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Safety of ketorolac in surgical neonates and infants 0 to 3 months old

Jennifer H. Aldrink[a,*], Michelle Ma[b], Wei Wang[c], Donna A. Caniano[a], Jonathan Wispe[d], Teresa Puthoff[b]

[a]*Division of Pediatric Surgery, Department of Surgery, Nationwide Children's Hospital, The Ohio State University College of Medicine, OH 43205, USA*
[b]*Department of Pharmacy, Nationwide Children's Hospital, The Ohio State University College of Medicine Columbus, OH, USA*
[c]*Department of Biostatistics, The Research Institute, Nationwide Children's Hospital, The Ohio State University College of Medicine Columbus, OH, USA*
[d]*Division of Neonatology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, USA*

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Abstract

Background: Ketorolac is a nonsteroidal antiinflammatory drug widely used as an adjunct to postoperative pain control in adult and pediatric patients. Minimal safety data exist regarding the use of ketorolac in neonates.

Methods: The charts of 57 postsurgical neonates between 0 and 3 months of age were retrospectively reviewed for bleeding events associated with ketorolac. Data included gestational age (GA), corrected gestational age (CGA) at the time of ketorolac, serum creatinine, platelet count, urine output (in milliliters per kilogram per hour), concomitant medications, enteral feeds, number of ketorolac doses, and surgical procedure performed.

Results: Of 57 patients, 10 (17.2%) demonstrated a bleeding event. Mean CGA and serum creatinine for those with bleeding events was 39.4 weeks ($P = .69$) and 0.64 mg/dL ($P = .03$), respectively. Patients with a bleeding event received ketorolac at a mean of 20.7 days of life with 70% receiving the drug at less than 14 days of age, whereas those without a bleeding event received ketorolac at a mean of 31.9 days ($P = .04$). Bleeding events correlated with glomerular filtration rate of less than 30 mL/min/1.73 m^2 or concomitant medications in all but 1 patient.

Conclusions: Infants younger than 21 days and less than 37 weeks CGA are at significantly increased risk for bleeding events and should not be candidates for ketorolac therapy.

Ketorolac is a nonsteroidal antiinflammatory agent that has been demonstrated to be an effective drug in relieving moderate postoperative pain in adults and children [1-5]. Ketorolac can reduce the narcotic requirements after surgery and may therefore prevent some of the opioid-

* Corresponding author. Tel.: +1 614 722 0440.
E-mail address: jennifer.aldrink@nationwidechildrens.org (J.H. Aldrink).

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induced undesirable adverse effects, including respiratory depression, central nervous system disturbances, urinary retention, and prolonged ileus. However, ketorolac carries its own risks of increased bleeding complications and renal insufficiency.

Neonates and young infants can be particularly challenging in the postoperative setting given legitimate concerns of respiratory depression after opioid administration [1]. However, minimal safety or efficacy data on ketorolac currently exist in this age group in whom this drug could be a potentially useful adjuvant to opioids. The purpose of this study was to characterize the safety profile of ketorolac in infants 0 to 3 months old.

1. Methods

1.1. Patients

After institutional review board approval (no. 10-00292), a retrospective chart review was performed on infants between 0 and 3 months of age who had received ketorolac in the postoperative setting from 2008 to 2009. The dosage administered was 0.5 mg/kg/dose intravenously every 6 hours, although 2 patients received the medication every 8 hours.

1.2. Data collected

The main outcome evaluated was the incidence of bleeding complications. Bleeding events included bloody drainage from chest tubes; orogastric, nasogastric, or gastrostomy tubes; ventricular shunts; surgical wound or intraabdominal bleeding; or guaiac-positive stools. Data collected also included birth weight, gestational age (GA), corrected gestational age (CGA) at the time of ketorolac administration, serum creatinine (SCr), platelet counts, urine output (UOP) before and during drug administration, concomitant medications, enteral feeds, surgical procedure performed, number of ketorolac doses administered, and time in hours postoperatively ketorolac was administered. Surgical stress scores were measured using the scoring system published by Anand and Aynsley-Green [6]. This scoring system grades procedures in the following categories: amount of blood loss, site of surgery, amount of superficial trauma, extent of visceral trauma, duration of surgery, associated stress factors, and cardiac surgery, enabling practitioners to anticipate varying degrees of discomfort and targeting pain control methods accordingly.

1.3. Statistics

For statistical analysis, Fisher's Exact test was used to compare the relationship between the presence of enteral feeds and bleeding events. Wilcoxon's 2-sample test was used to compare the variables that did not follow normal distribution between those with a bleeding event and those without at bleeding event. Student's *t* test was used to compare birth weight by bleeding events and UOP by bleeding events. A statistically significant difference was defined as *P* value less than .05.

2. Results

2.1. Baseline patient characteristics

The charts of 57 neonates who had received postoperative ketorolac between the ages of 0 and 3 months were reviewed. The mean CGA for those with a bleeding event was 39.4 weeks (range, 36-45 weeks), not significantly different from those without a bleeding event, which was 40 weeks (range, 34-50 weeks) ($P = .7$). The means for birth weight and weight at the time of ketorolac administration were 2800 g (range, 700-4615 g) and 3412 g (range, 1870-7030 g), respectively. These were not significantly different between the group that developed a bleeding event and the group that did not ($P = .8$) (Table 1). The surgical procedures performed were variable and are listed in Table 2. A surgical stress score was assigned to each neonate, based on a previously published scoring system [6]. There were no differences in the surgical stress scores between the 2 groups, with a mean score of 5 (SD, ±2.1) in the bleeding event group and a mean score of 4.6 (SD, ±2.7) in the no bleeding event group ($P = .4$).

2.2. Bleeding events

Of the 57 patients who received postoperative ketorolac, 10 (17.2%) demonstrated a bleeding event, 3 of whom required the transfusion of blood products. Of these 3 patients

Table 1 Clinical parameters comparing those with a bleeding event with those with no bleeding event

	Bleeding event	No bleeding event	*P*
CGA (wk)	39.4	42	.7
Birth weight (g)	2844	2755	.8
Surgical stress score	5	4.6	.4
Platelet count	237,000	309,000	.03
Mean days of life	20.7	31.9	.04
No. of doses	8	9	.5
Baseline SCr (mg/dL)	0.64	0.42	.03
UOP 24 h predrug (mL/kg/h)	2.1	3.1	.06
UOP 24 h postdrug (mL/kg/h)	1.9	3.4	.01