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Original Research

Incidence, risk and risk factors for acute kidney injury associated with the use of intravenous indomethacin in neonatal patent ductus arteriosus: A 16-year retrospective cohort study

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Abstract

Background: Intravenous indomethacin has been used in infants for many years as the pharmacological closure of ductus arteriosus, but the incidence, risk, and risk factors of acute kidney injury (AKI) among infants treated with indomethacin, were still scarce. **Objectives:** To determine the incidence, risk, and risk factors of AKI among infants treated with indomethacin (exposed group) for patent ductus arteriosus (PDA) closure compared with the matched non-exposed infants. **Methods:** A matched retrospective cohort study of infants admitted to the neonatal intensive care unit of Songklanagarind Hospital from January 2003 to December 2018 was performed. All data were collected from computerized medical records. A non-exposed infant was matched (1:1) by gestational age and birth weight to each exposed infant. AKI, the outcome of interest, was diagnosed according to neonatal AKI definitions. The incidence (95% CI) of AKI was estimated for each group. Conditional logistic regression was used to estimate the odds ratio (OR) of developing AKI among those who received indomethacin compared with those who did not, adjusted for potential confounders (concomitantly used nephrotoxic potential medications including aminoglycosides, amphotericin B, vancomycin, furosemide, systemic corticosteroids, and systemic vasopressors and inotropes). Kaplan-Meier estimate was performed to examine probability of recovery from AKI after AKI events. **Results:** The matching resulted in 193 pairs of exposed and non-exposed infants. The incidences [95% CI] of AKI in the exposed and the non-exposed group, were 33.7% [27.0%:40.4%] and 15.5% [10.4%:20.7%], respectively. Indomethacin statistically increased the risk for developing AKI, crude OR 2.94[95%CI 1.77:4.90], McNemar's chi square p<0.001, and adjusted OR 2.73 [95%CI 1.55:4.80], p=0.001. The risk of AKI associated with potentially nephrotoxic medications were inconclusive. Time to recovery from AKI was relatively rapid, median recovery time was 3 days in both groups and all infants who developed AKI recovered within 6 days. **Conclusions:** The incidence of AKI among infants treated with indomethacin for PDA closure were doubled that in the indomethacin-nonexposed infants. Indomethacin significantly increased the risk of AKI, while the risk associated with other concomitant nephrotoxic medications were inconclusive. Transient nephrotoxicity associated with indomethacin should be balanced with the risk associated with delayed PDA closure. All infants receiving indomethacin should be routinely monitored for serum creatinine and/or urine output, throughout the treatment and one to two weeks after treatment cessation. Alternatives with better renal safety profiles should be considered in the population with higher risk of AKI.

Keywords

Acute Kidney Injury; Cohort Studies; Indomethacin; Infant; Ductus Arteriosus, Patent; Renal Insufficiency

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INTRODUCTION

Patent ductus arteriosus (PDA) is a common congenital cardiovascular condition of prematurity. PDA occurs in an infant when a fetal vascular structure known as the ductus arteriosus (DA) fails to close soon after birth.[1] The incidence of a hemodynamically significant PDA (hsPDA) is as high as 70% in infants born at 23–24 weeks and 59% in those born at 25–28 weeks.[2] Infants with PDA are at increased risk of bronchopulmonary dysplasia, necrotizing enterocolitis, pulmonary edema, intracranial hemorrhage, and mortality.[1]

No evidence-based guidelines on optimal medication for PDA treatment is available. Pharmacological treatment using non-steroidal anti-inflammatory drug (NSAID) is the mainstay for PDA closure. NSAIDs suggested for PDA closure are intravenous (IV) indomethacin and IV ibuprofen.[3] IV ibuprofen lysine is available in some countries, thus limits its use in many developing countries including Thailand. Hence, IV indomethacin has been used in infants for many years as the pharmacological

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closure of PDA, with the overall rates of PDA closure approximately 75.0–95.0%.[3,4]

Despite its higher rates of PDA closure, indomethacin has been shown to cause higher adverse renal effects compared with ibuprofen that might limit its use, especially in this vulnerable population.[4] A decrease in glomerular filtration may proportionately reduce indomethacin renal clearance, the major route of elimination that occurs in approximately 60.0% of total clearance, and increases or prolongs the adverse effects.[5]Acute kidney injury (AKI) has been reported in 14.8-24.4% of infants treated with indomethacin.[6–10] In addition, AKI has been revealed as a risk factor for future chronic kidney diseases.[11,12] However, studies assessing indomethacin nephrotoxicity were limited in sample size, length and intensity of follow-up, variations in AKI definitions, study population, and study designs.[7,13–15] Several studies measured changes in serum creatinine and/or urine output without AKI determination. In addition, studies examining potential risk factors associated with AKI, such as gestational age, birth weight, presence of an umbilical artery catheter, clinical risk index for babies (CRIB) score, numbers of NSAID doses, and concomitant nephrotoxic potential medications, etc., in infants with PDA who received pharmacological treatment were still scarce and inconclusive.[16,17] Low gestational age and low birth weight are strongly related to kidney maturation and vulnerability to nephrotoxicity. Gestational age < 28 weeks was strongly associated with AKI in very low birth weight (VLBW) infants (OR 10.6, 95% CI 6.8:16.7).18 In addition, incidences of severe AKI during hospital course were related to gestational age i.e., 27.8%, 21.9%, 13.6%, and 9.4% for the 24-, 25-, 26-, and 27-week gestational age groups, respectively.19 An incremental 100 g in birth weight reduced AKI risk by 19% (OR 0.81, 95% CI 0.70:0.9). The matched retrospective cohort was designed to compare the incidence of AKI in the matched infants treated with indomethacin for PDA closure with the matched indomethacin non-exposed infants. Furthermore, the study aimed to examine the risk of AKI associated with indomethacin, controlling for the two most important risk factors (gestational weight and birth weight) used as matching variables, and to identify risk factors of AKI in this population.

METHODS

Design

This study used a matched retrospective cohort design. The study protocol was approved by the Ethics Committee Board of the Faculty of Medicine, Prince of Songkla University (REC.62-102-19-6).

Setting and study population

This study was conducted at the level IV neonatal intensive care unit (NICU) of Songklanagarind Hospital, a university-affiliated teaching hospital at Prince of Songkla University, Thailand. All infants admitted to the NICU between January 2003 and December 2018 who had a normal kidney function at baseline were the accessible population. Data were collected from computerized medical records of Songklanagarind Hospital. All diagnoses were recorded according to the International Classification of Diseases 10th revision (ICD-10). Infants were excluded if they were diagnosed prior to the study entry with congenital renal anomalies or congenital heart anomalies or receiving NSAIDs other than indomethacin or no baseline serum creatinine. The exposed group included infants diagnosed with PDA who received at least one dose of indomethacin for the treatment of PDA. The non-exposed group included infants with or without PDA who were not treated with indomethacin. A non-exposed infant was matched to each exposed infant based on gestational age (categorized as extremely preterm, very preterm, moderate/late preterm and term classified by the WHO) and birth weight (categorized as extremely low birth weight (ELBW), very low birth weight (VLBW), low birth weight (LBW), and normal, according to the CDC guidelines).[20,21] Diagnosis of PDA and PDA closure. Echocardiography was used to confirm the diagnosis of PDA in all infants. The criteria for diagnosis of a hsPDA were ductal size >1.5 mm, left atrial aortic root ratio (LA:Ao) >1, and left-to right shunting of blood.[3]

Sample size

The sample size was calculated based on the assumed AKI incidence of 6.3% in the non-exposed group and 2.5 folds AKI incidence in the exposed group.[9]The exposed infants and the non-exposed infants were matched 1:1. At a significance level of 0.05, a power of 80.0%, the study required at least 169 exposed infants and 169 non-exposed infants for the precise estimation of the AKI incidence and the AKI incidence rate ratio. To improve the precision of the estimates, this study performed matching selection for all exposed infants who met the selection criteria.

Data collection

Exposure data. The prescribed dose and duration of indomethacin were recorded in the computerized medical records by the neonatologists. Indomethacin administration was performed at the NICU and recorded in the computerized medication administration records. The exposed group included infants received at least one dose of indomethacin for the treatment of PDA. The number of indomethacin doses and time of drug administration were collected for each exposed infant. Ascertainment of exposure status was done prior to retrieving the outcome data, therefore prevented selection bias.

Outcome data. AKI was defined according to the current neonatal AKI definitions i.e. using either serum creatinine-based criteria or urine output-based criteria that incorporated the 7-day window of the absolute

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increase over baseline of serum creatinine and/or urine output.[22] Each exposed infant was collected serum creatinine and urine output at baseline (prior to receiving indomethacin) and on day 1, 2, 3, 4, 5, 6, 7 and 30 or at discharge. Sample collection time points were designed based on indomethacin induced AKI that usually occurs within 1-2 weeks of use.[6–8,10] Serum creatinine levels and urine output of the non-exposed infant were collected in the same manner as his/her matched exposed infant. Onset, offset, duration, and severity of AKI were determined. Severity of AKI was graded according to neonatal AKI definitions.[22]

Potential confounders. Known nephrotoxic potential medications including aminoglycosides (amikacin or gentamicin), amphotericin B, vancomycin, furosemide, systemic corticosteroids (dexamethasone or hydrocortisone), and systemic vasopressors and inotropes (adrenaline, dobutamine, dopamine, milrinone, and noradrenaline) were extracted.

Statistical analysis

Descriptive statistics were used to analyze the demographic data. As imbalanced distributions of several predictors (confounders) might be found in observational studies, some comparisons were performed. Categorical variables were compared using chi-squared test or Fisher's exact test when appropriate. Continuous variables were analyzed using Student's *t*-test or Mann-whitney U test, where appropriate. Incidence (95% CI) of AKI in the exposed and the non-exposed groups were estimated. A matched data contingency 2x2 table of exposure to indomethacin and development of AKI was presented and McNemar's statistic was performed. Univariate analyses of the matched data were done to identify potential risk factors of AKI i.e., individual concomitantly used nephrotoxic medications. These included aminoglycosides (amikacin or gentamicin), furosemide, vancomycin, systemic corticosteroids (dexamethasone or hydrocortisone), and vasopressors and inotropes. Variables with p-values ≤ 0.2 were considered potential risk factors and further examined in multivariate analysis using conditional logistic regression to estimate the risk of AKI associated with indomethacin, adjusted for other risk factors. The p-value of <0.05 were considered statistical significance. The dose-response relationship between indomethacin and AKI was examined. Indomethacin doses were categorized as overall number of doses ≤ 1 course or more than one course of the three-dose course. Kaplan-Meier failure estimate was performed to examine the probability of recovery from AKI after AKI events. All statistical analyses were performed using STATA program, version 15.0, Stata Corporation, Texas, USA.

RESULTS

There were 4,967 infants admitted to the NICU from 1

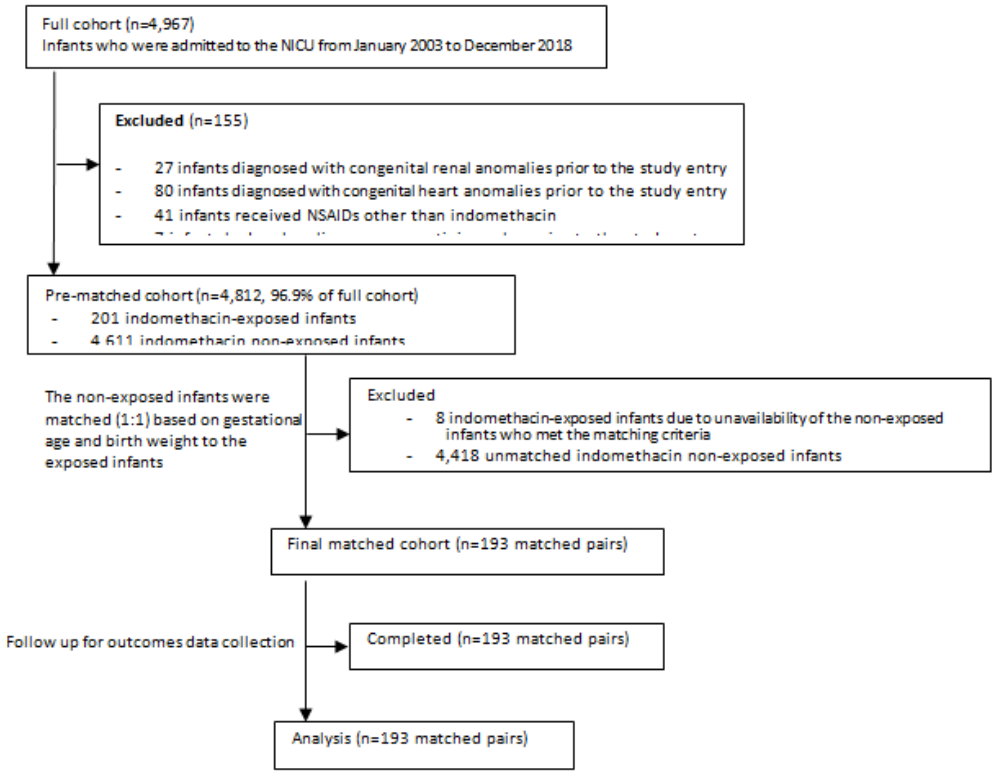

Figure 1. Flow diagram of study participants

Table 1. Baseline characteristics of matched exposed infants and matched non-exposed infants

Characteristic	Matched exposed infants	Matched non-exposed infants	p-value[a]
	n = 193	n = 193	
Sex, n (%)			
Female	105 (54.4)	81 (42.0)	0.014
Gestational age (weeks), mean (SD)	30.2 (SD=3.0)	30.5 (SD=3.2)	
Extremely preterm, n (%)	36 (18.7)	36 (18.7)	
Very preterm, n (%)	96 (49.7)	96 (49.7)	
Moderate/late preterm, n (%)	55 (28.5)	55 (28.5)	
Term, n (%)	6 (3.1)	6 (3.1)	
Birth Weight (g), median (IQR)	1,300 (1,080-1,700)	1,335 (1,060-1,610)	
Kidney function status at entry			
Serum creatinine (mg/dL), median (IQR), [range]	0.7 (0.5-0.9), [0.1-1.4]	0.7 (0.5-0.9), [0.2-1.4]	0.576[c]
Urine output criteria (ml/kg/hr), mean (SD), [range]	3.9 (SD=1.3), [1.1-6.9]	4.0 (SD=1.2), [1.0-7.6]	0.527[b]
Comorbidity, n (%)	193 (100.0)	193 (100.0)	1.000
Respiratory distress syndrome	145 (75.1)	125 (64.8)	0.026
Neonatal jaundice	123 (63.7)	107 (55.4)	0.097
Bacterial sepsis of newborn	92 (47.7)	105 (54.4)	0.186
Apnea of prematurity	75 (38.9)	77 (39.9)	0.835
Birth asphyxia	40 (20.7)	38 (19.7)	0.800
Bronchopulmonary dysplasia	43 (22.3)	30 (15.5)	0.091
Necrotizing enterocolitis	35 (18.1)	44 (22.8)	0.256
Intraventricular hemorrhage	33 (17.1)	36 (18.7)	0.690
Persistent pulmonary hypertension of the newborn	25 (13.0)	21 (10.9)	0.530
Meconium aspiration syndrome	1 (0.5)	3 (1.6)	0.315
Clinical risk index for babies (CRIB) score, median (IQR)	1 (0-4)	1 (0-3)	0.028[c]
Mechanical ventilation, n (%)	191 (98.9)	150 (77. 7)	<0.001
Concomitant nephrotoxic potential medications, n (%)			
Furosemide	122 (63.2)	101 (52.3)	0.030
Vasopressors and inotropes[d]	91 (47.2)	86 (44.6)	0.610
Amikacin	80 (41.4)	85 (44.0)	0.607
Gentamicin	76 (39.4)	83 (43.0)	0.469
Vancomycin	8 (4.2)	33 (17.1)	<0.001
Dexamethasone	8 (4.2)	7 (3.6)	0.792
Hydrocortisone	3 (1.6)	7 (3.6)	0.200
Amphotericin B	1 (0.5)	4 (2.1)	0.177

Abbreviation: IQR = interquartile range

[a]Chi-squared test, [b]Student's *t*-test, [c]Mann-Whitney *U*-test, [d]systemic adrenaline, dobutamine, dopamine, milrinone, and noradrenaline.

January 2003 to 31 December 2018. From 201 exposed infants and 4,611 non-exposed infants that met the selection criteria, the matching resulted in 193 matched pairs (Figure 1). Only 51 (26.4%) of matched non-exposed infants had PDA, most of them were asymptomatic PDA.

Demographic and baseline characteristics are presented in Table 1. As the exposed infants were matched (1:1) to the non-exposed infants according to gestational age and birth weight, these two variables were nicely balanced between groups. Both extremely preterm and VLBW were at high risk for neonatal AKI, matching based on these two factors therefore prevented confounding. The mean (SD) of gestational age for the exposed and the non-exposed groups were 30.2 (SD=3.0) and 30.5 (SD=3.2) weeks, respectively. The respective median (IQR) of birth

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Table 2. The matched pair 2x2 results of exposure to indomethacin and development of AKI

		Exposed to indomethacin		
		AKI[a]	No AKI	Total
Not exposed to indomethacin	AKI[a]	12	18	Incidence 30 (15.5% [95%CI 10.39:20.70])
	No AKI	53	110	163
	Total	Incidence 65 (33.7% [95%CI 26.95:40.40])	128	193
		OR 2.94 [95%CI 1.73:5.03], McNemar's chi square p<0.001		

Abbreviation: AKI = acute kidney injury
[a] Serum creatinine or urine output criteria

Table 3. Severity of AKI in the exposed and the non-exposed groups

Acute kidney injury[a]	**Exposed group**	**Non-exposed group**
	n = 193	**n = 193**
Overall AKI by serum creatinine criteria, n (%)	61 (31.6)	26 (13.5)
Stage 1	47 (24.4)	17 (8.8)
Stage 2	12 (6.2)	5 (2.6)
Stage 3	2 (1.0)	4 (2.1)
Overall AKI by urine output criteria, n (%)	14 (8.0)	7 (4.1)
Stage 1	7 (3.6)	4 (2.1)
Stage 2	1 (0.5)	0 (0.0)
Stage 3	6 (3.1)	3 (1.6)

Abbreviation: AKI = acute kidney injury
[a]Severity of AKI was graded according to neonatal AKI definitions.[22]

Table 4. Crude and adjusted ORs of factors associated with AKI

Explanatory variable	**Crude OR[a] [95% CI]**	**p-value**	**Adjusted[b] OR [95% CI]**	**p-value**
Indomethacin use	2.94 [1.73:5.03]	<0.001	2.73 [1.55:4.80]	0.001
Concomitant drug use[c]				
Aminoglycosides	1.50 [0.72:3.11]	0.277		
Corticosteroids	1.00 [0.06:15.99]	1.000		
Furosemide	2.08 [1.05:4.15]	0.037	1.80 [0.81:3.98]	0.150
Vancomycin	0.17 [0.02:1.38]	0.097	0.25 [0.02:2.58]	0.243
Vasopressors and inotropes	1.90 [0.88:4.09]	0.100	1.99 [0.77:5.15]	0.155

[a]Univariate conditional logistic regression

[b]Conditional logistic regression; OR adjusted for covariates i.e. concomitant drug use.

[c]Concomitant drug use: aminoglycosides (amikacin or gentamicin); systemic corticosteroids (dexamethasone or hydrocortisone); systemic vasopressors and inotropes (adrenaline, dobutamine, dopamine, milrinone, or noradrenaline).

weight were 1,300 (1,080-1,700) g and 1,335 (1,060-1,610) g. Two-thirds of infants were very preterm or extremely preterm. Approximately half of the matched infants were VLBW (< 1,500 g). Baseline kidney function of infants was similar in both groups, and all infants had normal kidney function at baseline. Several comorbidities related to preterm birth were similar between groups. As approximately one-fifth of infants included were born at gestational age < 28 weeks, these might be at high risk of severe intraventricular hemorrhage (IVH) that might be closely related to hemodynamic changes caused by PDA. Respiratory distress syndrome was the most common comorbidity, with the higher percentage among the exposed infants than the non-exposed infants (75.1% vs 64.8%, respectively, p=0.026), all were managed using mechanical ventilation. Despite statistical difference of the CRIB score between the two groups, it seemed not clinically relevant.

Indomethacin for PDA therapy is recommended as a three-dose course, i.e., three doses of 0.2 mg/kg given intravenously every 12 or 24 h, a maximum of two

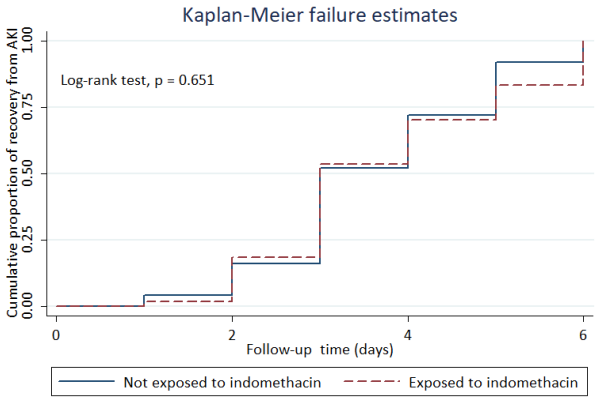

Figure 2. Cumulative proportion of recovery from AKI after AKI events

courses could be considered if required. One hundred and twenty-five (64.8%) infants received a three-dose course of indomethacin. Thirty-six (18.7%) received more indomethacin doses than the recommended three-dose course. The remainders 32 (16.6%) received one dose or

two doses of indomethacin, which were less than that recommended for PDA therapy. Early discontinuation was related to indomethacin adverse effects. The days of life while receiving the first dose of indomethacin, mean (SD) was 6.1 (SD=6.8) days, and median (IQR) was 4 (2-8) days. PDA closure rate was not determined in this study. The use of other concomitant medications in both groups was similar, except furosemide that was more frequently used and vancomycin that was less frequently used in the exposed group compared with the non-exposed group. Furosemide, vasopressors and inotropes, and aminoglycosides (amikacin and gentamicin) were commonly used in both groups.

The incidence of AKI was 33.7% [95%CI 26.95:40.40] in the exposed group and 15.5% [95%CI 10.39:20.70] in the non-exposed group (Table 2). Regarding diagnosis of AKI, serum creatinine-based criteria was much higher sensitive than the other. Among the exposed group, serum creatinine-based criteria detected 61/65 (93.8%) of all diagnosed AKI, while urine output criteria did only 14/65 (21.5%). These figures among the non-exposed infants were 26/30 (86.7%) and 7/30 (23.3%), respectively (Table 3). The number (%) of infants positive for AKI diagnoses by both criteria were 10 (15.3%) for the exposed group and 3 (10%) for the other group. The onset time of AKI, defined as time from indomethacin initiation to time at diagnosis of AKI, mean (SD) [range] for the exposed group was 3.2 (SD=1.7) [1-7] days, while that of the non-exposed was 3.0 (SD=1.8) [1-7] days. Most of AKI in both groups were mild in severity. High discrepancies were observed on severity gradings obtained from the two methods (serum creatinine-based and urine output-based criteria). Among infants positive for AKI by both methods the kappa value of severity grading was 0.052, p=0.387. Urine output-based criteria tended to give a higher degree of AKI severity (7 out of 13 cases identified by both diagnostic criteria). Poor agreement between the two methods was probably explained by variations or fluctuations in the measured values (creatinine level or urine output) that might be affected by several factors including physiologic change, concomitant medications/ treatment, hydration status, and time of serum creatinine measurement, etc.

Time to recovery from AKI was measured from the onset of AKI to the time the kidney function was normalized. Relatively rapid recovery from AKI was found in most infants (median recovery time was 3 days in both groups (Figure 2). Kaplan-Meier curves showed similar recovery rates in both groups, log-rank test p=0.651. Within 5 days after AKI onset, 45/54 (83.3%) of the exposed infants and 23/25 (92.0%) of the non-exposed infants recovered. Data revealed that all AKI recovered within 6 days after the onset. Rapid recovery from AKI should limit renal damage, nephrogenesis, and long-term consequences after indomethacin therapy in PDA infants. Among exposed infants who developed AKI, time from indomethacin initiation to AKI recovery ranged from 2 to 12 days (mean 6.5 days). While those non-exposed infants who developed AKI, time from study entry to AKI recovery ranged from 2 to 10 days (mean 6.2 days). Renal function monitoring up to 2 weeks after indomethacin initiation is suggested.

Indomethacin significantly increased the risk of AKI, matched crude OR 2.94 [95%CI 1.73:5.03] McNemar's chi square p<0.001 (Table 2), which was slightly decreased after adjusted for other confounding factors, adjusted OR 2.73 [95%CI 1.55:4.80], p=0.001 (Table 4). The dose-response relationship was examined. Compared with the non-exposed infants, the adjusted OR 2.48 [95%CI 1.34:4.58], p=0.004 among infants receiving indomethacin at the dose not greater than one course of the three-dose course recommended for PDA treatment (3 doses of 0.2 mg/kg given every 12 h or 24 h) was found. The corresponding adjusted OR was 4.20 [95%CI 0.88:19.90], p=0.071, among infants receiving indomethacin more than one course of the three-dose course compared with the non-exposed infants, however, the association was marginal as it was examined in a relatively small sample (36 matched-pairs).

Factors associated with AKI among infants are shown in Table 4. Furosemide, and vasopressors and inotropes seemed to increase the risk of AKI, however the ORs were imprecise as the matched pairs with no information were dropped from analysis. Despite a known nephrotoxicity of vancomycin, it seemed to lower the risk of AKI, adjusted OR 0.25 [95%CI 0.02:2.58], p=0.243. The explanation might be an avoidance of vancomycin use in the exposed infants who were at higher risk of AKI.

DISCUSSION

The incidence of AKI was doubled in the exposed group compared with that of the non-exposed group. Indomethacin statistically increased the risk of AKI. The associations between AKI and other concomitant nephrotoxic medications were imprecise. Most of infants diagnosed with AKI in both groups were detected by serum creatinine-based criteria, while only one-fifth were detected by urine output-based criteria. Most AKI were mild in severity. Onset time and duration of AKI in both groups were similar.

Overall AKI incidence identified in the indomethacin exposed infants was higher than those previously reported from other observational studies (14.8-24.4%).[6–10] Inconsistent findings could be resulted from variabilities in AKI definitions, study designs, study populations, indomethacin dosing regimens, renal function monitoring intensity, and the length of follow-up.[22] Renal susceptibility to nephrotoxic agents is much dependent on gestational age at delivery as nephrogenesis

is continuously developed from week 5 to week 34 or 36 of gestation.[23] As majority of infants included in the present study were very preterm or extremely preterm and half of them were VLBW, a relatively high incidence found was not unexpected. In addition, indomethacin half-life was significantly prolonged in infants less than 32 weeks gestation.[24] Renal blood flow, 2.5% to 4% at birth, which then increased to 10% at one week after birth, was highly maintained by prostaglandins and angiotensin II.[16] Inhibition of prostaglandin synthesis by indomethacin in the first few days after birth could even lower the already low renal blood flow and impair renal function. A delay of 48-72 h in the rise of serum creatinine after a significant reduction of renal function (> 50% GFR reduction) was reported, optimal serum creatinine monitoring schedule is necessary for renal function monitoring.[16] The present study found the mean onset time of approximately 3 days (range 1-7 days) for AKI development, in both groups. Daily serum creatinine measurement from day 1 through day 7 seemed to be appropriate to detect AKI. This study was conducted in the level 4 NICU setting where renal function monitoring was intensively performed, a missed AKI diagnosis should be unlikely. Since indomethacin used for PDA closure is a short-term therapy, adverse effects on the kidneys are expected to be minimal and temporary. The present study found a mean overall time from indomethacin initiation to AKI recovery of 6.5 days (range 2-12 days), renal function monitoring up to 2 weeks after indomethacin initiation should be sufficient to monitor AKI occurrence and recovery for most infants. The finding supported the advice that regular monitoring of serum creatinine should be performed for one to two weeks after indomethacin administration.[7,8]

In the present study, 34.2% of infants were initiated indomethacin before 48 h of life. To avoid false positive diagnostic errors that might be confounded by maternal creatinine among infants in whom AKI were evaluated in the first 48 h of life, the absolute rise of ≥ 50% serum creatinine from baseline and/or urine output over the 7-day follow-up period was used. These diagnostic criteria were also applied to the matched non-exposed infants (34.2%) who were evaluated for AKI development within 48 h of life. The higher incidence reported in the present study as a result of false positive diagnostic error would be unlikely.

Indomethacin significantly increased AKI risk of 2.7-fold. The present study matched the non-exposed infants to the exposed infants based on gestational age and birth weight, therefore these two variables were nicely balanced and thus did not confound the association between indomethacin exposure and AKI. The elevated risk of AKI in PDA infants treated with NSAIDs including indomethacin or ibuprofen, the adjusted RR 1.63 [95%CI 1.04:2.56], p=0.04 was lower than that reported by the present study.[8] The risk estimate might be diluted by ibuprofen use. Limited evidence demonstrated that furosemide had no renal beneficial effects but significantly increased incidence of acute renal failure.[25,26] In the present study, furosemide was prescribed more often in the exposed infants, the increased risk of AKI associated with furosemide was however not significant after being adjusted for other risk factors.

Likewise, vasopressors and inotropes seemed to increase the AKI risk, the association was still imprecise. A retrospective cohort study conducted by Constance et al., reported a significantly increased risk of AKI in PDA infants treated with vasopressors (RR 2.5 [95%CI 1.20:5.30], p= 0.01).[8] Vasopressors have been recommended for the management of episodes of shock which often precede neonatal AKI. Data on indomethacin-vasopressors and inotropes associated with AKI remains controversial and scarce. Controversial findings might be partially explained by dose-dependent effects of dopamine on kidney. At low-to-medium dose (1-15 mcg/kg/min), might reduce the risk of AKI. While dopamine at high-dose (20-50 mcg/kg/min) might increase the risk.[27,28] The present study, however did not find the dose-dependent effects (data not shown).

In the present study, vancomycin was used in a small number of infants, and less frequently used among indomethacin-exposed infants with PDA. A previous study reported that indomethacin coadministration reduced vancomycin clearance by 55% that might increase the risk of vancomycin nephrotoxicity.[29] Despite its potential nephrotoxicity, the present study found vancomycin seemed to lower the risk of AKI, this might explain an avoidance of vancomycin in these vulnerable indomethacin-exposed infants who were at increased risk of AKI.

As mentioned earlier that the risk of AKI associated with NSAIDs was dose dependent. The dose-response relationship was examined. Compared with the non-exposed infants, the adjusted OR 2.48 [95%CI 1.34:4.58], p=0.004 among infants receiving indomethacin at the dose not greater than one three-dose course (3 doses of 0.2 mg/kg given at 12 h or 24 h dosing interval) was found. The corresponding adjusted OR 4.20 [95%CI 0.88:19.90], p=0.071 in infants receiving indomethacin more than one three-dose course. This might demonstrate the dose-response relationship, although the latter association was still imprecise. The lowest effective dose of indomethacin is recommended for PDA closure.

This study has several strengths. Firstly, it determined the incidence of AKI in infants treated with indomethacin for PDA closure, using the most recent neonatal AKI definition.[22] This could help predict the magnitude of clinical consequence unless effective care were used. Secondly, a relatively large cohort of infants admitted to the level 4 NICU over 16-year practice allowed the

researchers to conduct a matched design that would give rise to a valid and conclusive finding on the risk of AKI associated with indomethacin treatment among PDA infants. Exclusion of infants diagnosed with congenital renal anomalies or with congenital heart anomalies prior to sample selection could prevent confounding as these infants might be at higher risk for developing AKI. In addition, if these conditions were contraindicated to nephrotoxic medications including indomethacin, it could lead to selection bias. Thirdly, all required data, such as patients' medical history, laboratory examination results, medication administration records, ultrasound and imaging study results, etc. were conveniently and completely retrieved from the hospital computerized medical record database that could eliminate errors in data extraction, and prevent misclassifications of the exposure and the outcome data. Fourthly, identification of exposure status was done prior to retrieving the outcome data, therefore prevented selection bias. In addition, actual doses of indomethacin given to each exposed infant were determined and a dose-response relationship has been found. All included infants were admitted to the NICU, where laboratory and clinical data required for diagnosis of AKI, the outcome of interest, were intensively and evenly performed in all infants in both groups, diagnostic suspicion bias would be unlikely. The results of this study are valid and well generalizable to the target population. The results confirmed transient nephrotoxicity of indomethacin among PDA-treated patients, that should be balanced by its high efficacy in PDA closure.[30] In addition, development of better AKI surveillance protocols and AKI mitigation strategies is essential to improve care for these vulnerable patients. Alternative pharmacological treatments for PDA closure with better safety profile have been investigated. Randomized controlled trials comparing IV paracetamol, IV indomethacin, and IV ibuprofen found a significantly less renal impairment in those treated with paracetamol compared with indomethacin or ibuprofen with a comparable efficacy for PDA closure.[3,31]

Despite these strengths, some limitations were acknowledged. Firstly, infants were seldom used indwelling urinary catheters, measurement of urine output was based on diaper weighing. Diaper weighing might lead to an underestimation if the infants had diarrhea or overestimation in the case of urine evaporation from radiant warmers.[20,36] However, chance variation in urine output measurement should not affect the incidence estimation of AKI using urine output-based criteria. Secondly, this study could not rule out confounding by severity as infants with more severe PDA (hsPDA) were likely to be treated with indomethacin. Confounding by severity might overestimate the risk associated with indomethacin. In contrary, infants contraindicated for indomethacin treatment might be at high risk of AKI, and could be included in the non-exposed group, though the possibility was low. Thirdly, non-exposed infants were matched regarding gestational age and birth weight to the exposed infants, the effects of these two factors on AKI could not examined in the present study. Lastly, although this study provided the precise estimation of the risk of AKI associated with indomethacin, it still lacked of power to detect the risk associated with other confounders. Further well-designed researches with larger sample sizes are needed.

CONCLUSION

One-third of infants receiving indomethacin for PDA closure developed AKI. Infants with PDA who received indomethacin treatment increased 2.7-fold AKI risk compared with infants who did not. All infants receiving indomethacin should be routinely monitored for at least one or two weeks on kidney function. Transient nephrotoxicity associated with indomethacin should be balanced with the risk associated with delayed PDA closure. Alternatives with better renal safety profiles should be considered in the population with higher risk of AKI. The risk of AKI associated with concomitant nephrotoxic medication, as well as long-term renal adverse effects should be investigated.

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CONFLICTS OF INTEREST

None.

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