Acute kidney injury among preterm infants receiving non-steroidal anti-inflammatory drugs for patent ductus arteriosus

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAID) are a frequently prescribed class of medication in the neonatal intensive care unit (NICU). Hospitalized patients receiving NSAID therapy are at an increased risk of acute kidney injury (AKI). Our primary objective was to reveal AKI epidemiology in NSAID-exposed premature infants admitted to the NICU using a standardized definition.

Methods: This retrospective study included infants born at ≤34 weeks gestational age who received NSAID for intraventricular haemorrhage prophylaxis ["prophylaxis group"] or symptomatic treatment for patent ductus arteriosus (PDA) ["treatment group"] between January and December 2014 at British Columbia Women's Hospital NICU. All available serum creatinine (SCr) and 12-hour urine output (UO) were recorded from admission till day 7 post NSAID exposure. AKI incidence was determined using the modified Kidney Disease: Improving Global Outcomes (KDIGO) classification with an increase in SCr (ΔSCr) (50% rise from prior SCr within 7 days or 26.5 mmol/L rise within 48 hours) and/or UO < 1 mL/kg/hour, excluding the first 24 h of life.

Results: We identified 70 eligible subjects, 32 of whom received prophylactic NSAID (prophylaxis group), and 38 received indomethacin or ibuprofen for treatment of symptomatic PDA (treatment group), with an overall AKI incidence of 23% (16/70). The treatment group had a higher proportion of infants with SCr monitoring during the NSAID than the prophylaxis group (87% vs. 13%, $p<0.001$). Based upon the above defined criteria (fulfilling at least one—either the UO or SCr monitoring criteria), the prophylaxis group had a significantly lower AKI rate compared with the treatment group (9% vs. 34%; $p=0.014$).

Conclusions: AKI incidence is higher in infants treated with NSAID for symptomatic PDA than in those treated prophylactically during the first day of life, based on the criteria applied. However, the burden of AKI may be underestimated in the prophylaxis group due to fewer available SCr values after exposure, and inability to utilize UO criteria in the 1st 24 hours of life. Standardized protocols for monitoring daily SCr and UO after exposure should be implemented for all neonates with NSAID exposure and should be considered to improve AKI recognition.

Background

Neonatal acute kidney injury (AKI) occurs in 40–70% of critically ill neonatal intensive care admissions, depending on the adopted definition and study population [1-5]. Neonatal AKI is independently associated with increased mortality and higher rates of chronic kidney disease in survivors [4, 6]. Preterm infants carry fewer functional nephrons as nephrogenesis is not complete between weeks 34 and 36 of gestational age (GA), which increases their susceptibility to renal impairment [7]. At the same time, they are also susceptible to hemodynamic alterations and nosocomial infections, and thus increased exposures to multiple nephrotoxic medications [4, 8].

Hemodynamically significant patent ductus arteriosus (PDA) is a common early cardiovascular problem in preterm infants. It has been found that 54% of extremely preterm infants (born at <29 weeks GA) in

Canada had signs of a PDA and 60% of those who had signs of a PDA required medical or surgical treatment[9]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed to preterm infants for two indications: 1) intraventricular haemorrhage (IVH) prophylaxis, aiming to reduce the probability of developing severe IVH [10] and 2) to control the heart failure symptoms related to patent ductus arteriosus [11]. Despite years of research, consensus has not been reached on the most optimal timing and modality of treatment for PDA [12]. Prostaglandins are needed to keep the afferent arteriole open in a vasoconstrictor dominant milieu and blocking prostaglandins with NSAIDs potentially reduces renal blood flow, resulting in an increased risk of AKI.

There is a paucity of data describing the relationship between NSAID treatment and development of AKI, specifically in preterm populations. Our primary objective was to compare the incidence of AKI in those infants exposed to NSAIDs for IVH prophylaxis versus for symptomatic treatment of PDA, using a standardized neonatal AKI definition. Due to practice variation of renal function monitoring of premature infants, we also determined the percentage of NSAID exposed patients with adequate serum creatinine (SCr) monitoring required to diagnose AKI confidently according to standardized criteria.

Methods

Study Population

We conducted a single centre retrospective cohort study at the British Columbia Women's Hospital (Vancouver, Canada), which has a 60-bed tertiary neonatal intensive care unit, with an annual admission of approximately 1400 infants. We included all infants born at ≤34 weeks of GA, who received NSAID (indomethacin and/or ibuprofen intravenously) as per our institution's standard of care. Infants who had underlying urinary tract anomalies diagnosed on antenatal ultrasound or other major congenital anomalies, including those with known syndromal or chromosomal disorders, were excluded. Demographics of patients, SCr values, timing and dosage of NSAID, and daily UO were obtained from medical records. Ethics approval was obtained from the University of British Columbia Children's and Women's Research Ethics Board. [H15-00939], and the study was carried out in accordance with relevant guidelines and regulations. The source of the clinical data was the patient's medical records, and individual written informed consents were waived by the same committee.

Study groups

Infants were grouped into two categories: 1) "Prophylaxis group": Those who received indomethacin prophylactically for IVH, and 2) Infants receiving indomethacin for symptomatic treatment of PDA ("Treatment group"). In the prophylaxis group, infants received IV indomethacin at 0.1 mg/kg Q24H for 3 days, with the first dose within the first 24 hours of life. Infants requiring symptomatic treatment received 0.4 and 0.6 mg/kg of indomethacin administered over 36 h for infants within and after one week of life, respectively. As there is no unified protocol in our unit, eligibility for indomethacin prophylaxis was at the discretion of the attending physician on admission.

Variable definitions

AKI was defined using a modified version of the Kidney Disease Improving Global Outcomes (KDIGO) UO and SCr criteria, as published in several recent neonatal AKI studies [13]. There are no existing monitoring protocols for renal function in relation to NSAID prescription in our neonatal intensive care unit (NICU). Available SCr and average 12-h UO were recorded from admission to the 7th day post NSAID exposure. Infants with SCr increase of 1.5-fold or greater from a baseline value within 7 days, or with an absolute increase of 26.5 µmol/L (0.3 mg/dL) within 48 hours were identified with creatinine-based AKI (Stage 1 or above per modified KDIGO criteria). Baseline SCr was defined as the lowest SCr value prior to administration of indomethacin. AKI based on UO was defined as an average UO rate of less than or equal to 1 mL/kg/h over at least 12 h (Stage 1 or above per modified KDIGO criteria). We only assessed UO from the 2nd day of life and onwards due to the variability in the onset of urine production in a newborn and the high likelihood of mixing a significant amount of meconium on their first day. As preterm infants rarely require urinary catheterization in the first week of life, diaper weight was measured as an approximate estimation of hourly UO. Day of life refers to the calendar day after birth (i.e. day 1 refers to day of birth). “Adequate SCr monitoring” referred to the presence of measurements prior to exposure and at least one post-exposure SCr value within 7 days post NSAID exposure. We calculated the maximum weight change, defined as the maximum percent increase in daily weight from baseline within one week of NSAID administration, with baseline weight defined as the weight on day 1 of treatment administration.

Statistical analysis

SPSS 25.0 [Chicago, IL] was used for the statistical analysis. Descriptive statistics were used to compare and characterise patient demographic and clinical parameters. Values are expressed as means with standard deviations or medians with interquartile ranges, when appropriate. AKI incidence in each group was reported as a proportion. Chi-squared analysis or Fisher’s Exact Test, as appropriate, were used to compare AKI incidence and other parameters between the prophylactic and symptomatic groups. A *p*-value of <0.05 was considered statistically significant.

Results

During the study period, we identified 70 eligible subjects, with 32 and 38 individuals receiving NSAID treatment for IVH prophylaxis and symptomatic PDA, respectively. The baseline demographic variables including maternal and neonatal aspects are summarised in Table 1, with infants in the symptomatic group having higher median GA at birth (28 vs. 26 weeks, $p<0.001$), and a lower likelihood to be exposed to antenatal steroids (27/38 [71%] vs. 30/32 [94%], $p=0.015$). Similar proportions of infants found in both the prophylaxis and treatment group also received intravenous aminoglycoside (gentamicin) during their courses of NSAID therapy (30/32 [94%] vs. 34/38 [89%], respectively).

Table 1: Baseline demographic variables and perinatal/ neonatal outcomes

	Prophylactic (n = 32)	Symptomatic (n = 38)	p-value
Gestational age (weeks), median (IQR)	26 (25 – 26.5)	28 (26.75 – 29)	<0.001
Birth weight (grams), median (IQR)	799 (665 – 931)	1020 (786 – 1025)	0.001
Small-for-gestational age, n (%)	3 (10)	4 (11)	NS
Apgar score 1 minute, median (IQR)	5 (3 – 6)	5 (2.75 – 7)	NS
Apgar score 5 minute, median (IQR)	7 (6 – 8)	7 (5 – 8.25)	NS
Apgar score 10 minute, median (IQR)	8 (7 – 9)	8 (7 – 9)	NS
Female, n (%)	15 (47)	22 (58)	NS
Inborn, n (%)	28 (88)	28 (74)	NS
Multiple gestations, n (%)	10 (31)	14 (37)	NS
Timing of first NSAID (hours), median (IQR)	5 hours (3 – 9)*	5 days (3.75 – 9.25) **	<0.001
Maternal pre-eclampsia	2 (6)	5 (13)	NS
Maternal diabetes	4 (13)	7 (18)	NS
Maternal steroids (betamethasone)	30 (94)	27 (71)	0.015
Antenatal indomethacin exposure, n (%)	0 (0)	2 (5)	NS
Concomitant gentamicin administration, n (%)	30/32 (94%)	34/38 (89%)	NS
Mortality, n (%)	2 (6)	1 (3)	NS

IQR: interquartile range; NSAID: non-steroid anti-inflammatory drug; n: number NS: non-significant

* In the prophylactic group, 31/32 patients received indomethacin within the first 15 hours, except one who received indomethacin at 19 hours of life. One received his first indomethacin dose at 4.5 hrs of life and then followed by 3 doses of ibuprofen (20 mg/kg total).

** In the symptomatic treatment group, 7/38 (18%) received ibuprofen as their medical treatment (10mg/kg once, followed by 5mg/kg Q24h for two doses).

We identified 23% (16/70) subjects in total who developed AKI by our criteria [Table 2]. The proportions of infants with adequate monitoring of serum creatinine around NSAID exposure were 4/32 (13%) and 33/38 (87%) in the prophylaxis and treatment groups, respectively (p<0.001). The treatment group had a higher proportion of infants with AKI than the prophylaxis group (3/32 [9%] vs. 13/38 [34%], p=0.014),

based upon the combined UO and SCr criteria (fulfilling at least one of the monitoring criteria either for UO or SCr). Similarly, the treatment group had a higher median maximum weight gain % than the prophylaxis group (11.1% [6.2% - 17.6%] vs. 2.3% [-1.4% - 5.9%], p<0.001).

Table 2: AKI phenotype

	Prophylactic (n = 32)	Symptomatic (n = 38)	p-value
AKI based on KDIGO criteria, n (%)	3/32 (9)	13/38 (34)	0.014
AKI (urine output criteria[#]), n (%)	2/32 (6)	13/38 (34)	0.005
AKI satisfying SCr criteria, n (%)*	1/4 (25)	2/33 (6)	NS
Maximum weight gain %, median (IQR)	2.3 (-1.4 – 5.9)	11.1 (6.2 – 17.6)	<0.001
Post-NSAID day of max weight gain, median (IQR)	4 (1 – 7)	5 (3 – 7)	NS

AKI: acute kidney injury; SCr: serum creatinine; IQR: interquartile range; NSAID: non-steroid anti-inflammatory drug; n: number NS: non-significant

* denominator = infants with adequate SCr information

[#] average UO rate of less than or equal to 1 mL/kg/h over at least 12 h

Based on the modified KDIGO AKI criteria[13], 15 infants from both groups had oliguria, among which 80% (12/15) of infants developed stage 1 oliguria (0.5-1mL/kg/hr) and 20% (3/15) had stage 2 oliguria (0.3-0.5mL/kg/hr). Among these infants, 26% (4/15) and 53% (8/15) had onset of oliguria within 24 hours and between 24-48 hours after commencement of NSAID treatment, respectively. Oliguria lasted for not more than 12 hours in 80% (12/15) infants, and all resolved in 36 hours.

Discussion

The reported incidence of AKI in the NICU varies widely depending on the included population and AKI definition used [13-16]. Studies focusing in very low birth weight (VLBW) or extremely low birth weight (ELBW) infant population reported an AKI incidence of 13–56% [4, 5, 14, 17, 18] in their NICU stay. To the best of our knowledge, this is the first study analysing the AKI epidemiology of NSAID exposed premature infants using the KDIGO neonatal AKI definition. In our cohort, we found that 23% of premature infants ≤34 weeks GA developed AKI after NSAID exposure, and infants being treated for symptomatic PDA developed higher AKI rates than those who received the medication for IVH prophylaxis purposes (34% vs. 6%, *p*=0.005). Majority of infants were identified to have AKI with UO criteria compared to SCr criteria. All

infants who had oliguria recovered by 36 hours after initiation of therapy, in line with a study focusing on the transient nature of renal impairment in neonates receiving indomethacin [19].

However, data from our symptomatic treatment cohort suggests that the transient oliguria may still be associated with clinically relevant fluid overload with a high maximal percentage of weight gain (median 11.1%, IQR 6.2-17.6%) observed from baseline. This is especially relevant with a recent analysis of 1007 premature infants from the landmark AWAKEN study showing that a positive peak fluid balance during the first postnatal week and the degree of positive fluid balance by day 7 of life were both independently associated for the need for mechanical ventilation at postnatal day 7[20].

In a recent study focusing on early-onset neonatal AKI (postnatal days 2–7, defined as an increase in serum creatinine >26.5 μmol/L (0.3 mg/dL) or UO <1 mL/kg/hour), the reported incidence was 21% [21]. Another study focusing on the cumulative incidence of AKI during the first two postnatal weeks in a prospective cohort study on 113 VLBW infants reported an incidence of 25%, though there was no mention of details of timing of administration of NSAID [22]. Reported risk factors associated with neonatal AKI include antenatal vascular damage such as maternal treatment of NSAID, lower GA and birth weight, lower Apgar score, small-for-gestational-age cases, necrotising enterocolitis, shock/dehydration, perinatal asphyxia, and administration of nephrotoxic medications. These factors are essentially concentrated in the most premature and severely ill infants [5, 23-25]. Understanding the aetiology of neonatal AKI is important, as these infants have been reported to have a significantly longer duration of mechanical ventilation and a higher mortality rate and/or chronic lung disease, even after adjusting for neonatal and maternal factors along with medication exposures [1, 4, 15, 18, 21, 26]. Cohort studies revealed that survivors of neonatal AKI may have an increased risk of developing hypertension, persistence of altered concentrating ability, focal segmental glomerulosclerosis, and renal dysfunction/insufficiency at five years of age or beyond [27-32].

Multiple autopsy studies in premature infants reported findings suggestive of early cessation of nephrogenesis, and increased glomerular volume, which is suggestive of hyperfiltration [7, 33]. The newborn kidney is particularly vulnerable to maldevelopment and dysfunction in an ex utero environment due to various stresses, mostly caused by decreased renal perfusion [23]. In a few studies, nephrotoxic injury is usually associated with the use of NSAID to close a PDA, especially with concomitant use of aminoglycosides [8, 34, 35]. However, the attributable risk of AKI associated with these 2 nephrotoxic agents is not clear. Commonly used medications to close PDA such as indomethacin or ibuprofen, inhibit the prostaglandin synthesis, and dramatically decrease renal blood flow and glomerular filtration rate, leading to oliguria [36]. A recent Cochrane review has suggested that, of these two medications, ibuprofen carries a lower risk of transient renal insufficiency, despite the fact that it has a similar effectiveness as indomethacin in closing a PDA [37].

After birth, the neonatal blood flow increases rapidly due to increased renal perfusion pressure and decreased renal vascular resistance due to neurohumoral changes, particularly in angiotensin II [38]. In premature infants, the glomerular filtration rate is even lower and increases more slowly than in term

infants [39]. Our finding of a higher incidence of AKI among infants who were prescribed NSAIDs at a later stage of life (“symptomatic treatment”), who were born at a more advanced GA and with heavier birth weights [Table 2], seems to contradict what is known about renal physiology and the general characteristics of preterm infants at highest risk. Srinivasjois et al. reported that a postnatal age ≥ 7 days at the start of indomethacin treatment is a predictor of significant rise in the level of SCr in extremely preterm neonates, compared with infants who were treated within their first seven days of life [40]. This group postulated that prolonged compromise of renal perfusion due to the aortic steal phenomenon is associated with a significant PDA, as well as with higher likelihood of hypovolemia/dehydration among infants beyond their first weeks of life [40]. The other reasons why AKI make have been significantly lower in our prophylaxis cohort include: 1) low availability of Cr values in the 1st day of life in our cohort, 2) difficulties in capturing a “rise” in SCr on the 1st day when Cr is known to peak and then decrease naturally over the first week in premature infants [41], 3) inability to capture UO based AKI accurately within the first day of life during NSAID exposure, especially in the context of the predominance of UO based AKI identified in the symptomatic treatment cohort and 4) a lower total dose compared to the symptomatic treatment group. A further study with a larger sample size, the use of more novel urinary AKI biomarkers outside of SCr and UO, and documentation of both cardiac output and renal perfusion by Near Infrared Spectroscopy is needed to address these postulations.

There are several limitations associated with this pilot study. Firstly, this is a relatively small retrospective study evaluating AKI with a sample size of 70 patients. Secondly, decisions concerning the treatment regimen, including the day of initiation and total doses, were at the discretion of attending physicians and not completely standardized. A minority of infants (8/70, 11%) in our cohort received ibuprofen, which might carry less nephrotoxic side effects, but we were not able to ascertain any differences in AKI risk with ibuprofen vs indomethacin. Lastly, it is challenging to quantify UO in the early days of life among small premature infants due to the risk of mixing of urine and meconium. Furthermore, the UO criteria and thresholds of defining AKI are not well validated in the most premature infants, which make the direct comparisons of results from various studies difficult.

Having said that, this is one of the few studies evaluating the impact of NSAID therapy on AKI incidence with a description of the course of AKI among preterm infants. A standardized evidence-based monitoring regimen of preterm infants exposed to NSAIDs and/or other nephrotoxic medications in NICU is desperately needed, as a systematic surveillance program to identify high-risk infants can prevent nephrotoxic-induced AKI and has the potential to prevent short and long-term consequences of AKI in critically ill infants [42]. Our study revealing a high signal of NSAID related AKI coupled with the lack of SCr monitoring has motivated further collaborative clinical, research, and quality improvement work between the nephrology and neonatology teams at our center to improve the renal health of these vulnerable infants in the short and long term.

Conclusions

AKI incidence is higher in infants treated with NSAIDs for symptomatic treatment for PDA compared with those who received the treatment prophylactically during the first day of life, based on the KDIGO criteria applied. Standardized protocols for monitoring daily SCr and UO after exposure should be implemented for all neonates with NSAID exposure and should be considered to improve early AKI recognition.

Abbreviations

AKI: acute kidney injury

ELBW: extremely-low-birth-weight

GA: gestational age

IVH: intraventricular haemorrhage

KDIGO: Kidney Disease Improving Global Outcomes

NICU: neonatal intensive care unit

NSAID: nonsteroidal anti-inflammatory drug

PDA: patent ductus arteriosus

SCr: serum creatinine

UO: urine output

VLBW: very low birth weight

Declarations

Ethics approval and consent to participate

Ethic approval was obtained from the Children's and Women's Research Ethics Board of the University of British Columbia [H15-00939]. This is a retrospective study, with data collected from existing records, per stand of clinical care. No individual consent is deemed necessary.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

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Drafting of the manuscript: Joseph Ting

Critical revision of the manuscript for important intellectual content: All authors.

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