

Ketorolac use in the Pediatric Surgical Patient: An Evidence-Based Practice Analysis

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Keywords: ketorolac, Toradol, blood loss, bleeding, perioperative, pediatric

Introduction

Opioid-based medications are often the first medications selected for pain control in young patients; however opioids possess several unwanted side effects such as respiratory depression, nausea, vomiting and allergic reactions. Administration of medications that support a multimodal approach to pain management is imperative. It is a longstanding belief that pediatric pain is significantly undertreated due to providers' hesitance to use non-steroidal anti-inflammatory drugs (NSAIDs). Baley et al.¹ cite that anesthesia providers have been challenged to eliminate the under treatment of pain in the pediatric population. The pediatric population is at high risk for inadequate pain management and providers should strongly consider adjunct medications in the treatment of pain.

Acute postoperative pain presents as a challenge because more patients are reporting concerns about their perioperative pain management. Smith² states 31% of patients' report severe, and 47% report moderate postoperative pain. Pain that is not managed properly in the postoperative period may result in physiological and psychological side effects. Inadequate perioperative analgesia may play an important role in decreased gastrointestinal motility, myocardial ischemia, delayed wound healing, atelectasis, hypoxia, anxiety, splinting, and the possibility of chronic pain. Furthermore, the pediatric patient may feel helpless and experience high levels of anxiety and other psychological symptoms.

Ketorolac is a widely available NSAID that may reduce inflammation and decrease pain. It may be administered intravenously, by mouth, and via the intranasal route. It is an alternative or adjunct to opioid-based analgesics in an effort to reduce opioid side effects, decrease pain and inflammation, and increase patient satisfaction. Ketorolac inhibits the cyclooxygenase (COX) pathway and is classified as a non-selective COX inhibitor. The inhibition of the COX-2 pathway is responsible for its' therapeutic effect; whereas, the inhibition of the COX-1 pathway is responsible for ketorolac's side effects. Gastrointestinal discomfort and decreased platelet function are two of the many side effects that patients experience.³ The inhibition of platelet function ultimately does increase blood loss in surgical patients to some degree, but it has been debated if the increase in blood loss has a negative effect on surgical outcomes.

Purpose Statement

The impact of ketorolac on blood loss and negative outcomes is especially unclear in the pediatric surgical population. Recent studies focus on the administration of ketorolac to the pediatric surgical patient and the significance of blood loss, surgical intervention, and possibility of blood transfusion. The purpose of this evidence-based practice analysis is to thoroughly investigate the role of ketorolac and perioperative blood loss in the pediatric surgical population.

Methodology

A population, intervention, comparison, and outcome (PICO) question was constructed to focus a review of the current literature. The PICO question selected was: "Do pediatric surgical

patients who receive perioperative ketorolac experience a significant increase in perioperative blood loss when compared to those who do not receive ketorolac?”

Current literature was reviewed using three electronic databases: PubMed, Medline, and CINAHL Complete. The following keywords were searched: *estimated blood loss (EBL)*, *perioperative*, *pediatric*, *Toradol*, *ketorolac*, and *bleeding*. Articles were filtered using the “peer reviewed” selection and narrowed by date. Article dates range from 2004-2016, with the majority of them published between 2009 and 2016.

Studies were included if ketorolac was administered perioperative, the patients were less than 21 years of age, and blood loss was assessed. Hemoglobin changes, chest tube output, requirement of surgical intervention, and blood transfusion were all indicators of significant blood loss. Six studies met the inclusion criteria with one randomized control trial (RCT) (Level III evidence) and five retrospective studies (Level IV evidence) analyzed. The Quantitative Research Article Rapid Appraisal Guide was utilized to assign the strength of evidence.

Literature Review

Six studies were examined to evaluate if perioperative ketorolac significantly increased perioperative blood loss in the pediatric surgical patient.⁴⁻⁹ Of the six studies, five studies reported using a standard ketorolac dose of 0.5 mg/kg every 6 to 8 hours. Two studies reported giving a one-time 1mg/kg-loading dose and then following a standard schedule.^{5,9} One study did not report the dosage of ketorolac.⁶ Each study reported differing methods of determining “significant” blood loss, but each definition was supplied.

Dawkins et al.⁴ retrospectively reviewed the charts of 19 patients, ages 0-6 months, with biventricular circulations who received ketorolac following cardiothoracic surgery. The ketorolac group was then compared to 19 age-matched control patients, who also underwent cardiothoracic surgery. Patients with univentricular anatomy were excluded from the study. The mean dose of ketorolac administered was 0.5 mg/kg intravenously every 6 to 8 hours with a range from 0.4-0.63. The number of doses received ranged from 2 to 12 with a mean of 4.5 doses. Hemoglobin and hematocrit values were obtained following the surgical procedure but prior to ketorolac administration, and within 24 hours after the initiation of ketorolac. Mean post-surgical, pre-ketorolac, hemoglobin was 12.9 +/- 2.5 (9.1-17.6) and hematocrit was 38.6 +/- 8 (26.3-52.8) in the ketorolac group. The control group had no significant differences with mean post-surgical hemoglobin of 12.9 +/- 1.8 (9.3-16.2) and hematocrit of 38.3 +/- 6.1 (27.4-49.8). The postoperative hemoglobin was 13 +/- 2 (9.6-15.9) in the ketorolac group compared to the control group hemoglobin 13.6 +/- 1.8 (9.6-13.5) (P = 0.35). The postoperative hematocrit of 39.9 +/- 7.5 (28-53) in the ketorolac group compared to a control group hematocrit of 41 +/- 5.5 (29-50.1) (P = 0.60). The number of transfusions required in either group was not reported, but there was no statistically significant difference in the number of blood transfusions administered between the two groups.

Gupta et al.⁵ retrospectively reviewed the charts of 842 infants and children who underwent congenital heart surgery between July 2001 and October 2002, in a single institution. Ninety-four patients who received perioperative ketorolac were selected as the ketorolac group and another

94 patients, who did not receive ketorolac, were selected as a control group. The mean age of the patients in the ketorolac group was 8.5 +/- (6.1) years compared to a mean age of 6.7 +/- (5.6) years in the control group. The authors defined “significant” blood loss as requiring the need for surgical exploration. In the ketorolac group, treatment was initiated on the day of surgery with an initial loading dose of 1mg/kg ketorolac in 38 of the patients, followed by the standard 0.5 mg/kg every 6 hours. The remaining 56 patients did not receive a loading dose of ketorolac, but did receive the 0.5 mg/kg dose every 6 hours. No patients in the ketorolac group experienced blood loss that required surgical exploration. Four patients in the control group did experience blood loss that required surgical exploration. The relative risk of significant postoperative blood loss in the ketorolac group compared with the non-ketorolac group was 0.2 (95% CI 0.02-1.67) (P = 0.1).

Richardson et al.⁶ retrospectively reviewed 1451 neurosurgical patients who underwent surgery between December 2006 and April 2012 in a single institution. Patients undergoing craniotomy/craniectomy, intra-dural catheter placement, Chiari malformation repair, spinal procedures and external ventricular drain placement were included. Of 1593 surgical procedures assessed, patients who underwent surgery within 7 days of either a traumatic injury, or an intracranial or intra-spinal hemorrhage were excluded. Medications associated with an increased risk of bleeding including system anticoagulants, antiplatelet agents, valproic acid and NSAIDs were defined as “pharmaceutical confounders” if administered within 24 hours preoperatively or 72 hours postoperatively. Outcomes were postoperative blood loss requiring surgical intervention for hematoma evacuation or radio-graphically identified hemorrhage. The ketorolac group received at least one dose either in the 24 hours prior to, or the 72 hours following surgery, but specific ketorolac dosing was not identified. The median age was 4.8 years with 453 procedures performed on patients less than 1 year old and 462 procedures performed on patients greater than 10 years old. More received ketorolac (n = 955) with 496 receiving no ketorolac. Seven clinically significant blood loss events were documented and four were in patients who received ketorolac (P = 0.70). Axial imaging was performed within 7 days of the surgical procedure for 539 patients (37.15%). Approximately 11% (35/313) in the ketorolac group compared to 9.3% (21/226) in the control group had bleeding identified in postoperative imaging (P = 0.48). A pharmaceutical cofounder was associated with a statistically significant increase in the chance of a postoperative blood loss event (P = 0.018).

Gupta et al.⁷ enrolled 70 pediatric congenital heart surgery patients with ages between 2 days and 18 years into their RTC. The children were randomized to either a ketorolac or control group with all patients receiving opioid analgesia. The authors identified the primary outcome as the incidence of blood loss complications with the administration of ketorolac for less than 48 hours. The mean age in the ketorolac group was 23.1 (+/- 29.1) months compared to 25.1 (+/- 38.4) months in the control group. Participants in each group had similar weights, cardiac defects and cardiopulmonary bypass times. The ketorolac group received a standard dose of 0.5 mg/kg of ketorolac with a maximum dose of 15 mg every 6 hours for a duration of less than 48 hours. The chest tube output was significantly more in the control group (median 16.5 ml/kg/day) compared to the ketorolac group (median 13.3 ml/kg/day) (P = 0.05). One patient in the control group experienced severe wound blood loss; whereas, one patient in the ketorolac group experienced a gastrointestinal bleed (P = 0.7).

Aldrink et al.⁸ retrospectively examined the use of ketorolac in neonates between the ages 0-3 months. Participants received postoperative ketorolac between the years 2008 to 2009. Fifty-seven patients received a standard dose of 0.5 mg/kg every 6 hours via the intravenous route, although 2 patients received ketorolac every 8 hours. The incidence of blood loss complications defined as bleeding from nasogastric tube, orogastric tube, gastrostomy tubes, ventricular shunts, and surgical wounds or intra-abdominal bleeding was the primary outcome evaluated. Of 57 participants, 10 demonstrated a significant blood loss event and 3 required blood transfusion.

Moffett et al.⁹ retrospectively examined the safety of ketorolac in 53 surgical neonates and infants less than 6 months of age. All patients were recipients of cardiothoracic surgery to repair a congenital heart defect. Seven infants received a loading dose of 0.93 +/- 0.14 mg/kg of ketorolac followed by a standard dose of 0.44 +/- 0.09 mg/kg every 6 hours while 46 infants/neonates received the standard dose without a loading dose. Hemoglobin and hematocrit levels were obtained prior to surgery and 48 hours postoperatively. Baseline hemoglobin was 12.14 +/- 2.15 and hematocrit 35.9 +/- 6.18 compared to 48 hours postoperative hemoglobin of 12.9 +/- 2.21 (P = 0.19) and hematocrit 37.9 +/- 6.1 (P = 0.15). There were 4 mild blood loss events noted, but zero resulted in significant changes in hemoglobin or hematocrit, changes in platelet counts or the requirement of blood transfusion or surgical intervention.

Reference	Sample (n) and study design	Ketorolac time and dose	No ketorolac	Preoperative lab values	Postoperative lab values	Results
Dawkins et al., 2009	N = 38 Retrospective study • Cardiothoracic surgery patients ages 0-6 months	N = 19 Dose = 0.5 mg/kg every 6-8 hours	N = 19	Ketorolac group • Hemoglobin 13.5 +/- 2.8 (9.4-19) • Hematocrit 41.3 +/- 9.3 (28.9-62) Control group • Hemoglobin 12.8 +/- 1.3 (10.1-15.3) • Hematocrit 38.2 +/- 4.7 (28.8-47.2)	Ketorolac group • Hemoglobin 13 +/- 2 (9.6-15.9) • Hematocrit 39.9 +/- 7.5 (28-53) Control group • Hemoglobin 13.6 +/- 1.8 (9.6-13.5) • Hematocrit 41 +/- 5.5 (29-50.1)	No significant different in Postoperative Hgb (P = 0.35) No significant different in Postoperative Hct (P = 0.60)
Gupta et al., 2005	N = 842 Retrospective study • Cardiothoracic surgery patients ages 2-14 years	N = 94 Dose = 0.5 mg/hg every 6 hours 38 received loading dose of 1 mg/kg	N = 94	• Normal bleeding times for all.	None	Ketorolac group • Zero patients developed bleeding Control group • Four patients developed bleeding (P = 0.01)
Richardson et al., 2015	N = 1451 Retrospective study • Neurosurgery patients ages 0-30 years	N = 955	N = 496	None	None	Ketorolac group • Four bleeding events Control group • Three bleeding events (P = 0.70)

Reference	Sample (n) and study design	Ketorolac time and dose	No ketorolac	Preoperative lab values	Postoperative lab values	Results
Gupta et al., 2004	N = 70 Randomized control trial • Cardiothoracic patients age 0-18 years	N = 35 Dose = 0.5 mg/kg every 6-8 hours with a max dose of 15 mg/kg	N = 35	None	None	Ketorolac group • Chest tube drainage 13.3 ml/kg/day (4-22) Control group • Chest tube drainage 16.5 ml/kg/day (3-24) (P = 0.05)
Aldrink et al., 2011	N = 57 Retrospective study • Surgical neonates ages 0-3 months	N = 57 Dose = 0.5 mg/kg every 6-8 hours	NA	None	Ketorolac group • Mean platelet count 237 (91-721) Control group • Mean platelet count 309 (78-736)	Ketorolac group • Ten patients experienced bleeding events (P = 0.03)
Moffett et al., 2006	N = 53 Retrospective study • Surgical infants ages 0-6 months	N = 53 Dose = 0.44 +/- 0.09 mg/kg every 6-8 hours 7 received loading dose of 0.93 +/- 0.14 mg/kg	NA	Ketorolac group • Mean hemoglobin 12.4 +/- 2.15 • Mean hematocrit 35.9 +/- 6.18	Ketorolac group • Mean hemoglobin 12.9 +/- 2.21 • Mean hematocrit 37.9 +/- 6.1	Ketorolac group • Four patients experienced bleeding events but none required intervention

Conclusion

Four studies focused on pediatric patients undergoing cardiothoracic surgery, with most procedures some variant of congenital heart defect (CHD) repair. Of these four studies, one was a RTC and three were retrospective chart reviews. In three retrospective reviews, the authors selected age comparable surgical patients as the control^{4,5,7} and one review⁹ only included patients who received ketorolac. Of the patients undergoing cardiothoracic surgery, two studies reported findings on patients exclusively less than 6 months of age and two studies included patients with a range of 0-21 years of age.

Five studies reported no significant risk of blood loss with the administration of perioperative ketorolac.^{4,5,6,7,9} Of the five, two enrolled patients ages 0-6 months and three studies included patients 0-21 years of age. Three studies identified “statistically significant blood loss” as returning to the operating room for hematoma evacuation, surgical intervention or significant changes in hemoglobin and hematocrit levels.^{5,9} The final two studies defined “statistically significant blood loss” as either hemoglobin levels less than 10gm/dl or chest tube/wound output requiring a blood transfusion.^{4,6,7}

Aldrink et al. reported findings that supported increased blood loss risk associated with the perioperative administration of ketorolac. The study was specific to infants’ ages 0-3 months of age.⁸ This study determined that neonates under 21 days old or a corrected gestational age (CGA) of less than 37 weeks, are at a statistically significant risk of increased perioperative

blood loss requiring surgical intervention or blood transfusion. The 0-3 month old infant has immature liver and kidneys cells, so further investigation regarding the potential role the immature liver and kidney might play in bleeding events is warranted. In review, five studies reported no significant risk of increased perioperative blood loss with the administration of ketorolac while one study demonstrated a relative increased risk given certain circumstances.

Providing adequate pain control and minimizing side effects for the pediatric surgical patient should be every anesthetist's goal; however, the road to achieving adequate postoperative pain control may not always be easy. Optimizing available resources and using current research play an important role in building a multimodal pain management strategy. Evidence shows pediatric surgical pain is under treated, so vigilance is always necessary.¹ The goal of this EBP analysis was to determine if the administration of perioperative ketorolac increased the pediatric surgical patients' risk of requiring an intervention due to increased blood loss. Five of the six studies demonstrated no significant blood loss risk while receiving ketorolac as an adjunctive intravenous medication in the perioperative period. The dose most commonly administered was 0.5 mg/kg every 6 to 8 hours. One study did demonstrate an increased blood loss risk, but was specific to infants less than 3 months of age. More RCTs are needed to determine absolute safety, but five studies demonstrated ketorolac could be administered without a significant increase in blood loss. Other considerations such as kidney and liver function should be evaluated prior to administration.

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Mentor: Sharon Hadenfeldt, PhD, CRNA