PDA) [2]. Current management of PDAs in preterm neonates is variable and includes expectant, medical, and procedural management with surgical ligation or catheter-based device closure. The patency of this vessel after preterm birth creates the potential for increased pulmonary blood flow after the pulmonary vascular resistance decreases after birth. Excessive pulmonary blood flow from a left to right shunting PDA can result in decreased systemic output, manifesting as reduced perfusion and tissue oxygen delivery to end-organs, including the kidney, putting neonates at risk for acute kidney injury (AKI).

Guillet et al. previously reported on the association between PDA management and neonatal AKI using data from the Incidence and outcomes of neonatal acute kidney injury (referred to as AWAKEN) [3] study and confirmed that very low birth weight (VLBW) infants with a PDA had an increased odds (3.7) of developing AKI. However, there was not a significant difference in AKI incidence between conservative and active PDA management [4]. Other studies have also reported similar rates of both AKI as well as hypertension amongst ELGANs [5] with hemodynamically significant PDAs (hsPDA) during the NICU stay. Despite multiple studies evaluating the risk of AKI in the neonatal intensive care unit (NICU) and its association with a PDA, little is known about kidney function in former ELGANs with PDAs after NICU discharge and during childhood.

To address this knowledge gap, we used data collected for the Preterm Erythropoietin Neuroprotection Trial (PENUT) [6–8]. We sought to describe the differences in PDA management within the cohort and differences in measures of kidney dysfunction (estimated glomerular filtration rate (eGFR), proteinuria, and blood pressure) at two years of age. Our primary hypothesis was that at two years of age, ELGANs with a history of treated PDA would have higher rates of kidney dysfunction (lower eGFR, higher proteinuria, and higher blood pressure) than those without a treated PDA.

Methods

Patients

The study is a secondary analysis of the prospectively collected data from PENUT (ClinicalTrials.gov Identifier: NCT01378273), a placebo-controlled, intention-to-treat randomized clinical trial that took place at 19 academic centers and within 30 NICUs in the United States from December 1, 2013, to September 31, 2016. The inclusion criteria for PENUT were (1) neonates born between 24 0/7 weeks and 27 6/7 weeks' gestational age, (2) enrolled at less than 24 h of age, and (3) with arterial or venous access. Exclusion criteria for PENUT were (1) major life-threatening anomalies, (2) hematologic crises, (3) hematocrit higher than 65%, (4) hydrops fetalis, and (5) congenital infection. The University of Washington institutional review board (IRB) served as the central institutional review board, with each center involved in the study also receiving IRB or human research ethics committees' approval from their respective site. Informed written consent was obtained from the neonate's parent or legal guardian.

Kidney outcomes, both short and long-term, have been previously reported in the ancillary Recombinant Erythropoietin for Protection of Infant Renal Disease (REPAIReD) study, to investigate kidney outcomes in ELGANs [9]. For this secondary analysis, we included all ELGANs randomized for PENUT who had follow-up at two years of age and excluded infants who died prior to two years, those who were alive but did not have follow-up at two years, and those who did not have blood or urine collected or blood pressure measured at the two years follow-up visit. The previous REPAIReD study did not find any systematic differences between those who were evaluated at follow-up vs. those who were lost to follow-up.

Data collection

PDA and treatment modalities

The PENUT trial documented only whether an infant had a PDA treated medically and or surgically and the dates of procedural treatment. We analyzed infants who received acetaminophen, ibuprofen, or indomethacin for medical treatment. Medications that were administered were recorded along with their dates of administration. We excluded medications administered between days 0–3 under the assumption they were for IVH prophylaxis and not treatment of a PDA. For procedural treatment, the date of the procedure was recorded, and the time

to surgical closure was interpreted as time to definitive closure of the PDA. It was used to evaluate the effect of shunt burden. We compared groups of infants who had their PDA surgically closed between days of life 0–14, 15–29, and 29 + and evaluated for differences in kidney outcomes measured at two years of age. For infants with the designation of PDA treatment but an unknown type, we included them in the medical treatment group. Echocardiograms were not recorded, nor were any measurements of the PDA.

Kidney function measurements

For those who followed up at two years, blood, urine, and blood pressure were collected as possible. Kidney function measurements included estimated glomerular filtration rate (eGFR) using Children under age 25 equation(CKiD U25), including sCr and cystatin C [10], albumin to creatinine ratio (ACR), and comprehensive blood pressure measurements [9].

Clinical definitions

The PENUT trial defined bronchopulmonary dysplasia (BPD) as the use of supplemental oxygen at 36 weeks postmenstrual age [11]. Necrotizing enterocolitis (NEC) was defined according to Bell's stage, using stages one to three [12]. Interventricular hemorrhage (IVH) was defined using Papile grades one to four [13]. Sepsis was defined by culture-positive status.

Study aims

The primary aim of this study was the association between receipt of treatment for PDA and either an eGFR < 90 mL/min/1.73 m^2 at two years of age using CKiD U25 equation or an ACR > 30 at two years of age. The secondary aims included the association between the receipt of treatment for PDA and either a systolic or diastolic blood pressure > 90th percentile for age, or a systolic or diastolic blood pressure > 95th percentile for age; and the association between medical treatment etiologies for PDA and the measures of kidney dysfunction at two years.

Statistical analysis

Characteristics related to maternal and infant demographics, infant growth parameters, and clinical outcomes were compared between the neonates treated for a PDA and those who were not. Categorical variables were compared using a chi-square. Continuous variables with normal distribution were evaluated using t-test, while Wilcoxon rank sums tests were used for non-parametric comparisons. A generalized estimating equation (GEE) logistic regression was used to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs) for the association between PDA status and two-year outcomes. Adjusted models included characteristics that were statistically significant in bivariate analyses, which included gestational age, birth weight, intubation, bronchopulmonary dysplasia at 36 weeks corrected gestational age, vasopressor administration, indomethacin administration, vancomycin administration, severe sepsis, and 5-minute Apgar. In a secondary, post-hoc analysis, the risk of two-year outcomes was compared among exposure groups based on nephrotoxic non-steroidal anti-inflammatory drug administration within days of life 4 to 28 using a Fisher's exact test. A similar secondary, post-hoc analysis was conducted for two-year outcomes by time to surgical closure of PDA. SAS v9.4 was used for all analyses, and a p-value < 0.05 was considered statistically significant.

Results

Patients

Of the 936 infants in the PENUT analysis, 606 were included in our secondary analysis. Their median gestational age was 26 weeks (IQR 25–27), median birthweight was 819 g (IQR 680–950), 49% ($n = 298$) were female, a majority were White ($n = 417$, 69%) with 22% of participants identifying as Black race ($n = 134$), and a majority were non-Hispanic/Latino ($n = 463$, 76%).

PDA status

Of the 606 infants included for analysis, 345 (57%) had documentation of a treated PDA, and 261 (43%) had no documentation of receiving treatment for a PDA. Of those receiving treatment, 64.4% received medical treatment alone, 4.6% received surgical treatment alone, 21.8% received medical and surgical treatment, and 9.2% had documentation of treatment but an unknown type and were included in the medical treatment group. No infants underwent transcatheter percutaneous closure.

Characteristics of infants with PDA treatment (Table 1)

Infants with PDA treatment were born at younger gestational ages (25.2 weeks vs. 25.8 weeks), with the biggest difference between infants born at 24 weeks GA (33.3% vs. 16.2%, $p < 0.0001$) and had lower birth weights (772.8 g (187.1 SD) vs. 846.3 g (188.2 SD), $p < 0.001$). Infants with PDA treatment had higher rates of BPD (80.5% vs. 53%, $p < 0.0001$), NEC that was Bells stage 2a or higher (11.1% vs. 6.4%, $p = 0.04$), and severe sepsis (9.2% vs. 4.3%, $p = 0.02$). There was no significant difference in rates of severe IVH (13.8% vs. 10.7%, $p = 0.25$) (Table 2).

Outcomes

At two years of age, the eGFR and ACR for infants with and without PDA treatment were not statistically significantly different. The breakdown of the follow up data

Table 1 Comparison of maternal and infant characteristics, delivery room resuscitation, and infant baseline growth parameters by patent ductus arteriosus (PDA) treatment status

	Treated PDA (*n* = 261)	No treatment of PDA (*n* = 345)	*p*-value*
Gestational age at birth n (%)			
24 Weeks	87 (33.3)	56 (16.2)	< 0.0001
25 Weeks	83 (31.8)	68 (19.7)	
26 Weeks	50 (19.2)	94 (27.2)	
27 Weeks	41 (15.7)	127 (36.8)	
Female Sex	125 (47.9)	173 (50.1)	0.58
Maternal Race			
Black/African American n (%)	49 (18.8)	85 (24.6)	0.12
Other n (%)	22 (8.4)	17 (4.9)	
Unknown n (%)	6 (2.3)	11 (3.2)	
White n (%)	184 (70.5)	232 (67.2)	
Maternal Ethnicity			
Hispanic/Latino	55 (21.1)	80 (23.2)	0.46
Not Hispanic/Latino	201 (77.0)	262 (75.9)	
Unknown	5 (1.9)	3 (0.9)	
Multiple gestations (≥ 2 live born infants) n (%)	77 (29.5)	81 (23.5)	0.09
Diabetes n (%)	14 (5.4)	21 (6.1)	0.71
Hypertension n (%)	19 (7.3)	30 (8.7)	0.53
Pre-eclampsia n (%)	43 (16.5)	49 (14.2)	0.44
Prenatal steroids, n (%)			
None	19 (7.5)	25 (7.4)	0.28
1 dose	59 (23.2)	61 (18.0)	
2 doses	160 (63.0)	220 (65.1)	
> 2 doses	16 (6.3)	32 (9.5)	
Delivery room resuscitation			
Apgar 1 min, median (IQR)	4 (2–6)	4 (2–6)	0.02
Apgar 5 min, median (IQR)	7 (5–8)	7 (6–8)	0.01
Infant baseline growth parameters			
Small for Gestational Age n (%)	38 (14.6)	44 (12.8)	0.51
Birth weight, g, mean (SD)	772.8 (187.1)	846.3 (188.2)	< 0.0001
Birth length, cm, mean (SD)	32.1 (3.1)	33.7 (2.8)	< 0.0001
Occipitofrontal circumference, cm, mean (SD)	22.9 (2.3)	23.5 (1.7)	0.0003

* Estimated from a chi-square or t-test/Wilcoxon rank sums test for categorical and continuous variables, respectively

collected among subjects based on PDA treatment type is presented in supplemental Table 1.

Infants with PDA treatment had decreased odds of having systolic blood pressure > 90th percentile for age (adjusted odds ratio 0.59, 95% CI 0.36–0.99, Fig. 1) but not for systolic blood pressures > 95th percentile at two years of age. There was no difference in diastolic blood pressure. The two-year death rate between those with PDA treatment and those with no PDA treatment was not different (9.1% treated PDA vs. 11.9% no PDA treatment, $p = 0.18$).

Table 2 Comparison of clinical outcomes by patent ductus arteriosus (PDA) treatment status

	Treated PDA (*n* = 261)	No treatment of PDA (*n* = 345)	*p*-value*
BPD n (%)	210 (80.5)	183 (53.0)	< 0.0001
Necrotizing enterocolitis (Bells stage 2a or higher) n (%)	29 (11.1)	22 (6.4)	0.04
PDA treated medically n (%)	168 (64.4)	-	-
PDA treated surgically n (%)	12 (4.6)	-	
PDA treated both medically and surgically n (%)	57 (21.8)	-	
Treatment unknown n (%)	24 (9.2)	-	
Vasopressor Medications n (%)			
None	150 (57.5)	245 (71.0)	0.02
Vasopressors alone	45 (17.2)	45 (13.0)	
Vasopressors + hydrocortisone	66 (25.3)	55 (15.9)	
Severe Sepsis n (%)	24 (9.2)	15 (4.3)	0.02
Severe IVH n (%)	36 (13.8)	37 (10.7)	0.25
Nephrotoxic Medications n (%)			
Indomethacin	172 (65.9)	116 (33.6)	< 0.0001
0–3 DOL	68 (26.1)	114 (33.0)	0.06
4 + DOL	140 (53.6)	4 (1.2)	< 0.0001

* Estimated from a chi-square or t-test for categorical and continuous variables, respectively

Comparison of kidney outcomes among infants with Pharmacologic PDA treatment

For medication treatment between days four to 28, infants treated with indomethacin or a combination of multiple medications, had increased rates of eGFR < 90 compared to infants who received acetaminophen or ibuprofen (Table 3) ($p = 0.05$). All but two of the infants treated with a combination of medications were treated with indomethacin and an additional agent. Infants treated with indomethacin or a combination of multiple agents had increased systolic and diastolic blood pressure rates ≥ the 95th percentile for age. However, these differences were statistically significant but may be an avenue for larger study.

Comparison of kidney outcomes among infants PDAs procedurally closed

The effect of shunt burden was evaluated by comparing outcomes of neonates with surgical closure based on the date of closure. For neonates with PDAs closed at older chronological age, there were trends towards decreased eGFR ($p = 0.08$) but no differences were seen in rates of hypertension or ACR (Table 4). Evaluation of surgery DOL as a continuous variable shows the odds of eGFR being < 90 increases by 50% (OR 1.50, 95% CI 0.97–2.32, $p = 0.07$) with every 7-day increase in surgery DOL; this

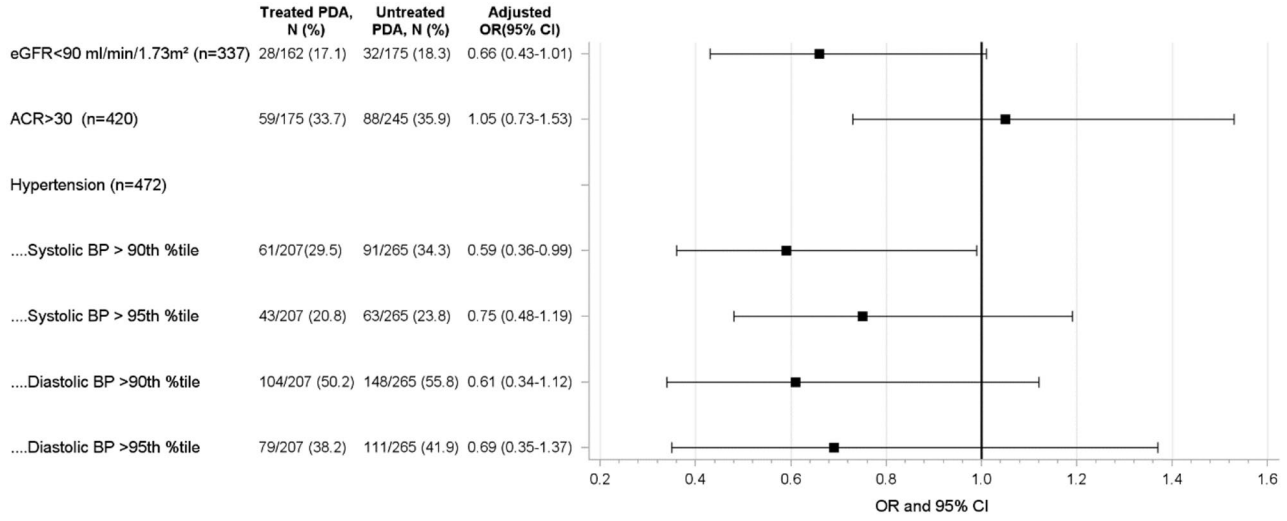

Fig. 1 Forest plot of odds ratios for the association between patent ductus arteriosus and two-year outcomes. Odds ratios estimated from generalized estimating equation logistic regression and adjusted for gestational age, birthweight, intubation, bronchopulmonary dysplasia at 36 weeks gestational age, vasopressor administration, indomethacin administration, vancomycin administration, severe sepsis, and 5-minute Apgar

Table 3 Comparison of two-year outcomes by exposure to non-steroidal anti-inflammatory drugs and acetaminophen within days of life 4 to 28

	Indomethacin day 4–28 (*n* = 129)	Ibuprofen day 4–28 (*n* = 40)	Acetaminophen day 4–28 (*n* = 3)	Combination (*n* = 15)	*p*-value*
eGFR < 90 (*n* = 115)	14/74 (18.9)	2/28 (7.1)	0/2 (0.0)	5/11 (45.5)	0.05
ACR > 30 (*n* = 123)	27/76 (35.5)	9/33 (27.3)	2/3 (66.7)	5/11 (45.5)	0.40
Hypertension (*n* = 148)					
Systolic pressure-based					
<90th percentile	73/105 (69.5)	23/30 (76.7)	1/1 (100.0)	8/12 (66.7)	0.92
90-94th percentile	7/105 (6.7)	2/30 (6.7)	0/1 (0.0)	1/12 (8.3)	
≥95th percentile	25/105 (23.8)	5/30 (16.7)	0/1 (0.0)	3/12 (25.0)	
Diastolic pressure-based					
<90th percentile	49/105 (46.7)	17/30 (56.7)	1/1 (100.0)	7/12 (58.3)	0.74
90-94th percentile	13/105 (12.4)	2/30 (6.7)	0/1 (0.0)	2/12 (16.7)	
≥95th percentile	43/105 (40.9)	11/30 (36.7)	0/1 (0.0)	3/12 (25.0)	

*Estimated from a Fisher's exact test

ACR: albumin/creatinine ratio

association is only slightly attenuated when including GA and AKI status in the model (OR 1.46, 95% CI 0.89–2.38, $p = 0.13$). These associations were also not significant.

Discussion

In this secondary analysis of the prospectively collected PENUT trial data, we evaluated two-year kidney outcomes from ELGANs to assess whether infants who received PDA treatment compared to those who did not receive PDA treatment had differences in their outcomes. We found that infants treated for a PDA had no difference in their eGFR and ACR at two years of age but were less likely to have systolic blood pressure > 90% compared to those without PDA treatment; however, given the limitations within this data set, these results should be interpreted with caution. Results from this study support future investigations, specifically evaluating the effects of PDA therapy on long-term kidney outcomes to better understand the potential pathophysiology, as there could be signals towards kidney-protective effects of treatment. Due to the hypothesis generating nature of this study we mentions trends as sample sizes were small in the various analyses and the results could point to venues for more detailed study.

We also found that at the time of the PENUT study, indomethacin was the most frequently used medication for medical PDA treatment and that exposure to indomethacin resulted an increased rate of kidney dysfunction at 24 months of age. Among those infants with a PDA definitively closed by surgical measures, we found

Table 4 Comparison of two-year outcomes by days to surgery to close PDA

	0–14 days (*n* = 11)	15–29 days (*n* = 36)	≥ 30 days (*n* = 21)	*p*-value*
eGFR < 90 (*n* = 38)	0/8 (0.0)	2/22 (9.1)	4/11 (36.4)	0.08
ACR > 30 (*n* = 50)	3/8 (37.5)	10/28 (35.7)	3/14 (21.4)	0.70
Hypertension (*n* = 51)				
Systolic pressure-based				
<90th percentile	6/7 (85.7)	20/26 (76.9)	14/18 (77.8)	0.31
90-94th percentile	1/7 (14.3)	0/26 (0.0)	1/18 (5.6)	
≥95th percentile	0/7 (0.0)	6/26 (23.1)	3/18 (16.7)	
Diastolic pressure-based				
<90th percentile	4/7 (57.1)	13/26 (50.0)	9/18 (50.0)	0.93
90-94th percentile	0/7 (0.0)	4/26 (15.4)	3/18 (16.7)	
≥95th percentile	3/7 (42.9)	9/26 (34.6)	6/18 (33.3)	

*Estimated from a Fisher's exact test

ACR: albumin/creatinine ratio

that increased duration of shunt burden, quantified by later timing of shunt closure, was associated with higher rates of eGFR being < 90 at 24 months, though given the small sample size it is important to recognize this as a nonstatistically significant trend, however, this could be better evaluated in a larger prospective study. The increased rates of lower eGFR could be due to sustained hypoperfusion from diastolic steal from a left to right shunt; however, given the confines of the data set, we cannot say with certainty that the PDA was always shunting left to right. However, even if it was shunting right to left for a period of time before definitive closure, it still could have led to kidney hypoxia.

Previous studies evaluating the effects of PDA treatment on kidney health have focused on short-term rates of AKI and found that infants with a PDA are at increased risk of AKI regardless of treatment approach [4]. This is the first study to identify factors associated with PDA treatment and the development of long-term kidney dysfunction.

Our results indicate that treatment of the PDA may impart some level of kidney protection, with those infants receiving treatment having significantly decreased odds of developing systolic hypertension. Likewise, infants with a clinically significant PDA who were exposed to a longer duration of shunt burden, as defined by definitive surgical closure at an older age, had higher rates of decreased eGFR. This suggests that earlier treatment may be better.

We did not find a significant difference in some of the kidney outcomes at two years of age between infants who were treated for a PDA versus infants who were not which indicates that more robust prospective studies are needed to understand this multifactorial condition better.

Indomethacin use has been associated with AKI in neonates. Some studies have gone so far as to evaluate whether the effectiveness of indomethacin as closing the PDA can be measured by the AKI that occurs [14]. This is concerning because it was the most commonly used medication in this study's era, and long-term kidney outcomes were worse amongst infants who were treated with indomethacin compared to acetaminophen or ibuprofen. This implies that the short-term AKI that occurs could also be impacting kidney health much later in life for these babies and caution should be taken when using this agent compared to the others, especially when no definitive trial has proven one to be superior to the other [15–17]. It is important to note that since the data collection for this cohort, indomethacin use has decreased nationally [18]. Raaijmakers et al. evaluated longer term kidney affects (eGFR and kidney length) of neonatal exposure to ibuprofen and found no significant difference among adolescents with neonatal ibuprofen compared to those without, thus ibuprofen could be a better option for PDA medical management from a kidney health perspective, though this would be better definitively evaluated with a randomized control trial [19].

In an attempt to evaluate the effect of shunt burden on two-year kidney outcomes, we used the surrogate marker of time to definitive closure via surgical closure, accepting that this is not a perfect measure. Within this population, we could be assured that once the shunt was surgically closed, it would not open again, and it would be a safe assumption that the PDA would be open for most of the time until definitive closure. Within this group, we found that infants with a longer time to surgical shunt closure and, therefore, a more prolonged shunt burden had increased rates of lower eGFR at two years. This is concerning for the development of kidney dysfunction and potentially CKD within this population. Given that, at this time, there is no standard recommendation for when to close a PDA via medical or procedural means, these data support investigating if there is a benefit to earlier closure to decrease longer-term kidney morbidity within this at-risk population [20]. A 2023 Danish cohort study evaluated the lifetime risk of developing CKD in infants with simple congenital heart disease, which included PDAs, and found no difference in risks. However, this did not specifically evaluate the duration of PDA shunt burden and the risk of CKD [9, 21]. No study to our knowledge has evaluated the effect of shunt burden on these outcomes and this should continue to be investigated in future studies.

Limitations

This study is limited by the nature of the secondary analysis and not having input in the details related to the data elements collected for the prospective study. PDA diagnosis and treatment decisions were not protocolized in the PENUT study. The duration and dose of exposure to medication were unknown. The rationale for specific medication selection was also unknown. Without echocardiographic information on all PENUT participants we could not determine if those who were not treated did or did not have a PDA. Similarly, in the PDA treatment group, the hemodynamic significance of the PDA is unclear. Likewise, for the infants with surgical closure, we could not be sure without the echocardiographic results whether the PDA was open for the entirety of the time prior to surgical closure. In addition, among infants who underwent surgical ligation, the degree and duration of medication exposure were unknown and hence not addressed.

Further, there are widely variable practice differences in NICUs where these data were collected, so while our measurements were looking at specific outcomes, it is possible that these outcomes were influenced by outside factors not accounted for due to practice variation. We adjusted for multiple potentially confounding variables in our statistical models, but residual confounding cannot be ruled out. We were able to account for potential survival bias by confirming there was no difference in the two-year death rate between the groups. We didn't account for multiple tests in this hypothesis-generating study. Lastly, the at two years of age there were not additional measures of kidney dysfunction made including end organ screening, blood pressure was recorded at only one visit (lowest of two values) during the follow-up, and there was not an echocardiogram done at that time to evaluate the cardiovascular effects of hypertension. Because the blood pressure was only measured at one visit, if the elevation in blood pressure is situational or sustained is not known.

Conclusions

In this study, we found that at two years of age, infants who received treatment for a PDA, compared with infants who did not receive treatment for a PDA, had no difference in their eGFR and ACR at two years of age but were less likely to have elevated systolic blood pressure. This could indicate a kidney protective component to PDA treatment. This is consistent with prolonged shunt exposure potentially increasing the rates of having a low eGFR at two years and that perhaps having a PDA for longer harms the kidneys long term which may explain why the treatment group showed some signs of improved kidney outcomes. Among those infants treated medically for their PDA, infants with exposure to indomethacin were more likely to have have a lower eGFR at two years of age compared to those exposed to ibuprofen and acetaminophen. Results from this study support future investigations specifically evaluating the effects of PDA therapy on long-term kidney outcomes to understand the potential pathophysiology better as there could be a signal towards kidney-protective effects of treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04065-8.

Supplementary Material 1

Acknowledgements

We would like to thank all of the original PENUT investigators and sites, as well as the patients and their families who participated.

Author contributions

P.E.C wrote the main manuscript text.P.E.C., R.G., R.L.G., D.J.A., and M.W.H were involved with designing the study and data analysis. R.L.G. did the statistical analysis.P.E.C., R.G., D.C.K, R.L.G., S.H., D.J.A., and M.W.H edited and reviewed the manuscript.All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

The study is coordinated by the Neonatal Kidney Collaborative Research Committee. Statistical support for this study is provided by Nuwellis.

Data availability

The data that support the findings of this study are available from the authors.

Declarations

Ethics approval and consent to participate

This is a retrospective observational study using existing data. There were no study intervention and the existing data was received and used in a de-identified manner to protect subject privacy. The original PENUT trial received ethics approvals from all participating centers with the University of Washington institutional review board (IRB) serving as the central institutional review board.

Consent for publication

Not applicable.

Disclosure

For full disclosure, we provide here an additional list of other author's commitments and funding sources that are not directly related to this study: In the last 24 months, David J Askenazi has consulted with Nuwellis, Seastar, and Abbott. Over the last 24 months, his institution has received funding for education and research that is not related to this project from Nuwellis, Bioporto, Leadiant and Seastar. He has financial interests in patent/innovations pending in the area of kidney support therapies and urine collection devices. He is the Founder and Chief Scientific Officer for Zorro-Flow Inc. Ronnie Guillet: Ronnie Guillet is a stockholder in Zorro-Flow Inc. Dinushan Kaluarachchi: Dinushan Kaluarachchi serves as a consultant for ONY Biotech.

Competing interests

The authors declare no competing interests.

Author details

[1]Division of Neonatology, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[2]Division of Neonatology, Golisano Children's Hospital, University of Rochester, Rochester, NY, USA
[3]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA

[4]Division of Pediatric Nephrology, Department of Pediatrics, Stanford University, Palo Alto, CA, USA
[5]Division of Nephrology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA
[6]NICU Fellow, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Received: 22 December 2024 / Accepted: 10 March 2025
Published online: 19 March 2025

References

1. Dice JE, Bhatia J. Patent ductus arteriosus: an overview. J Pediatr Pharmacol Ther. 2007;12(3):138–46.
2. 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(4):1113–21.
3. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1(3):184–94.
4. Guillet R, Selewski DT, Griffin R, Rastogi S, Askenazi DJ, D'Angio CT. Relationship of patent ductus arteriosus management with neonatal AKI. J Perinatol. 2021;41(6):1441–7.
5. Velazquez DM, Reidy KJ, Sharma M, Kim M, Vega M, Havranek T. The effect of hemodynamically significant patent ductus arteriosus on acute kidney injury and systemic hypertension in extremely low gestational age newborns. J Matern Fetal Neonatal Med. 2019;32(19):3209–14.
6. Juul SE, Comstock BA, Wadhawan R, Mayock DE, Courtney SE, Robinson T, et al. A randomized trial of erythropoietin for neuroprotection in preterm infants. N Engl J Med. 2020;382(3):233–43.
7. Askenazi DJ, Heagerty PJ, Schmicker RH, Brophy P, Juul SE, Goldstein SL, Hingorani S. The impact of erythropoietin on short- and long-term kidney-related outcomes in neonates of extremely low gestational age. Results of a multicenter, Double-Blind, Placebo-Controlled randomized clinical trial. J Pediatr. 2021;232:65–e7267.
8. Askenazi DJ, Heagerty PJ, Schmicker RH, Griffin R, Brophy P, Juul SE, et al. Prevalence of acute kidney injury (AKI) in extremely low gestational age neonates (ELGAN). Pediatr Nephrol. 2020;35(9):1737–48.
9. Hingorani S, Schmicker R, Ahmad KA, Frantz ID, Mayock DE, La Gamma EF, et al. Prevalence and risk factors for kidney disease and elevated BP in 2-Year-Old children born extremely premature. Clin J Am Soc Nephrol. 2022;17(8):1129–38.
10. Pierce CB, Muñoz A, Ng DK, Warady BA, Furth SL, Schwartz GJ. Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int. 2021;99(4):948–56.
11. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics. 1988;82(4):527–32.
12. Kliegman RM, Walsh MC. Neonatal necrotizing Enterocolitis: pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr. 1987;17(4):213–88.
13. 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(4):529–34.
14. Dias Maia P, Rodrigues KK, Gien J, Turner MJ. Neonatal acute kidney injury during indomethacin therapy: does it predict ductal closure? J Nephrol. 2023;36(6):1591–7.
15. Jensen EA, DeMauro SB, Rysavy MA, Patel RM, Laughon MM, Eichenwald EC et al. Acetaminophen for patent ductus arteriosus and risk of mortality and pulmonary morbidity. Pediatrics. 2024;154(2).
16. 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–e4846.
17. Mitra S, de Boode WP, Weisz DE, Shah PS. Interventions for patent ductus arteriosus (PDA) in preterm infants: an overview of cochrane systematic reviews. Cochrane Database Syst Rev. 2023;4(4):Cd013588.
18. 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.
19. Raaijmakers A, Zhang ZY, Levtchenko E, Simons SH, Cauwenberghs N, Heuvel L, et al. Ibuprofen exposure in early neonatal life does not affect renal function in young adolescence. Arch Dis Child Fetal Neonatal Ed. 2018;103(2):F107–11.
20. Good PI, Li L, Hurst HA, Serrano Herrera I, Xu K, Rao M et al. Low nephron endowment increases susceptibility to renal stress and chronic kidney disease. JCI Insight. 2023;8(3).
21. El-Chouli M, Meddis A, Christensen DM, Gerds TA, Sehested T, Malmborg M, et al. Lifetime risk of comorbidity in patients with simple congenital heart disease: a Danish nationwide study. Eur Heart J. 2023;44(9):741–8.

Publisher's note