Cardiology in the Young

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Ketorolac in neonates and infants following congenital heart surgery: a retrospective review

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Abstract

Introduction: Pain management is essential in the immediate post-surgical period. We sought to describe the ketorolac dose regimen in neonates and infants following cardiac surgery. Secondary outcomes included renal dysfunction, bleeding, and pain management. *Methods:* We performed a single-centre retrospective cohort study of neonates and infants (aged < 12 months) who received ketorolac following cardiac surgery, from November 2020 through November 2021 (inclusive). Ketorolac was administered at 0.5 mg/kg every 6 hours. Safety was defined by absence of a clinically significant decline in renal function (i.e., increase in serum creatinine [SCr] by ≥ 0.3 mg/dL from baseline within 48 hours and/or urine output ≤ 0.5 mL/kg/hour for 6 hours) and absence of clinically significant bleeding defined as major by International Society on Thrombosis and Hemostasis paediatric criteria or Severe/Fatal Bleeding Events by Nellis et al. Efficacy measures included pain scores and opioid utilisation. *Results:* Fifty-five patients met eligibility criteria. The median (range) dose and duration of ketorolac administration was 0.5 mg/kg/dose for 48 (6–90) hours. Among all patients, there was not a statistically significant difference observed in median SCr within 48 hours of baseline ($p > .9$). There were no major or severe bleeding events. The median (range) opioid requirements (morphine intravenous equivalents per kg per day) at 48 hours post-ketorolac initiation was 0.1 (0–0.8) mg/kg/day. *Conclusions:* If validated prospectively, these findings suggest that a ketorolac regimen 0.5 mg/kg/dose every 6 hours in neonates and infants post-cardiac surgery may be safe with regard to renal function and bleeding risk, and effective regarding opioid-sparing capacity.

Congenital heart disease (CHD) has a reported global prevalence of 9/1000 live births, and surgical intervention is often required within the first year of life among these patients.[1] Pain management is essential in the immediate post-surgical period, as inadequate pain control following cardiac surgery may result in increased metabolic demand, energy consumption, inadequate cardiac output, and decreased ventilation.[2] In the long term, inadequate pain control may lead to increased pain sensitivity to noxious stimuli and chronic postsurgical pain.[2,3] However, there is limited guidance regarding perioperative pain management in neonates and infants. Although opioids have historically been utilised for managing pain in neonates, infants, and children following cardiac surgery, there is recent piqued interest to move away from opioid use given the association with respiratory depression, delayed bowel function, extubation failure, long-term neurodevelopmental impacts, and potential risk of crossing of the blood–brain barrier.[4,5] Consequently, there is growing interest in the utilisation of other non-opioid analgesic agents, specifically ketorolac, a non-steroidal anti-inflammatory drug, in the immediate post-operative setting for pain management.[6–12]

Ketorolac is available in intravenous formulation at a relatively low cost. Analgesic properties are attributed to decreased prostaglandin synthesis and non-selective competitive inhibition of cyclooxygenase (COX-1 and -2).[13–16] It is approved for use in children>2 years of age. Pharmacokinetic data in neonates and infants are limited and heterogeneous, although a few studies note decreased ketorolac clearance compared with adults.[14–15] The Society for Pediatric Anesthesia recommends ketorolac be considered as an adjunct to opioids in paediatric pain control, and data indicate potential opioid-sparing effects in non-cardiac surgery post-operative children.[17] Safety concerns of ketorolac include acute renal dysfunction via vasoconstriction of the afferent arteriole and increased risk of bleeding due to inhibition of platelet function.[18–24]

Although some studies provide insight on the use of ketorolac in paediatrics, there remains a gap in the literature to support use in clinical practice, particularly in neonates and infants following cardiac surgery using validated definitions of renal impairment and bleeding.

Accordingly, we conducted the present study to describe the ketorolac dose regimen in neonates and infants following cardiac surgery. Secondary outcomes included renal dysfunction, bleeding, and pain management.

Patients and methods

Study population and design

We performed a single-centre retrospective cohort study of neonates and infants (aged < 12 months) who received ketorolac in the immediate post-operative period following cardiac surgery, from November 2020 through November 2021 (inclusive). Exclusion criteria were as follows: (1) preterm birth; (2) allergy to non-steroidal anti-inflammatory drugs; (3) mechanical circulatory support, (4) serum creatinine > 0.8 mg/dL; 5) active bleeding; 6) disseminated intravascular coagulation; and 7) recent history of intraventricular haemorrhage. Measurements were performed prior to the initiation of ketorolac dosing (henceforth referred to as "baseline"), and 24-, 48-, and 72- hours post-baseline. This study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB 00315665) with a waiver of the need for consent.

Pain management protocol

Patients received ketorolac as part of an institutional analgesia and sedation protocol. Following cardiac surgery, if extubated or extubation anticipated within 24 hours, neonates and infants received dexmedetomidine infusion, scheduled acetaminophen and ketorolac, and as needed morphine. If intubation anticipated > 24 hours, patients received continuous hydromorphone infusion in addition to dexmedetomidine infusion.

Ketorolac dosing

Ketorolac was initiated at 0.5 mg/kg/dose every 6 hours post-cardiac surgery when platelets were > 100×10^9/L, SCr < 0.8 mg/dL, and chest tube output < 3 mL/kg/hr. Therapy was continued for up to 48 hours in neonates and up to 120 hours in infants 1 month to < 12 months of age.

Study outcomes

Safety was defined by the absence of clinically significant decline in renal function, indicated by (1) an increase in SCr by≥0.3 mg/dL from baseline within 48 hours or urine output ≤ 0.5 mL/kg/hour for 6 hours[25] and (2) the absence of clinically significant bleeding episodes, defined as major by International Society on Thrombosis and Hemostasis paediatric criteria or severe/fatal bleeding events by Nellis et al.[26–29] Measures of efficacy included pain control, assessed by pain scores, and opioid utilisation in morphine equivalents.

Covariates

Concomitant medications collected included diuretic administration (furosemide mg/kg/24 hours), antiplatelet agents (i.e., aspirin, clopidogrel), anticoagulants (i.e., enoxaparin, unfractionated heparin, warfarin), and nephrotoxic antimicrobials (i.e., vancomycin and gentamicin). All opioids administered (i.e., hydromorphone, fentanyl, morphine, and oxycodone) were collected, converted to morphine intravenous (IV) equivalents, and reported as morphine IV mg/kg/day.

Statistical analyses

Patient clinical characteristics were summarised by age category (neonates, 1 to < 6 months, and 6 to < 12 months). Continuous variables were described with medians and range (minimum to maximum), while categorical variables were described with frequencies and percentages. Wilcoxon signed-rank tests determined intra-individual differences in continuous clinical measurements over time among the entire cohort pooled. Two-sided p-values < 0.05 were considered statistically significant. All analyses were performed with Stata/SE Version 17.0.[30] The study was approved by the Johns Hopkins Medicine Institutional Review Board, IRB00315665. Informed consent for this study was waived.

Results

Among 55 patients included in the final analytic sample, 20% (n = 11) were neonates, 54.6% (n = 30) were infants aged 1 to < 6 months, and 25.5% (n = 14) were aged 6 to < 12 months (Table 1). The majority (80%, n = 44) of patients had undergone STAT 1 or 2 operations. Of note, 54.5% (n = 6) of neonates in this study were STAT 3, 4, or 5 operations. Median cardiopulmonary bypass and cross-clamp times among patients with non-zero times were 128 (65–301) and 74 (14–185) minutes, respectively. One patient underwent circulatory arrest. Of the 55 patients, 92.7% (n = 51) received intraoperative caudal anaesthesia, and most patients were extubated in the operating room (87.3%, n = 48) (Table 1).

Ketorolac dosing

All 55 patients received a ketorolac dose of 0.5 mg/kg/dose, with median frequency of every 6 (6 to 12) hours. Ketorolac was initiated at a median 7.2 (2.5–22.5) hours following ICU admission and was continued for a median of 48 (6 to 90) hours. As shown in Table 2, 10.9% (n = 6), 63.6% (n = 35), 18.2% (n = 10), and 7.3% (n = 4) received therapy for ≤ 24 hours, >24 to ≤ 48 hours, >48 to ≤ 72 hours, and > 72– ≤ 90 hours, respectively.

Renal outcomes

Serum creatinine

Among all patients, 49.1% (n = 27) had decreased SCr, 41.8% (n = 23) had increased SCr, and 9.1% (n = 5) had no change in SCr following ketorolac initiation. Of those with increased SCr, the median increase from baseline to 48 hours post-ketorolac initiation was 0.05 (0.01 to 0.26) mg/dL (Fig. 1). There was no statistically significant difference observed in median SCr between baseline and 48 hours post-ketorolac initiation ($p > .9$) when age groups were pooled. Among neonates, 54.6% (n = 6) had increased SCr between baseline and 48 hours post- ketorolac initiation, while 33.3% (n = 10) of infants aged 1 to < 6 months and 50% (n = 7) of infants aged 6 to <12 months had increased SCr during this time period. The SCr at 72 hours following ketorolac discontinuation did not reflect AKI in any patients (Fig. 1). Of note, four patients received vancomycin concomitantly with ketorolac.

Urine output

There were 16 patients (29.1%) with decreased urine output between baseline and 48 hours post-ketorolac initiation, and 39 patients (70.1%) with increased urine output during this time period. Across age groups, 18.2% (n = 2), 36.7% (n = 11), and 21.4% (n = 3) of neonates, infants aged 1 to < 6 months, and

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Table 1. Demographics and ketorolac by age group.

Variable	Neonates (n = 11)	Age 1 to <6 mo. (n = 30)	Age 6 to <12 mo. (n = 14)	All (n = 55)
Age at surgery, months (median, range)	0.3 (0.07–0.9)	4.8 (1.1–5.9)	8.2 (6.1–11.2)	4.9 (0.07–1.2)
Gender, malen (%)	8 (72.7)	18 (56.3)	9 (64.3)	35 (62.5)
Weight, kg (median, range)	3.1 (2.5–4.5)	5.7 (3.1–11.3)	7.1 (4.6–11)	5.6 (2.5–11.3)
Surgical case complexity, n (%)				
STAT 1	4 (36.4)	11 (36.7)	9 (64.3)	24 (43.6)
STAT 2	1 (9.1)	16 (53.3)	3 (21.4)	20 (36.4)
STAT 3	3 (27.3)	–	1 (7.1)	4 (7.3)
STAT 4	1 (9.1)	3 (10)	–	4 (7.3)
STAT 5	2 (18.2)	–	1 (7.1)	3 (5.5)
Cardiopulmonary bypass time, minutes[1] (median, range)	154 (113–215)	120 (65–237)	123.5 (70–301)	128 (65–301)
Cross clamp time, minutes[2] (median, range)	61.5 (15–121)	73 (14–157)	82 (17–185)	74 (14–185)
Intra-operative caudal, Yes (n, %)	10 (90.9)	29 (96.7)	12 (85.7)	51 (92.7)
Intubated at ICU admission, Yes (n, %)	2 (18.2)	3 (10)	1 (7.1)	6 (10.9)
Time to ketorolac initiation post ICU admission, hours (median, range)	7.3 (4.5–22.5)	6.7 (2.5–12)	8.2 (2.6–11.5)	7.2 (2.5–22.5)
Ketorolac dose, mg/kg/dose (median, range)		0.5 (0.5–0.5)		
Ketorolac dose frequency, hours (median, range)	6 (6–12)	6 (6–6)	6 (6–6)	6 (6–12)
Ketorolac duration, hours (number, %)				
≤ 24 hours	4 (36.4)	1 (3.3)	1 (7.1)	6 (10.9)
>24 hours to ≤ 48 hours	7 (63.6)	20 (66.7)	8 (57.1)	35 (63.6)
>48 hours to ≤ 72 hours	0 (0)	8 (26.7)	2 (14.3)	10 (18.2)
>72 hours to ≤ 90 hours	0 (0)	1 (3.3)	3 (21.4)	4 (7.3)

[1]n = 3 (neonates) and n = 3 (1 to <6 months) with cardiopulmonary bypass time of 0, excluded from calculations.
[2]n = 1 (neonate) and n = 7 (1 to <6 months) with cross-clamp time of 0, excluded from calculations.

infants aged 6 to <12 months had decreased urine output, respectively (Fig. 2).

Hematologic outcomes

Haemoglobin

There were 23 patients (41.8%) with decreased Hg, 26 patients (47.3%) with increased Hg, and 6 patients (10.9%) with no change in Hg from the time of ketorolac initiation to 24 hours post-discontinuation (Table 2).

Platelets and other bleeding outcomes

Between ICU admission and ketorolac discontinuation, there were 16 patients (29.1%) with increased platelets, 34 (61.8%) with decreased platelets, and 5 (9.1%) with no change in platelet count (Table 2). The median decrease in platelet count in neonates, infants aged 1 to <6 months, and infants aged 6 to <12 months from ICU admission to ketorolac discontinuation was 17, 15, and 7×10^9/L, respectively. One infant had ketorolac stopped for a platelet count $< 100 \times 10^9$/L. A total of four patients (7.3%) required blood transfusions following ketorolac initiation, although this was noted to be for desaturations (Table 2). Two patients (3.6%) had blood in the endotracheal tube (ETT) tube, and one patient (1.8%) had bleeding associated with blood pressure changes specifically noted to be due to surgical factors (Table 2). Of note, six patients (10.9%) received ketorolac and aspirin concomitantly for greater than 48 hours. One patient (1.8%) received unfractionated heparin and ketorolac simultaneously. There were no adverse bleeding events reported in patients receiving concomitant aspirin and ketorolac or unfractionated heparin and ketorolac.

Pain management

Opioids

Among all patients, the median (range) opioid requirement in morphine equivalents was 0.2 (0–2.1) mg/kg at the time of ketorolac initiation and 0.1 (0 to 0.8) mg/kg at 48 hours post-ketorolac initiation (Table 2). There were 8 patients (14.6%) with an increase in opioid requirements, 35 patients (63.6%) with a decrease, and 12 patients (21.8%) with no change within 48 hours of ketorolac initiation. The median (range) opioid requirement (morphine IV equivalents per kg per day) at 48 hours post-ketorolac initiation amongst neonates, infants aged 1 to < 6 months, and infants aged 6 to < 12 months was 0.1 (0–0.4), 0.1 (0–0.8), and 0.1 (0–0.7) mg/kg/day, respectively (Table 2). Among all patients, we observed a statistically significant difference between requirements at the time of ketorolac initiation to 48 hours (median decrease: 0.05 mg/kg/day, $p = .0001$).

Pain scores

At 24 hours from ketorolac initiation, median FLACC pain scores decreased by 1 point ($p = .005$); the maximum decrease in scores was 6 and the maximum increase in scores was 5 points. At 48

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Table 2. Bleeding and pain outcomes.

Variable	Neonates (n = 11)	Age 1–6 mo. (n = 30)	Age 6–<12 mo. (n = 14)	All (n = 55)
Haemoglobin, g/dL (median, range)				
ICU admission	14 (8.3–17.8)	13.8 (8.9–16.4)	13.3 (10.6–5.1)	13.7 (8.3–17.8)
Ketorolac discontinuation	13.5 (10.1–17)	12.8 (8.6–16)	12.4 (9.6–16.4)	12.8 (8.6–17)***
Platelets, median (range)				
ICU admission	288 (134–575)	247 (124–522)	183.5 (119–312)	250 (119–575)
Ketorolac discontinuation	200 (82–575)	209.5 (78–522)	195 (49.9–327)	204 (49.9–575) **
Post-op blood transfusion within 48 hours of ketorolac initiation, yes n (%)				
Chest tube output, mL/kg/hr (median, range)	2 (18.2)	1 (3.3)	1 (7.1)	4 (7.3)
Pre-ketorolac initiation	1.94 (0.8–3.3)	1.61 (0.57–2.61)	1.09 (0.73–2.54)	1.54 (0–3.3)
24 hours ketorolac initiation	1.0 (0.3–2.2)	1.0 (0–2.7)	1.0 (0.3–2.8)	1 (0–2.8)
48 hours ketorolac initiation	0.4 (0–1.6)	0.4 (0–2.0)	0.7 (0–1.2)	0.4 (0–2)***
Bleeding leading to organ dysfunction (PELOD score) n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Bleeding associated with>20% change baseline HR or 20% change blood pressure n (%)	0 (0)	1 (3.3)	0 (0)	1 (1.8)
Blood in ETT tube/NG tube, Yes n (%)	0 (0)	1 (3.3)	1(7.1)	2 (3.6)
Macroscopic haematuria, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Wound bleed, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
GI bleed, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Intracranial/CNS bleed, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Retroperitoneal bleed, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Bloody dressing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Opioid requirement, morphine intravenous equivalents mg/kg/day (median, range)				
24 hours post-ketorolac initiation	0.2 (0–0.4)	0.2 (0–2.1)	0.2 (0.03–0.7)	0.2 (0–2.1)
48 hours post-ketorolac initiation[1]	0.1 (0–0.4)	0.1 (0–0.8)	0.1 (0–0.7)	0.1 (0–0.8)***
72 hours post-ketorolac initiation[2]	0 (0–0)	0.1 (0–0.8)	0.1 (0–0.7)	0.1 (0–0.8)

An asterisk denotes a statistically significant difference between time points of the specified row variable among all age groups pooled, where * $p < 0.05$, ** $p < 0.01$, *** $p < .001$.
CNS = central nervous system; ETT = endotracheal tube; GI = gastrointestinal; NG = nasogastro.
[1]For 48 hours, sample sizes were: neonates n = 7, 1 to <6mo. n = 27, 6 to <12 mo. n = 13.
[2]For 72 hours, sample sizes were: neonates n = 0, 1 to <6 mo. n = 4, 6 to <12 mo. n = 3.
Differences in pain scores between ketorolac initiation and 72 hours post-ketorolac initiation were not computed due to restrictions in sample size. Differences in opioid requirements between 24 and 72 hours post-ketorolac initiation were not computed due to restrictions in sample size.

hours from ketorolac initiation, median FLACC pain scores decreased by 3 points ($p < .0001$); the maximum decrease was 4 and the maximum increase was 1 point.

Comment

This study demonstrates that ketorolac as part of a protocol can be used in neonates and infants in the post-cardiac surgery period for at least 48 hour with low risks of bleeding or renal impairment. Furthermore, ketorolac may minimise exposure to opioids in the post-operative setting.

Pain management following cardiac surgery in neonates and infants historically has employed opioids or acetaminophen. Recent efforts have focused on mitigating potential respiratory depression and minimising opioid exposure to ensure optimal outcomes. Ketorolac is a potential adjuvant for effective analgesia in adults and children. Studies in non-cardiac surgery infants report decreased morphine requirements in patients administered ketorolac versus patients only given morphine.[19]

Literature on ketorolac in neonates and infants following cardiac surgery is limited to small retrospective studies. For example, Dawkins et al. reported the use of ketorolac 0.5 mg/kg IV every 6 hours for 48 hours in infants less than 6 months of age with biventricular circulation following cardiac surgery. In this retrospective case–control chart review of 19 infants that were age-matched to 19 controls who did not receive ketorolac, there were no observed inter-group differences in serum creatinine (SCr) or haematologic outcomes.[6] Moffett et al. described the utilisation of ketorolac in 53 infants less than 6 months of age following cardiac surgery, with 11 (21%) being < 1-month of age. The average reported dose was 0.44 mg/kg every 6 hours for less than 48 hours. The SCr was reported to increase from baseline at 48 hours, although remained within normal limits; and minor bleeding was reported in four patients.[11] Additional studies in infants, children, and

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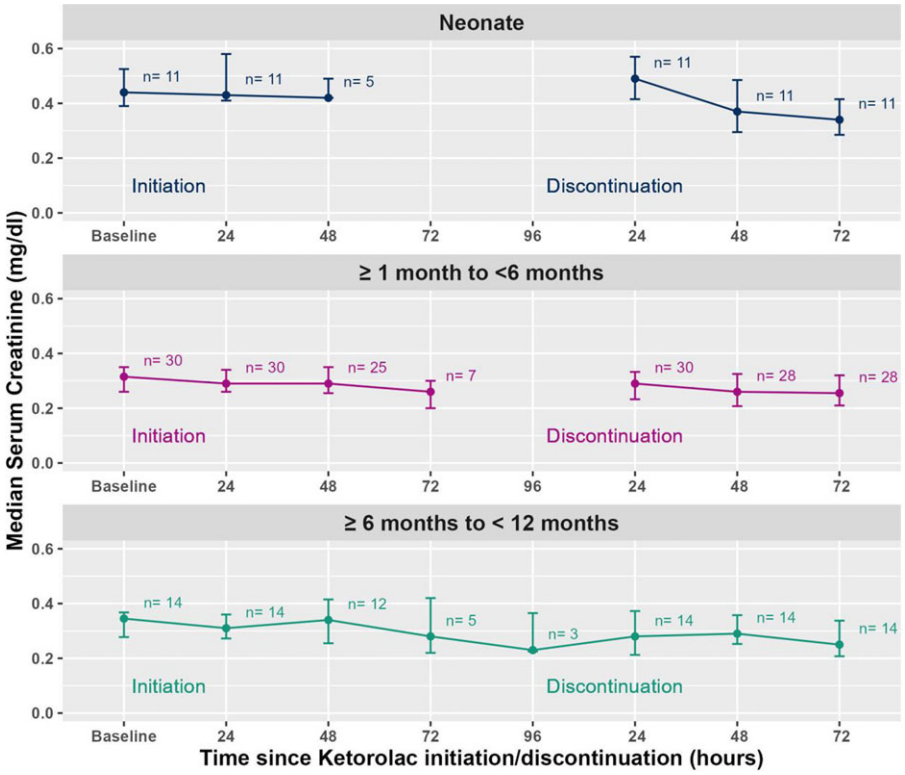

Figure 1. Ketorolac administration and serum creatinine.

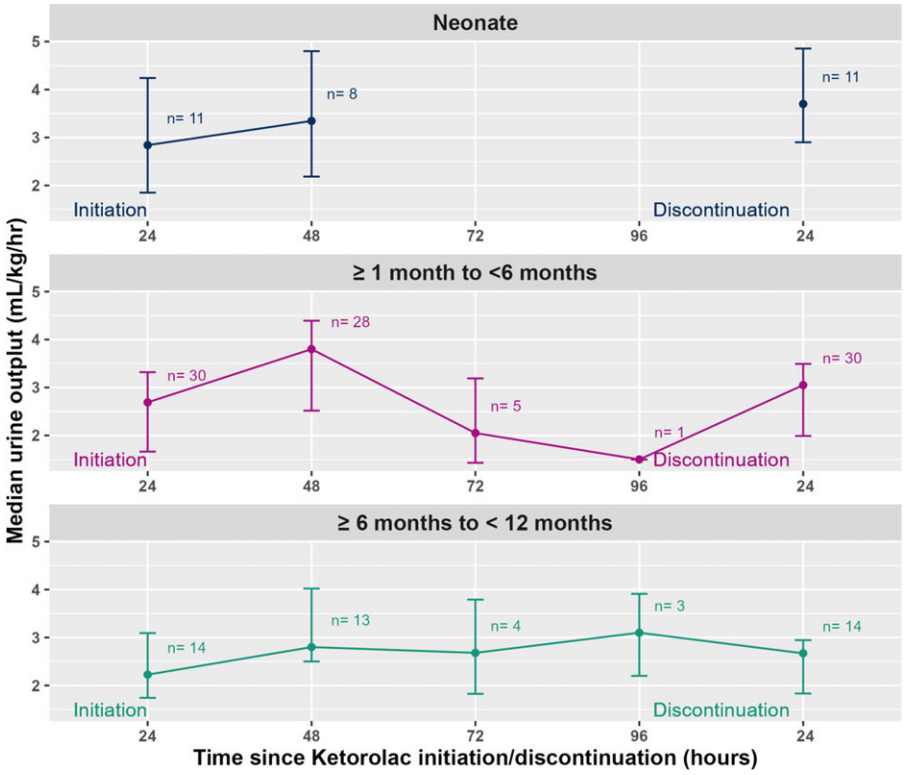

Figure 2. Ketorolac administration and urine output.

adolescents report minimal safety concerns with regard to bleeding and renal dysfunction, although careful assessment of other nephrotoxic medications should be considered.[8,10,20,21] This study is novel as it describes ketorolac use in the neonate and infant cardiac surgery patient populations and utilises standard validated definitions for renal impairment and bleeding to assess safety.[24,26,27]

Ketorolac is a standard agent at our institution for post-operative pain management in neonates and infants following cardiac surgery. Dosing is 0.5 mg/kg/dose every 6 hours, which is similar to other dosing regimens described in neonates and infants for pain management following surgical intervention[6,8–11,28]. Only one patient had ketorolac stopped at<12-hour post initiation, and

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this was due to concern for increased chest tube output and decreased urine output.

Furthermore, the results of this study depict the absence of renal dysfunction associated with ketorolac therapy in neonates and infants, per the KDIGO and Neonatal AKI KIDGO Classifications. To date, other studies in neonatal and infant cardiac surgery patients have trended urine output, SCr, and blood urea nitrogen to assess renal function.[6,10,11,20] With regard to urine output, our study noted an increase in median (range) hourly urine output from baseline to 48 hours post-ketorolac initiation. This is likely attributed to a high diuretic utilisation in the immediate post-operative phase of care, as most patients received greater than 4 mg/kg/day IV furosemide. There were no significant increases in SCr across all age groups and no occurrences of renal dysfunction.

The present study also did not find any significant bleeding associated with ketorolac. Of note, six (10.7%) of the patients (two neonates and four infants) in our cohort received aspirin and ketorolac concomitantly for 48 hours, and there were no bleeds reported in any of these patients (Supplemental Table 1). Of note, one infant did experience a bleed leading to hemodynamic instability, but this was attributed to other surgical factors. The findings of minimal occurrence of bleeding, few blood transfusions, and lack of observation of a significant decrease in haemoglobin are similar to findings of other studies published assessing ketorolac in neonate and infant surgical patients.[8,9,11,28]

With regard to pain management, we observed a decrease over time in morphine requirements and pain scores. While there was statistical significance at 48 hours following ketorolac administration, it is difficult to conclude clinical significance given a small patient number, and that most were lower STAT 1 and 2 cases. However, most neonate cases were STAT 3 and 5 and still observed decrease in morphine requirements. Further studies that include case–control groups would be useful to confirm the opioid-sparing effect of ketorolac in complex cardiac surgical patients.

This study is not without limitations, namely its retrospective design, small patient sample, and reliance on documentation in the electronic medical record. Although most neonatal surgical cases in this study were STAT 3 or 5, most cases for the entire cohort were STAT 1 or 2, which could impact the generalisability of this study to highly complex cardiac surgical cases. Due to variable documentation with urine output, detection of renal dysfunction may have been hindered. However, given that most patients experienced an increase in urine output following cardiac surgery, we anticipate this is minimal. Additionally, given the subjective documentation of bleeding events, it is difficult to account for bleeds due to inconsistencies or absence of documentation. The scoring and documentation of pain scores are also subjective and may have affected overall pain score. Furthermore, given that most patients at our institution receive ketorolac as part of a pain regimen, it would be difficult to have a comparison group for purposes of documenting differences in opioid requirements and therefore relied on other published literature reporting opioid requirements in evaluating utilisation in this study.

Our findings suggest that a ketorolac regimen 0.5 mg/kg/dose every 6 hours in neonates and infants following cardiac surgery with normal baseline renal function may be safe and is not associated with major bleeding. Further prospective studies are warranted to confirm and extend these findings regarding renal dysfunction and bleeding risks in complex cardiac surgical cases.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123004262.

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