MEDDOCS Open Access Publisher

Journal of Nephrology and Hypertension

Open Access | Research Article

Does indomethacin exposure increase risk for chronic kidney disease in very low birth weight infants?

Amy C Blake[1]; Katja M Gist[2]; Claire Palmer[3]; Danielle E Soranno[4*]

[1]Neonatology, Section of Neonatology, Department of Pediatrics, Marshfield Clinic, Marshfield, WI

[2]Cardiology, Department of Pediatrics, University of Colorado and Children's Hospital Colorado, USA

[3]Child Health Research Biostatistical Core, Department of Pediatrics, University of Colorado and Children's Hospital Colorado, USA

[4]Nephrology, Department of Pediatrics, University of Colorado and Children's Hospital Colorado, USA

***Corresponding Author(s): Danielle E Soranno,**

Assistant Professor, Bioengineering & Medicine Pediatric Nephrology/the Kidney Center, University of Colorado, Anschutz Medical Campus, Colorado

Tel: 720-777-6263, Fax: 720-777-7200
Email: Danielle.Soranno@childrenscolorado.org

Received: Jan 26, 2017

Accepted: Feb 15, 2018

Published Online: Feb 19, 2018

Journal: Journal of Nephrology and Hypertension

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Copyright: © Soranno DE(2018). *This Article is distributed under the terms of Creative Commons Attribution 4.0 international License*

Keywords: Indomethacin; Patent ductus arteriosus; PDA; Neonate; VLBW; Hypertension.

Abstract

Objective: To determine the association between indomethacin exposure and risk for chronic kidney disease defined by hypertension in very low birth weight (VLBW) infants.

Study design: Retrospective chart review including VLBW infants admitted from January 2011-December 2014 at the University of Colorado Level III Neonatal Intensive Care Unit (NICU). Data collected included: indomethacin administration, presence of hypertension, and clinically relevant confounders. The primary outcome was hypertension at discharge. Logistic regression was performed to determine association between indomethacin and hypertension while controlling for confounding variables.

Result: 503 VLBW infants were admitted to the NICU during study time period (19.4% of admissions). 202 infants were excluded (death, congenital anomaly, intrauterine growth restriction, prenatal indomethacin exposure, or missing data), with 301 infants included in final analysis. 132 (44%) received indomethacin during their NICU course. Infants exposed to indomethacin had lower gestational ages (26.4±1.9 weeks vs. 29.1±1.9, P<0.0001) and birth weights (921.8±226.7 g vs. 1244.5±214.7, P<0.0001) compared to non-exposed infants. Exposed infants had an increased incidence of hypertension compared to non-exposed (6% vs. 2%). After adjusting for confounders, this was not statistically significant (P=0.12).

Conclusions: In VLBW infants, indomethacin is not independently associated with increased rates of hypertension at discharge. Infants receiving indomethacin tended to be those already at highest risk for long-term renal impairment given lower gestational age and birth weight, and increased illness severity. More judicious use of indomethacin and further studies of long-term renal functionare warranted in this vulnerable population.

Cite this article: Blake CA, Gist KM, Palmer C, Soranno DE. Does indomethacin exposure increase risk for chronic kidney disease in very low birth weight infants? J Nephrol Hypertens. 2018; 1: 1004.

Introduction

In the United States, 10-12% of infants are delivered prematurely, with greater than 75,000 infants per year delivered at less than 32 weeks [1]. Failure of the ductus arteriosus to close within 72 hours of birth (patent ductus arteriosus [PDA]) is a known complication of preterm birth, with a prevalence of 20-50% in infants less than 32 weeks [2]. The incidence of PDA is additionally increased in infants born at altitude [3]. Presence of a PDA is associated with worse pulmonary morbidities [4-7] and increased odds for intraventricular hemorrhage, necrotizing enterocolitis, and death [2,8-9].

Intravenous indomethacin, which inhibits prostaglandin, is the most commonly used medication for management of a PDA. Indomethacin is a potent inhibitor of prostaglandin synthesis via non-specific cyclooxygenase inhibition, and is believed to cause ductal closure via decreased circulating levels of prostaglandin, with successful closure of the PDA seen in 60-80% of treated patients [8]. In addition, fluid restriction is commonly used in the setting of PDA to minimize the effect of excessive pulmonary blood flow in the setting of a left to right shunt across the ductus, as well as to maintain normal serum electrolyte concentrations in the setting of oliguria.

In addition to prostaglandin's effect on ductal patency, prostaglandin also plays a critical role in renal blood flow in the neonate. Glomerular capillary pressure is maintained by the balance of vasodilation at the afferent arteriole, mediated by prostaglandin, and vasoconstriction at the efferent arteriole, mediated by angiotensin II. Inhibition of prostaglandin by non-steroidal anti-inflammatory medications, including indomethacin, results in decreased circulating prostaglandin levels. Decreased prostaglandin levels lead to unopposed angiotensin II and afferent arteriole vasoconstriction, with subsequent decreased renal blood flow with a corresponding decrease in glomerular filtration rate [10-12].

Due to the decrease in renal blood flow during indomethacin treatment, common adverse effects of treatment include transient oliguria and elevated creatinine [7,13]. These effects are generally believed to be self-limited, with normalization of creatinine by day 30 of life [14]. however, there is a paucity of evidence regarding the long-term effects of indomethacin therapy on renal function. One study found no evidence of long-term influence on renal function or structure following indomethacin exposure [15], however, this study was limited by small numbers, and did not differentiate between antenatal and postnatal indomethacin exposure. Meanwhile, there is growing evidence that even transient acute kidney injury (AKI) predisposes to chronic kidney disease (CKD) in children [16-19].

Premature infants, those most likely to require treatment for PDA, are a particularly vulnerable population with respect to long-term renal function. Preterm infants have decreased nephron numbers compared to term infants despite ongoing postnatal nephrogenesis until 40 days of life [20], as well as histologic abnormalities of up to 13 percent of their glomeruli [21]. Acute kidney injury (AKI) in pediatric patients has been shown to increase long-term risk for chronic kidney disease in patients without pre-existing kidney disease [17-19]. Given the public health burden of adult chronic kidney disease, it is vital to determine whether there exists an association between indomethacin therapy and long-term risk for chronic kidney disease in this vulnerable population of infants.

The aim of this study was to determine whether infants receiving indomethacin treatment had increased risk for developing CKD at NICU discharge compared to infants not receiving indomethacin. Prognostic factors for CKD include systemic hypertension and proteinuria. The literature reports incidence of systemic hypertension in 1-1.4% of all preterm neonates [22-23]. We hypothesized that neonates receiving indomethacin would have higher rates of hypertension and/or proteinuria at NICU discharge compared to control infants.

Methods

We conducted a retrospective case-control study to evaluate the effect of indomethacin therapy in neonates with PDA. This study was carried out via chart review of all patients classified as very low birth weight (VLBW, birth weight less than 1500 grams) admitted to University of Colorado Hospital Level III NICU between January 2011 and December 2014. Patients were assigned to two groups based on the administration of indomethacin during their NICU admission. In exposed patients, the typical course of indomethacin was intravenous dosing daily x 3 days. Exclusion criteria were death prior to NICU discharge, presence of congenital anomaly, prenatal diagnosis of renal anomaly, prenatal exposure to indomethacin, congenital heart disease, diagnosis of intrauterine growth restriction, exposure to prostaglandin, and need for Extra corporeal membrane oxygenation (ECMO) therapy. Data was collected for each infant as shown in **Table 1**.

The primary outcome for this study was the incidence of systemic hypertension in infants at time of NICU discharge, as a marker for increased risk for CKD. We estimated an incidence of hypertension of 1% in neonates not receiving indomethacin, and an estimated 25% increase to 1.25% incidence of hypertension in indomethacin-exposed neonates at discharge. For an α= 0.05 and β=0.2, we estimated a sample size of 125 per group needed to detect a difference of 25%. Secondary outcomes were presence of proteinuria, and increased serum creatinine concentration at 30-60 days of age.

Demographic and clinical characteristics were compared using two-sample t-tests and Fisher's exact tests for continuous and categorical variables, respectively. Logistic and linear regression models were used with indomethacin exposure as the primary explanatory variable to assess its association with diagnosed hypertension and creatinine level from day 30 to 60. Significant demographic and clinical confounders (gestational age, birth weight, exposure to diuretic medications, and need for vasoactive support) were included in both models. All hypothesis tests were two-sided and significance was set at 0.05. Statistical analyses were performed using R version 3.1.1 software (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

Results

For 2011-14, a total of 2592 infants were admitted to the University of Colorado NICU. Infants (n=503) (19.4% of total admissions) were categorized as VLBW. Infants (n = 202) were excluded from analysis due to death prior to NICU discharge (n=40), congenital anomaly (n=60), intrauterine growth restriction (n=90), prenatal exposure to indomethacin (n=1), and relevant data missing from the medical record (n=11). The remaining 301 infants had data collected for analysis. Infants were categorized into two groups based on their post-natal exposure to indomethacin (Group 1, any indomethacin exposure; Group 2, no indomethacin exposure).

Table 2 summarizes the demographic and clinical characteristics of the study cohort. Overall, among all 301 subjects for which data was collected, those exposed to indomethacin were younger (mean [±SD] age, 26.4±1.9 vs. 29.1±1.9 weeks; P<0.0001), had a lower birth weight (921.8±226.7 vs. 1244.5±214.7 g; P<0.0001), higher proportion of PDA diagnosis (103 (78%) vs. 24 (14%); P<0.001), vasoactive medication exposure (50 (38%) vs. 17 (10%); P<0.001) and diuretic exposure at any time (73 (55%) vs. 29 (17%); P<0.001).

Using multivariable logistic regression, we evaluated for the association between the presence of hypertension at discharge and indomethacin use (**Table 3**). Gestational age, birth weight, exposure to vasoactive medication and exposure to diuretics at any point were included in the model as confounders based on their clinical relevance and significant association with hypertension and risk for CKD. There was no significant association between hypertension and indomethacin exposure after adjusting for these confounders; p=0.1259. Although not significant, the odds of hypertension were higher by 3.2 (0.7, 14.9) for subjects exposed to indomethacin compared to those who were not. The overall incidence of hypertension in our study population was 3.98 percent.

We then tested for the association between an elevated serum creatinine (from day of life 30-60) and indomethacin exposure (**Table 4**). Gestational age (weeks), birth weight (g), exposure to vasoactive medication and exposure to diuretics at any point were included in the model as confounders based on their clinical relevance and significant association with risk for CKD. There was no association between creatinine levels from day 30 to 60 and indomethacin exposure after adjusting for these confounders; P=0.4726. Creatinine was, on average, 0.04 mg/dL (-0.071, 0.152) higher in the group exposed to indomethacin compared to the non-exposed group.

Discussion

Persistent patency of the ductus arteriosus occurs commonly in premature and very low birth weight infants, and is associated with significant morbidities as well as increased mortality. Attempts to close the ductus arteriosus are commonly undertaken in clinical practice, both via surgical ligation and with pharmacologic therapy. Indomethacin has been the most commonly used medication for this purpose, given its mechanism of prostaglandin synthase inhibition [24]. However, indomethacin's known side effect of decreasing renal blood flow with subsequent oliguric acute kidney injury raises concern for long term effects on renal function following indomethacin therapy early in life. De rigueur fluid restriction in the setting of oliguric AKI in order to prevent hyponatremia may further worsen renal perfusion and result in increased severity of AKI. Prior studies have shown normalization of creatinine by day of life 30 following indomethacin treatment [15], which is supported by our data. However, there has been a paucity of studies evaluating longer term renal risks in these patients. Our study attempted to evaluate the long-term risk for chronic kidney disease in VLBW infants receiving indomethacin therapy for PDA using known prognostic markers of increased CKD risk including hypertension and proteinuria. Due to limited data, we were unable to evaluate the incidence of proteinuria in our population. The incidence of diagnosed hypertension for all VLBW infants in our population was higher than what has been previously reported in the literature (3.98 overall vs 1-1.5 percent) [22-23]. When adjusted for clinical confounders, the incidence of hypertension was similar in infants exposed to indomethacin and non-exposed infants. Our data demonstrated that infants receiving indomethacin had significantly lower gestational ages and birth weights, as well as increased illness severity, with significantly increased need for vasoactive support and diuretic medications, all of which are associated with risk for renal injury. While indomethacin treatment was not independently associated with hypertension in our population, our data suggest that those infants being treated with indomethacin tend to be those already at higher risk for the development of CKD. Given these findings, a more judicious approach to the use of indomethacin in this high-risk population is warranted. Several studies have proposed the use of acetaminophen as an alternative therapy for closure of the ductus arteriosus [25-27], with early evidence demonstrating some efficacy of this therapy. However, large-scale trials as well as long term follow up data are not yet available, limiting the application of this as a true alternative therapy. Given the findings of our study, further studies are warranted, including more robust evaluation of alternative pharmacologic therapies for PDA, and evaluation of the risk of indomethacin therapy in additional vulnerable patient groups, such as those infants with decreased nephron mass secondary to intrauterine growth restriction. In addition, evaluation of the long-term renal outcomes of these infants is indicated. With the most vulnerable infants being the most likely to receive indomethacin, routine post-NICU care for VLBW infants should include follow-up with a pediatric nephrologist around 2 years of age for comprehensive renal evaluation, with blood pressure measurement and laboratory studies including renal function panel, urine protein: creatinine ratio, and measurement of cystatin C. Cystatin C can be used to estimate glomerular filtration rate (GFR), and has been correlated with more invasive measures of GFR such as iohexol clearance [28]. In addition, studies have identified several biomarkers that may have utility in monitoring for development and progression of CKD, including neutrophil gelatinase-associated lipocalin, liver-type fatty acid-binding protein, and kidney injury molecule-1 [21]. These biomarkers may prove useful in the evaluation of CKD risk in children with a history of preterm birth and indomethacin exposure.

Our study is limited in its single center design and limited number of infants included. However, this study highlights the renal vulnerability of the infants most likely to receive indomethacin, as well as an incidence of hypertension significantly higher than previously published. These findings underscore the need for further research into long-term effects of indomethacin therapy, alternative pharmacologic management of PDA, and need for long term renal follow up of VLBW neonates.

Tables

Table 1: Data collected for included infants.

Gestational age
Gender
Birth weight
Single/multiple gestation
Total indomethacin dose (mg/kg)
Diagnosis of hypertension at NICU discharge
Mean blood pressure measurements at NICU discharge
Antihypertensive medication exposure during NICU course
Diagnosis of PDA
Diagnosis of acute kidney injury
Echocardiogram results
Urinalysis results obtained at 30-60 days of age
Presence of proteinuria at 30-60 days of age
Serum creatinine levels at 30-60 days of age, or NICU discharge if prior to 30 days
Serum sodium levels at 30-60 days of age, or NICU discharge if prior to 30 days
Total daily fluid intake prior to and during indomethacin exposure
Urine output prior to, during, and after indomethacin exposure
Exposure to nephrotoxic medication during NICU course
Renal ultrasound results obtained during NICU course
Exposure to high frequency oscillatory ventilation
Exposure to vasoactive medications
Exposure to calcium supplementation
Exposure to diuretic therapy during NICU course
Exposure to diuretic therapy during first two weeks of life, or within one week of indomethacin exposure

Table 2: Demographic and clinical characteristics of included infants.

Variable	Indomethacin	No indomethacin	P Value
	n=(132)	n=(169)	
Gestational age (weeks)	26.4±1.9	29.1±1.	<0.0001
Birth weight (g)	921.8±226.7	1244.5±214.7	<0.0001
Discharge blood pressure (mmHg)	50.3±6.7	51.3±5.7	0.1846
Creatinine (mg/dL)	0.4±0.2	0.3±0.1	0.0558
Sodium (mEq/L)	136.7±2.8	136.9±2.8	0.6882
Gender			0.163
Male	62 (47%)	94 (56%)	
Female	70 (53%)	75 (44%)	
Birth order			0.5554
Singleton	107 (81%)	126 (75%)	

Twin	17 (13%)	29 (17%)	
Triplet	4 (3%)	9 (5%)	
Quadruplet	4 (3%)	5 (3%)	
Hypertension			0.1388
No	124 (94%)	165 (98%)	
Yes	8 (6%)	4 (2%)	
Diagnosis of PDA			<0.001
No	29 (22%)	145 (86%)	
Yes	103 (78%)	24 (14%)	
Antihypertensive treatment			1
No	130 (98%)	167 (99%)	
Yes	2 (2%)	2 (1%)	
High frequency ventilation			0.1801
No	119 (90%)	160 (95%)	
Yes	13 (10%)	9 (5%)	
Vasoactive medication exposure			<0.001
No	82 (62%)	151 (90%)	
Yes	50 (38%)	17 (10%)	
Diuretic exposure (any)			<0.001
No	59 (45%)	140 (83%)	
Yes	73 (55%)	29 (17%)	
Diuretic exposure in first two weeks			0.7872
No	57 (78%)	24 (83%)	
Yes	16 (22%)	5 (17%)	
*Plus-minus values are means ±SD			

Table 3: Association of hypertension with indomethacin exposure and clinical confounders.

Predictor	OR (95% CI)	P Value
Indomethacin exposure	3.2 (0.7, 14.9)	0.1259
Gestational age (weeks)	0.8 (0.5, 1.4)	0.4653
Birth weight (g)	1 (1, 1)	0.1109
Vasoactive medication exposure	0.2 (0, 1)	0.1109
Diuretic exposure (any)	1.3 (0.3, 5.1)	0.7373

Table 4: Association os serum creatinine contration at 30-60 days of life with indomethacin exposure and clinical confounders

Predictor	Estimate (95%CI)	PV value
indomeethacin exposure	0.04(-0.071, 0.152)	0.4726
Gestational agee (Weeks)	-0.03 (0.076, 0.016)	0.1971
Birth Weight (g)	0 (0, 0)	0.6967
Vasoactive medication exposure	0.012 (0.091,0.115)	0.8149
Diuretic exposure(any)	0.005 (-0.098,0.108)	0.9280

References

1) Martin JA, Hamilton BE, Osterman MJ, et al. Births: Final data for 2013. National vital statistics reports. 2015; 64.

2) Sellmer A, Bjerre JV, Schmidt MR et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. Arch Dis Child Fetal Neonatal Ed. 2013; 98: F505-F510

3) Miao CY, Zuberbuhler JS, Zuberbuhler JR. Prevalence of congenital cardiac anomalies at high altitude. J Am CollCardiol. 1990; 12: 224-228

4) Merritt TA, Harris JP, Roghmann K, et al. Early closure of patent ductus arteriosus in very low-birth weight infants: a controlled trial. J Pediatr. 1981; 99: 281-286

5) Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate. 1980; 38: 96-100

6) Bancalari E, Claure N, Gonzalez A. Patent ductus arteriosus and respiratory outcome in premature infants. Biol Neonate. 2005; 88: 192-201

7) Van Overmeire B, Smets K, Lecoutere D et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med. 2000; 343:674 -681

8) Hamrick SEG, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics . 2010; 125: 1020-1030

9) Mahony L, Carnero V, Brett C, et al. Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birth-weight infants. N Engl J Med. 1982; 306: 506-510

10) Chevalier RL. Developmental renal physiology of the low birth weight pre-term newborn. J Urology. 1996; 156: 714-719

11) Drukker A. The adverse renal effects of prostaglandin- synthesis inhibition in the fetus and the newborn. Paediatr Child Health. 2002; 7: 538-543

12) Guignard JP. The adverse renal effects of prostaglandin-synthesis inhibitors in the newborn rabbit. SemPerinatol. 2002; 26: 398-405

13) Betkerur MV, Yeh TF, Miller K, et al. Indomethacin and its effects on renal function and urinary kallikrein excretion in premature infants with patent ductus arteriosus. Pediatrics. 1981; 68:99-102

14) Akima S, Kent A, Reynolds GJ, et al. Indomethacin and renal impairment in neonates. PediatrNephrol. 2004; 19: 490-493

15) Ojala R, Ala-Houhala M, Ahonen S et al. Renal follow up of premature infants with and without perinatal indomethacin exposure. Arch Dis Child Fetal Neonatal Ed. 2001; 84: F28-F33

16) Mammen C, Al Abbas A, Skippen P et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis. 2012; 59: 523-530

17) Shaw NJ, Brocklebank JT, Dickinson DF, et al. Long-term outcome or children with acute renal failure following cardiac surgery. Int J Cardiol. 1991; 31: 161-165

18) Slack R, Hawkins KC, Gilhooley L, et al. Long-term outcome of meningococcal sepsis-associated acute renal failure. PediatrCrit Care Med. 2005; 6: 477-479

19) Goldstein SL, Devarajan P. Progression from acute kidney injury to chronic kidney disease: a pediatric perspective. Adv Chronic Kidney Dis. 2008; 15: 278-283

20) Rodrigues MM, Gomez AH, Abitbol CL, et al. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. Pediatr Dev Pathol. 2004; 7: 17-25

21) Sutherland ME, Gubhaju L, Moore L, et al. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. J Am SocNephrol. 2011; 22: 1365-1374

22) Sahu R, Pannu H, Yu R, et al. Systemic hypertension requiring treatment in the neonatal intensive care unit. J Pediatr. 2013; 163: 84-88

23) Blowey DL, Duda PJ, Stokes P, et al. Incidence and treatment of hypertension in the neonatal intensive care unit. J Am SocHypertens. 2011; 5: 478-483

24) Mehta SK, Younaszai A, Pietz J, et al. Pharmacological closure of the patent ductus arteriosus. Images PaediatrCardiol. 2003; 5: 1-15.

25) Harkin P, Harma A, Aikio O et al. Paracetamol accelerates closure of the ductus arteriosus after premature birth: a randomized trial. J Pediatr. 2016; 177: 72-77

26) Oncel MY, Yurttutan S, Erdeve O et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Pediatr. 2014; 164: 510-514

27) Nadir E, Kassem E, Foldi S, et al. Paracetamol treatment of patent ductus arteriosus in preterm infants. J Perinatol. 2014; 34: 748-749

28) Filler G, Yasin A, Medeiros M. Methods of assessing renal function Pediatr Nephrol. 2014;29: 183-192