

# Incidence of bleeding in children undergoing circumcision with ketorolac administration

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## Abstract

**Introduction:** Circumcision is the most common surgical procedure performed by pediatric urologists. Ketorolac has been shown to have an efficacy similar to morphine in multimodal analgesic regimens without the commonly associated adverse effects. Concerns with perioperative bleeding limit the use of ketorolac as an adjunct for pain control in surgical patients. As such, we sought to evaluate our institutional outcomes with respect to ketorolac and postoperative bleeding.

**Methods:** We retrospectively reviewed all pediatric patients undergoing circumcision from January 1, 2014 to December 31, 2015 at the Alberta Children's Hospital. Demographics, perioperative analgesic regimens, and return to emergency department or clinic for bleeding were gathered through chart review.

**Results:** A total of 475 patients undergoing circumcisions were studied, including 150 (32%) who received perioperative ketorolac and 325 (68%) who received standard analgesia. Patients receiving ketorolac were more likely to return to the emergency department or clinic for bleeding (ketorolac group 19/150 [13%], non-ketorolac group 16/325 [5.0%];  $p=0.005$ ). Patients receiving ketorolac were more likely to have postoperative sanguineous drainage (ketorolac group 96/150 [64%], non-ketorolac group 150/325 [46%];  $p<0.001$ ). There was no significant difference in the number of patients requiring postoperative admission or further medical intervention.

**Conclusions:** Although a promising analgesic, ketorolac requires additional investigation for safe usage in circumcisions due to possible increased risk of bleeding.

## Introduction

Circumcision is a common surgical intervention in pediatric urology indicated in instances of refractory balanitis, pathological phimosis, or paraphimosis. The control of postoperative pain is essential in order to decrease patient morbidity and to improve patient and parent satisfaction. Methods to reduce postoperative morbidity in circumcision include the

use of general anesthesia combined with regional block. Common regional blocks include dorsal penile nerve blocks (DPNB) or caudal epidural blocks (CB). Neither has been shown to be more effective than the other in terms of the need for rescue or other analgesia.<sup>1,2</sup> DPNB may be preferred over CB in the case of ambulatory children, as CB carries the risk of temporary leg weakness after use.

Even with current analgesia standards, pediatric surgical patients are often at risk of being undertreated for postoperative pain when the regional anesthesia resolves.<sup>3</sup> Pain is by far the most common complaint of parents after circumcision<sup>2</sup> and a common reason for parents to avoid pursuing circumcision for their child.<sup>4</sup> Ketorolac is an effective non-steroidal anti-inflammatory drug (NSAID) that provides an analgesic effect through inhibition of COX-1 and COX-2 within the body.<sup>5</sup> Compared to opioids, ketorolac offers equivalent levels of pain relief with a decreased incidence of postoperative nausea and vomiting.<sup>6,7</sup> A single dose of systemic ketorolac has been demonstrated to be an effective adjunct in multimodal analgesia regimens in order to reduce postoperative pain.<sup>8</sup>

Although ketorolac is a promising analgesic, trials for tonsillectomies have suggested an increased risk of postoperative bleeding.<sup>9,10</sup> This finding, however, is not consistent.<sup>6</sup> The fear of bleeding has led many otolaryngologists and anesthesiologists to avoid ketorolac in tonsillectomies and other conditions that may have an increased risk of bleeding. Bleeding, although uncommon, is the most common complication suffered by children receiving ketorolac.<sup>10</sup> Overall, the favourable side effect profile of ketorolac is balanced by concerns of postoperative bleeding. With circumcision being a high-volume pediatric urological procedure, we sought to evaluate the bleeding outcomes of children receiving ketorolac for circumcision.

## Methods

We conducted a retrospective study of pediatric patients (<18 years old) at the Alberta Children's Hospital who underwent circumcision for refractory balanitis, pathologi-

cal phimosis, paraphimosis, penile torque, or hypospadias from January 1, 2014 to December 31, 2015. Only charts of patients undergoing circumcision for refractory balanitis, pathological phimosis, and paraphimosis were included. The retrospective review spanned operative notes, nursing care notes, emergency charts, and clinic followups of each patient. Demographics, perioperative analgesic regimens, and bleeding events in postoperative care, emergency department, and clinic were gathered through chart review. Three incomplete charts were excluded and all information was anonymized. Two databases were cross-referenced (one provided by anesthesia and another by health records) to ensure that charts were congruent and complete.

Informed consent was obtained from all parents after an explanation of the procedure, alternate options, and possible risks. Three surgeons were performing the procedures at the time and surgical and anesthetic technique was similar in all cases. Based on the preference of the anesthetist and surgeon, children received either a standard analgesic regimen or a regimen augmented with intravenous ketorolac (0.5 mg/kg, maximum 30 mg). All children received a 15 mg/kg oral dose of acetaminophen prior to surgery unless contraindicated. General anesthesia was induced with sevoflurane via facemask. After establishing venous access, a laryngeal mask was inserted and anesthesia was maintained with one minimum alveolar anesthetic concentration (MAC) of sevoflurane in oxygen/air 50/50 mixture. The DPNB nerve block was performed by a pediatric urologist using a 23 GA needle inserted below the Buck fascia. Once the needle tip was positioned appropriately, and after a negative aspiration test, 0.2 mL/kg (maximum 10 mL) of 0.25% bupivacaine was injected in small aliquots, with intermittent aspiration throughout. In all patients, skin incision was performed at least five minutes after placement of the nerve block. At the beginning of the circumcision procedure under general anesthesia, patients in the ketorolac group received a 0.5 mg/kg (maximum 30 mg) intravenous dose of ketorolac. Patients were advised to take ibuprofen and acetaminophen postoperatively as needed, but not ibuprofen within six hours of the procedure due to increased bleeding risk. Non-invasive blood pressure monitoring, electrocardiography monitoring, and pulse oximeter were routinely used.

The surgical technique was similar in all cases — an excision technique with use of an artery clamp.<sup>11</sup> After being prepped and draped in supine position, the phimotic ring was stretched and preputial adhesions were bluntly dissected. Excess foreskin was clamped by an artery clamp then transected with monopolar cautery. Bipolar cautery was used to obtain good hemostasis. 5-0 Vicryl Rapide was used to reapproximate the foreskin. Dermabond glue was used and polysporin applied. The patient was then transferred to the postanesthetic care unit (PACU). No dressings were applied to the surgical site.

After the procedure, children were observed in the PACU by a nurse. If necessary, analgesics (acetaminophen) were given by a member of the anesthesia team. Children were discharged from the hospital after a period of observation and spontaneous micturition. Statistical analysis via chi-square was performed using SPSS analytical software.

## Results

Patient demographics are shown in Table 1. Between the two-year period (January 1, 2014 to December 31, 2015), 475 children aged five days to 17 years (mean age 5.3±4.2) underwent circumcision at the Alberta Children's Hospital. A general analgesic regimen was used in 325 children (68%), while perioperative ketorolac was used in 150 children (32%). There was no significant difference in age between groups (ketorolac group 5.6±4.1 years, non-ketorolac group 5.2±4.2 years;  $p=0.496$ ) and perioperative ketorolac was administered in the ketorolac group (0.44±0.14 mg/kg; range 0.11–1.14).

Results of data analysis are displayed in Table 2. There was a significantly higher incidence of postoperative sanguineous drainage for ketorolac patients: 64% ketorolac vs. 46% non-ketorolac (odds ratio [OR] 2.07; 95% confidence interval [CI] 1.39–3.09;  $p<0.001$ ). There was a significantly higher return to the emergency department or clinic for bleeding for ketorolac patients: 13% ketorolac vs. 5% non-ketorolac (OR 2.63; 95% CI 1.30–5.32;  $p=0.005$ ). There was no difference in postoperative admission between the groups: 0% ketorolac vs. 0.9% non-ketorolac (OR 0.991; 95% CI 0.98–1.00;  $p=0.238$ ).

## Discussion

Circumcision is the most common surgical procedure performed by pediatric urologists. Ketorolac has been shown to have an efficacy similar to morphine in multimodal analgesic regimens without the commonly associated adverse effects.<sup>6,7</sup> Unfortunately, the most common side effect of ketorolac is increased bleeding.<sup>5</sup> As such, the objective of this study was to retrospectively evaluate bleeding outcomes in children under-

**Table 1. Patient demographic information in children undergoing circumcision with or without ketorolac administration**

	Overall	Ketorolac	Non-ketorolac
Number of patients (all males)	475	150	325
Age in years, M (SD)	5.3 (4.2)	5.6 (4.1)	5.2 (4.2)
Ketorolac dosage in mg/kg, M (SD)	N/A	0.44 (0.14)	0

M: mean; SD: standard deviation.

**Table 2. Comparative analysis with chi-square for children undergoing circumcision with or without ketorolac administration**

	Absolute count without ketorolac	Absolute count with ketorolac	Odds ratio (95% CI)	P
Postoperative sanguineous drainage	150/325 (46.2%)	96/150 (64.0%)	2.07 (1.39–3.09)	<b>p&lt;0.001</b>
Return to ED or clinic for bleeding	16/325 (4.9%)	19/150 (12.7%)	2.63 (1.30–5.32)	<b>p=0.005</b>
Postoperative admission within 30 days	3/325 (0.9%)	0/150 (0.0%)	0.991 (0.98–1.00)	p=0.238

CI: confidence interval; ED: emergency department.

going circumcision with ketorolac. In addition, any serious adverse events would help in the design of future randomized trials involving ketorolac in pediatric surgeries.

Overall, there was a significantly higher incidence ( $p<0.001$ ) of postoperative sanguineous drainage for ketorolac patients (96/150, 64%) compared to the non-ketorolac group (150/325, 43%). In other words, the surgical site of ketorolac patients looked bloodier than those of standard analgesia patients. With ketorolac patients exhibiting a bloodier surgical site, surgeons may be called to the PACU more frequently. In addition, patients receiving ketorolac were found to be more likely to return to the emergency department or clinic for bleeding (ketorolac group 19/150 [13%], non-ketorolac group 16/325 [5%];  $p=0.005$ ). This suggests a possible safety concern towards ketorolac administration in pediatric patients. Furthermore, additional visits to a physician increase the burden to our healthcare system. There was no significant difference for postoperative admission between groups. Although promising, the low incidence of admissions makes this result inconclusive.

An attempt was made to evaluate a dose-response relationship between ketorolac and risk of bleeding; however, anesthesiologists at the Alberta Children's Hospital tended to use an average 0.5 mg/kg dosage of ketorolac for each patient and, therefore, no dose response was seen. Furthermore, the number of patients with postoperative bleeding requiring return to medical attention was low, making this a small sample size to evaluate.

There are currently no studies regarding circumcision and ketorolac in previous literature to our knowledge. That being said, pediatric tonsillectomy studies have demonstrated increased risk of bleeding with ketorolac.<sup>9,10</sup> This finding, however, is not consistent.<sup>6</sup> Although findings in literature are conflicting, the fear of bleeding has led many otolaryngologists and anesthesiologists avoid ketorolac in tonsillectomies and other conditions that may have an increased risk of bleeding. The results of this circumcision study raise

concerns about bleeding and supports the findings of most pediatric tonsillectomy studies.

As a retrospective cohort study, this study was limited in a few areas. Firstly, key outcomes, such as postoperative pain control, were not recorded. This means that although ketorolac resulted in more bleeding events, we have no indication of whether the pain control may have been worth the risk. To further explore this area, a randomized, controlled trial of pain control in ketorolac and non-ketorolac patient is currently underway. In addition, rare outcomes, such as postoperative admission or additional surgical intervention, were difficult to evaluate. A meaningful conclusion for these outcomes would require a much larger sample size than the number of studies we had for review at the Alberta Children's Hospital.

Another limitation was that patients could have presented to hospitals other than the Alberta Children's Hospital for bleeding. As a result, some bleeding cases could have been missed. To reduce this effect, patients were given a standardized sheet that instructed them to come back to Alberta Children's Hospital given any concerns; however, this may not have always been followed by patients. In addition, patients were instructed to take ibuprofen and acetaminophen for postoperative pain and, unfortunately, adding an NSAID could have increased the anticoagulation effect. With this database, it was not possible to tell which patients took ibuprofen or how much they took. An ongoing prospective study with postoperative home phone calls aims to evaluate this parameter further.

Overall, ketorolac patients had significantly more bleeding events requiring medical attention than patients receiving standard analgesia during circumcision. In addition, surgeons may be called to the PACU more frequently with more sanguineous ooze noted in ketorolac patients. Although a promising analgesic, ketorolac requires additional investigation for safe use in circumcisions due to possible increased risk of bleeding. We have launched a randomized, controlled trial evaluating the pain control and safety of ketorolac in pediatric circumcisions and hope to provide more answers on this topic.

**Competing interests:** Dr. Weber has participated in a clinical trial supported by Allergan. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

## References

1. Cyna AM, and Middleton P. Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. *Cochrane Database Syst Rev* 2008;4:CD003005. <https://doi.org/10.1002/14651858.CD003005.pub2>
2. Brady-Fryer B, Wiebe N, Lander JA. Pain relief for neonatal circumcision. *Cochrane Database Syst Rev* 2004;4:CD004217. <https://doi.org/10.1002/14651858.CD004217.pub2>

3. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;116:248-73. <https://doi.org/10.1097/ALN.0b013e31823c1030>
4. Adler R, Ottaway MS, Gould S. Circumcision: We have heard from the experts; now let's hear from the parents. *Pediatrics* 2001;107: E20.
5. National Center for Biotechnology, US National Library of Medicine. Ketorolac compound summary. Available at <http://pubchem.ncbi.nlm.nih.gov/compound/3826>. Accessed June 24, 2015.
6. Sutters KA, Levine JD, Dibble S, et al. Analgesic efficacy and safety of single-dose intramuscular ketorolac for postoperative pain management in children following tonsillectomy. *Pain* 1995;61:145-53. [https://doi.org/10.1016/0304-3959\(94\)00166-C](https://doi.org/10.1016/0304-3959(94)00166-C)
7. Gunter JB, Varughese AM, Harrington JF, et al. Recovery and complications after tonsillectomy in children: A comparison of ketorolac and morphine. *Anesth Analg* 1995; 81:1136-41.
8. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: A meta-analysis of randomized trials. *Anesth Analg* 2012;114:424-33. <https://doi.org/10.1213/ANE.0b013e3182334d68>
9. Rusy LM, Houck CS, Sullivan LJ, et al. A double-blind evaluation of ketorolac tromethamine vs. acetaminophen in pediatric tonsillectomy: Analgesia and bleeding. *Anesth Analg* 1995;80:226-9.
10. Splinter WM, Rhine EJ, Roberts DW, et al. Preoperative ketorolac increases bleeding after tonsillectomy in children. *Can J Anaesth* 1996;43:560-3.
11. Abdulwahab-Ahmed A, Mungadi I. Techniques of male circumcision. *J Surg Tech Case Rep* 2013;5:1-7. <https://doi.org/10.4103/2006-8808.118588>

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