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Ketorolac Dosing and Outcomes in Neonates Following Congenital Heart Surgery: A Retrospective Analysis

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BACKGROUND: Pain management is essential for postoperative surgery. Given the association of opioids with adverse outcomes, interest in the use of nonopioid analgesics, such as ketorolac, has increased. Published data on use in neonates are limited.

OBJECTIVES: To describe ketorolac dosing and safety and efficacy outcomes in the first 48 hours postcardiac surgery in neonates.

DESIGN: We performed a single-center retrospective cohort study of neonates (ages < 28 d) who received ketorolac following cardiac surgery from November 2020 to July 2023 (inclusive). The primary safety outcome was a clinically significant decline in renal function, as defined by the composite of an increase in serum creatinine by greater than or equal to 0.3 mg/dL from baseline within 96 hours of ketorolac initiation and urine output less than or equal to 0.5 mL/kg/hr for 6 hours. The secondary safety outcome was clinically significant bleeding, defined as the composite of major bleeding by the International Society on Thrombosis and Hemostasis pediatric criteria and severe/fatal bleeding by the criteria of Nellis et al (2019). Efficacy was measured by opioid utilization based on a standardized pain score-driven analgesia protocol.

INTERVENTIONS: Ketorolac was administered at 0.5 mg/kg every 6 hours as per an institutional clinical management algorithm.

MEASUREMENTS AND MAIN RESULTS: Thirty-nine patients met the eligibility criteria. The median ketorolac dose was 0.5 mg/kg/dose, and median (interquartile range [IQR]) duration of therapy was 48 hours (6–48 hr). No patients experienced a significant decline in renal function, and there were no clinically significant bleeding events. The median (IQR) IV morphine milligram equivalents (MMEs)/kg/d of opioid administration was 0.2 MME/kg/d (0.1–0.25 MME/kg/d) at the time of ketorolac initiation and 0.1 MME/kg/d (0.1–0.2 MME/kg/d) at 48 hours post-ketorolac initiation.

CONCLUSIONS: If validated prospectively, these findings suggest that a ketorolac regimen of 0.5 mg/kg/dose every 6 hours in neonates postcardiac surgery may be safe with regard to renal function and bleeding risk. Additional randomized studies would be needed to determine efficacy with regard to opioid-sparing capacity.

KEYWORDS: cardiac intensive care; cardiac surgery; ketorolac; neonate; pain management

Congenital heart disease is a common birth defect, with a reported global prevalence of nine of 1000 live births, and the timing of neonatal cardiac surgery is often important within the first weeks of life (1). Pain management is essential following cardiac surgery, as inadequate pain control in neonates postcardiac surgery may lead to increased energy consumption, a higher metabolic demand, inadequate cardiac output, and decreased ventilation (2, 3).

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KEY POINTS

Question: Can ketorolac be used in neonates following cardiac surgery?

Findings: Ketorolac 0.5 mg/kg/dose every 6 hours for up to 48 hours in neonates following cardiac surgery did not result in renal impairment or bleeding.

Meaning: If validated prospectively, these findings suggest that a ketorolac regimen of 0.5 mg/kg/dose every 6 hours in neonates postcardiac surgery may be safe with regard to renal function and bleeding risk.

However, there is limited guidance regarding postoperative pain management in neonates. Traditional use of opioids for postoperative analgesia has been reported to have long-term neurologic impact on development and may contribute to respiratory depression, extubation failure, and delayed bowel function (4, 5). The negative impact of opioids in the postoperative recovery period has raised the interest in utilizing nonopioid agents such as ketorolac in neonates (6–12).

Ketorolac's analgesic properties are attributed to decreased prostaglandin synthesis and nonselective competitive inhibition of cyclooxygenase-1 and cyclooxygenase-2. It is available in an IV formulation, making it ideal for patients in the postoperative setting who are unable to tolerate enteral medications (13–16). Pharmacokinetic data in neonates are limited and heterogeneous, with studies reporting a variation in clearance when comparing neonates to older children, with some indicating increased clearance, and others slower clearance (14–16). The Society for Pediatric Anesthesia recommends that ketorolac be considered as an adjunct to opioids in pediatric pain control, and data support its potential opioid-sparing effects in noncardiac surgery postoperative pediatric patients (17). In neonates, there is concern for acute renal dysfunction, necrotizing enterocolitis, and an increased risk of bleeding (18–26). Additionally, there are limited data on the use of ketorolac in neonates postcardiac surgery employing validated standardized definitions of renal impairment and bleeding. We therefore conducted the present retrospective study to describe ketorolac dosing and safety and efficacy outcomes from a single-institutional experience of a clinical care algorithm for the management of neonates postcardiac surgery.

MATERIALS AND METHODS

Study Population and Design

We performed a single-center retrospective cohort study. Neonates (age ≤ 28 d) who received ketorolac in the immediate postoperative period following cardiac surgery according to an institutional clinical care algorithm from November 2020 to July 2023 (inclusive) were included. Exclusion criteria consisted of: 1) preterm birth, 2) mechanical circulatory support, 3) active bleeding, 4) disseminated intravascular coagulation, or 5) recent history of intraventricular hemorrhage. In accordance with the clinical algorithm, ketorolac was not initiated in neonates if the serum creatinine (SCr) was greater than 0.8 mg/dL, platelet count less than 100×10^9/L, or chest tube output greater than 3 mL/kg/hr and sanguineous in appearance. Of note, the 2020 The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT) categories were used for reporting patient cardiac case complexity (27). Informed consent for this study was waived. This study was approved by the Johns Hopkins Medicine Institutional Review Board (00315665).

Pain Management Protocol

Neonates received ketorolac as part of an institution-approved postcardiac surgery analgesia and sedation protocol (**Supplement Fig. 1**, http://links.lww.com/CCX/B332). Following cardiac surgery, if extubation was performed at the conclusion of the case or anticipated within 24 hours, neonates received a dexmedetomidine infusion, scheduled acetaminophen, scheduled ketorolac if criteria regarding SCr, platelet count, and chest tube output were met, as well as morphine as needed for pain. If intubation was anticipated for greater than 24 hours, patients typically received a low-dose continuous hydromorphone infusion in addition to the dexmedetomidine infusion. Opioid dosing was based on an institutional protocol and standardized pain score assessment.

Ketorolac Dosing

Ketorolac was initiated at 0.5 mg/kg/dose every 6 hours postcardiac surgery if platelet count remained greater

than 100×10^9/L, the SCr less than 0.8 mg/dL, and the chest tube output less than 3 mL/kg/hr and serious in quality. Therapy was continued for up to 48 hours.

Outcome Measures

The primary safety outcome was a clinically significant decline in renal function, as defined by the composite of an increase in SCr by greater than or equal to 0.3 mg/dL from baseline within 96 hours of ketorolac initiation and urine output less than or equal to 0.5 mL/kg/hr for 6 hours (28, 29). Baseline was defined as the SCr before cardiac surgery. The secondary safety outcome was clinically significant bleeding, defined as the composite of major bleeding by the International Society on Thrombosis and Hemostasis pediatric criteria and severe/fatal bleeding by the criteria of Nellis et al (30). Efficacy was measured by opioid utilization based on a standardized pain score-driven analgesia protocol (31).

Covariates

Concomitant medications collected included diuretics, aspirin, clopidogrel, enoxaparin, unfractionated heparin, warfarin, vancomycin, gentamicin, and tobramycin. All opioid agents that were administered were converted to IV morphine equivalents for the purposes of analysis.

Statistical Analyses

Patient demographics and clinical characteristics, including bleeding and opioid utilization, were reported. Continuous variables were summarized with medians and interquartile ranges (IQRs), whereas categorical variables were described using frequencies and percentages. Wilcoxon signed-rank tests determined intra-individual differences from baseline over time in continuous measurements. Two-sided p values of less than 0.05 were considered statistically significant. All analyses were performed with Stata/SE, Version 17.0 (StataCorp, College Station, TX).

RESULTS

Among the 39 neonates included in the final analytic sample, 69% (n = 27) underwent STAT 3, 4, or 5 cardiac operations. The median (IQR) cardiopulmonary bypass and cross-clamp times were 152 minutes (134–179 min) and 64 minutes (40.5–86 min), respectively. Of the 39 patients, 35 (90%) received intraoperative caudal anesthesia, and 25 (64%) were extubated in the operating room (**Table 1**).

Ketorolac Dosing

Ketorolac was administered at 0.5 mg/kg/dose every 6 hours (as per clinical protocol) and was initiated at a median (IQR) time of 9.5 hours (7.1–18 hr) following ICU admission. Of the 39 neonates, 16 (41%) received therapy for less than or equal to 24 hours, and 23 neonates (59%) received therapy for greater than 24 hours to less than or equal to 48 hours (**Table 2**).

Primary Safety Outcome and Other Renal Findings

The median (IQR) SCr at baseline (precardiac surgery) was 0.42 mg/dL (0.33–0.5 mg/dL). Among all

TABLE 1.
Neonate Characteristics

Variable, Unit[a], Statistic	Total Cohort (n = 39)
Gestational age at birth, wk, median (IQR)	38.1 (38.0–39.1)
Gender, male, n (%)	24 (61.5)
Weight, kg, median (IQR)	3.3 (3.1–3.7)
Surgical case complexity, n (%)	
STAT 1	7 (17.9)
STAT 2	5 (12.8)
STAT 3	10 (25.6)
STAT 4	6 (15.4)
STAT 5	11 (28.3)
Cardiopulmonary bypass time, min, median (IQR)	152 (134–179)
Cross-clamp time, min, median (IQR)	64 (40.5–86)
Intraoperative caudal, n (%)	35 (89.7)
Intubated at ICU admission, n (%)	14 (35.9)
Delayed sternal closure, n (%)	0 (0)
Genetic disorder[b], n (%)	12 (30.8)

IQR = interquartile range, STAT = Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery score.
[a]Units stated where applicable.
[b]Genetic conditions documented included: 22q11 deletion (n = 2), trisomy 21 (n = 1), and other/not specified (n = 9).

TABLE 2.
Ketorolac Dosing Among Neonates

Variable, Unit, Statistic	Total Cohort ($n = 39$)
Time to ketorolac initiation post-ICU admission, hr, median (IQR)	9.5 (7.1–18)
Ketorolac dose, mg/kg/dose, median (IQR)	0.5 (0.5–0.5)
Ketorolac dose frequency, hr, median (IQR)	6 (6–6)
Ketorolac duration, *n* (%)	
≤ 24 hr	16 (41)
> 24 hr to ≤ 48 hr	23 (59)

IQR = interquartile range.

neonates, 11 (28%) had a decrease in SCr, whereas 26 (67%) had an increase in SCr. Two neonates (5%) had no observed change in SCr from baseline (pre-cardiac surgery) to 48 hours post-ketorolac initiation. Of those with an increase in SCr, the median (IQR) increase from baseline to 48 hours post-ketorolac initiation was 0.05 mg/dL (0.01–0.26 mg/dL; $p = 0.13$) (**Fig. 1**). At 48 hours following discontinuation of ketorolac, there were no neonates who met the criteria for a clinically significant decline in renal function (Fig. 1). Fourteen neonates (36%) had decreased urine output from baseline to 48 hours post-ketorolac initiation, and 25 (64%) had increased urine output. The median (IQR) urine output (mL/kg/hr) at baseline, 48 hours post-ketorolac initiation, and 24 hours following ketorolac initiation was 3.3 mL/kg/hr (2.9–3.9 mL/kg/hr), 3.4 mL/kg/hr (2.5–4.6 mL/kg/hr), and 4.3 mL/kg/hr (3.5–5.1 mL/kg/hr), respectively. No patients had a clinically significant decline in urine output. Of note, only one patient had ketorolac stopped at less than 12-hour post-initiation due to a concern for increased chest tube output and decreased urine output. Additionally, one patient received vancomycin concomitantly with ketorolac without any noted concerns. In summary, no patients experienced a primary safety composite outcome of a clinically significant decline in renal function.

Secondary Safety Outcome and Other Hematologic Findings

Of the neonates who received ketorolac, 29 (74%) had increased hemoglobin, whereas 10 (26%) had a decrease in hemoglobin from ICU admission to 24 hours after ketorolac discontinuation (**Table 3**). Nine neonates (23%) had an increase in platelets, whereas 30 neonates (77%) had a decrease in platelet count from ICU admission to 24 hours following ketorolac discontinuation (Table 3). Of note, 1 (3%) neonate had a gastrointestinal bleed (with endoscopy findings of gastric wall lacerations) and 2 (5%) neonates had documented wound bleeds. Blood transfusions were reported in 8 (21%) neonates during ketorolac administration, although these were noted to be for desaturations.

No patients developed major bleeding by the International Society on Thrombosis and Hemostasis pediatric criteria and no patients developed severe/fatal bleeding by the criteria of Nellis et al (30. Among the 39 neonates, there were no occurrence rate of bleeding leading to organ dysfunction, blood in the ETT tube, macroscopic hematuria, and intracranial or retroperitoneal bleeds (Table 3). Of note, 7 (18%) neonates received ketorolac and aspirin concomitantly, whereas 3 (8%) received unfractionated heparin and ketorolac simultaneously for at least 24 hours. Although no major bleeding events were observed, two neonates who received aspirin and ketorolac simultaneously were noted to have blood on their wound dressing. In summary, no patients experienced a composite safety outcome of clinically significant bleeding.

Efficacy Outcome: Opioid Requirements

The median (IQR) opioid requirement in IV morphine milligram equivalents (MMEs), dosed based on a standardized pain score-driven analgesia protocol, was 0.2 MME/kg/d (0.1–0.25 MME/kg/d) at the time of ketorolac initiation and 0.1 MME/kg/d (0.1–0.2 MME/kg/d) at 48 hours post-ketorolac initiation (**Fig. 2**). Although clinically meaningful, this difference was not statistically significant ($p < 0.05$) according to our a priori definition and in the context of the relatively small sample size of the study population. Four of neonates (10%) had an increase in opioid requirements, 7 (18%) had no change in opioid requirements, 22 (56%) had a decrease in opioid requirements, and 6 (15%) required no opioids within 48 hours of ketorolac initiation. At 24 hours from ketorolac initiation, median FLACC pain scores decreased by one point from baseline (before ketorolac initiation), and at 48 hours after ketorolac initiation, median FLACC pain scores decreased by three points ($p < 0.0001$).

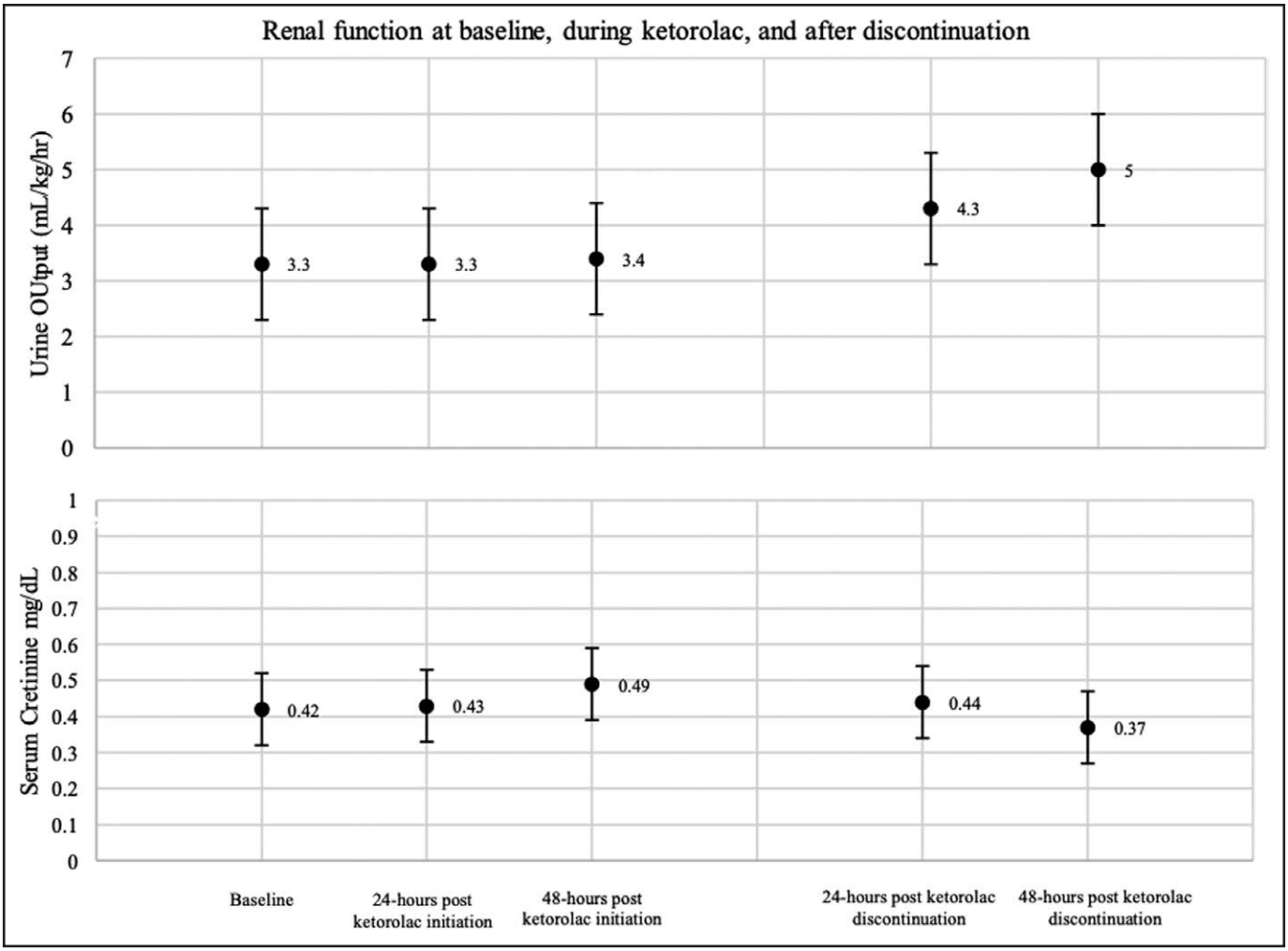

Figure 1. Renal function among neonates who received ketorolac. Serum creatinine and urine output changes in neonates postcardiac surgery following initiation of ketorolac.

DISCUSSION

The findings of this retrospective study suggest that ketorolac 0.5 mg/kg IV every 6 hours may be safe in regard to renal function and bleeding risk and effective in reducing opioid requirements during the first 48 hours postcardiac surgery in neonates. Given the retrospective single-institutional design and relatively small sample size, these findings should be interpreted with caution, and warrant further evaluation in a controlled prospective (and ideally multicenter) study. Our institutional regimen of 0.5 mg/kg every 6 hours is similar to other ketorolac dosing regimens described in the literature for pain management following surgical intervention among neonates (11, 16, 18, 26). Additionally, our institutional regimen used intraoperative caudal anesthesia, with most patients (90%) receiving a clonidine and morphine caudal. We also have a small number of patients with delayed sternal closure, most of whom are on extracorporeal membrane oxygenation or others and would not be candidates for ketorolac based on the algorithm at that time point.

Data among neonates are limited for nonopioid analgesia options such as ketorolac. While a study in noncardiac surgery infants reported decreased morphine requirements with ketorolac (19), no published studies to the knowledge of the authors have described the use of ketorolac specifically in only neonates undergoing cardiac surgery. Aldrink et al (18) retrospectively evaluated the safety of ketorolac 0.5 mg/kg IV every 6 hours in 57 surgical patients 0–3 months old and reported that ten patients (17%) demonstrated a bleeding event. Of the patients experiencing a bleeding event, the median age was 20.7 days, and correlated with a glomerular filtration rate less than 30 mL/min/1.72 m^2 (18). Unlike Aldrink et al (18), we did not find similar

TABLE 3.
Hematologic Indices and Bleeding Among Neonates

Variable, Unit[a], Statistic	Total Cohort (*n* = 39)
Hemoglobin, g/dL, median (IQR)	
ICU admission	14.3 (13.1–15.9)
Ketorolac discontinuation	13.5 (11.5–14.2)
Platelets, median (IQR)	
ICU admission	332 (248.5–400)
Ketorolac discontinuation	207 (182.5–279.5)
Postoperative blood transfusion within 48 hr of ketorolac initiation, *n* (%)	8 (20.5)
Chest tube output, mL/kg/hr, median (IQR)	
Pre-ketorolac initiation	1.7 (1.1–2.3)
24-hrs after ketorolac initiation	0.9 (0.6–1.2)
48-hrs after ketorolac initiation	0.4 (0.2–0.7)
Bleeding leading to organ dysfunction, Pediatric Logistic Organ Dysfunction score, *n* (%)	0 (0)
Bleeding associated with > 20% change baseline heart rate or 20% change blood pressure, *n* (%)	0 (0)
Blood in endotracheal tube tube/nasogastric tube tube, *n* (%)	0 (0)
Macroscopic hematuria, *n* (%)	0 (0)
Wound bleed, *n* (%)	2 (5.1)
Gastrointestinal bleed, *n* (%)	1 (2.6)
Intracranial/CNS bleed, *n* (%)	0 (0)
Retroperitoneal bleed, *n* (%)	0 (0)
Bloody dressing, *n* (%)	3 (7.7)

IQR = interquartile range.
[a]Units stated where applicable.

bleeding rates in our study of neonates (age 0–28 d) postcardiac surgery, although the diverse patient population and surgeries included may have impacted outcomes. Moffett et al (11) reported ketorolac use in 53 infants younger than 6 months old postcardiac surgery, with 11 (21%) being younger than 1 month old. The SCr was reported to increase from baseline at 48 hours, although it remained within normal limits, and minor bleeding was reported in four patients (11). Similarly, we observed a small rise in SCr at 48 hours but remained within normal limits and urine output was not concerning for renal impairment. Additional studies in infants, children, and adolescents have suggested low rates of bleeding and renal dysfunction, concomitant use with other nephrotoxic medications should be undertaken with caution and warrants further study (8, 10, 20, 21).

The results of this study depict the absence of renal dysfunction as defined per the Neonatal Acute Kidney Injury (AKI) Kidney Disease: Improving Global Outcomes Classification, in neonates who receive ketorolac (28). No patients in this study experienced AKI, in the neonates who had an increase in SCr, it was not statistically significant, and most reported an increase in urine output following ketorolac initiation likely due to a high diuretic utilization in the immediate postoperative phase of care. While other studies evaluating ketorolac in cardiac surgery infants have trended urine output, SCr, and blood urea nitrogen to assess renal function, this study reports renal impairment using standard definitions (6, 10, 11, 20).

The study also did not report any significant bleeding associated with ketorolac use in neonates following cardiac surgery. Furthermore, 7 (18%) neonates received ketorolac and aspirin concomitantly, whereas 3 (8%) received unfractionated heparin and ketorolac concomitantly for a minimum

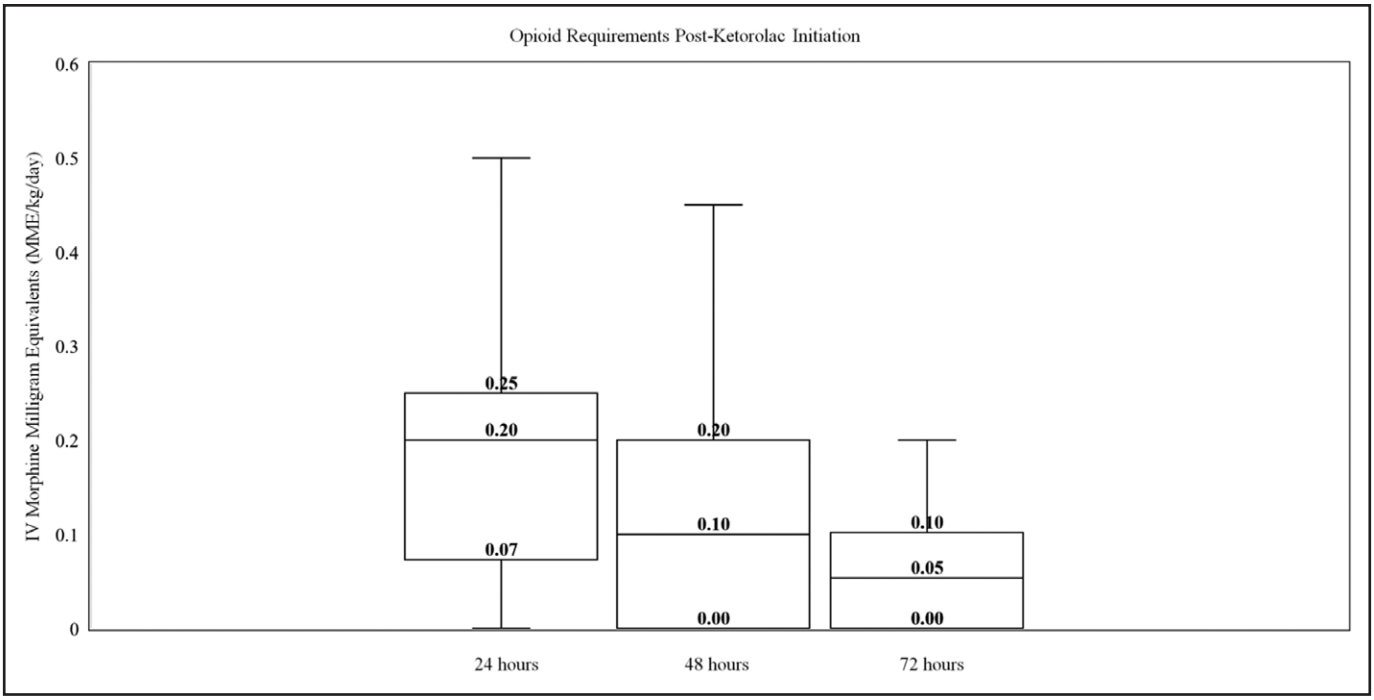

Figure 2. Opioid utilization among neonates. Opioid requirements among neonates postcardiac surgery who received ketorolac for pain management.

of 24 hours. Of the patients receiving both aspirin and ketorolac, two patients were documented to have blood on their wound dressing. Overall, we observed no clinically significant bleeding events, few blood transfusions, and no significant decrease in hemoglobin, which is similar to other published studies reporting the use of ketorolac in the neonate and infant post-surgical patient population (8, 9, 11, 24).

With regard to pain management, there was a decrease in morphine requirements and pain scores from baseline to post-48 hours after ketorolac initiation. Papacci et al (26) retrospectively evaluated ketorolac in 18 neonates and reported achieving pain control in 17 (94%) of the neonates, without reports of hematologic or renal concerns changes. Similarly, in this study, there was a decrease in opioid utilization following the initiation of ketorolac, with a reported requirement of median (IQR) morphine equivalents of 0.1 mg/kg/d (0.1–0.2 mg/kg/d) at 48 hours post-ketorolac initiation. However, given the descriptive nature of this study and the expectation that opioid requirements would decline after ketorolac administration, future prospective studies that include nonketorolac controls are warranted to further evaluate the potential opioid-sparing effects of ketorolac in neonates following cardiac surgery.

Limitations of this study include its retrospective study design (including reliance on documentation in the electronic medical record) and a relatively small study population. Furthermore, due to variable documentation of urine output and the lack of availability of other measurements of renal impairment (e.g., cystatin C), detection of renal dysfunction may have been hindered. However, given that most neonates experienced an increase in urine output following cardiac surgery, we anticipate the likelihood of underestimating renal dysfunction to be low. Additionally, given bleeding events were reliant on retrospective data collection, there may have been inconsistencies or gaps in documentation. Scoring pain is also a partially subjective measure and could impact the reliability of pain score findings. Furthermore, there was no concomitant comparison group given the use of ketorolac as part of an institutional analgesia protocol. Because any effort to construct a concomitant or historical control group would engender substantial selection bias, we have simply contextualized our findings in regard to previously published literature in similar or relevant pediatric populations.

CONCLUSIONS

In conclusion, our findings suggest that a ketorolac regimen 0.5 mg/kg/dose every 6 hours in neonates following cardiac surgery in patients meeting protocolized clinical criteria did not result in renal dysfunction or major bleeding events. Further prospective studies are warranted to confirm and extend these favorable findings regarding renal dysfunction and bleeding risks. Prospective controlled studies are needed to determine the efficacy with regard to potential opioid-sparing effects in neonates postcardiac surgery.

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