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Postoperative Ketorolac Administration Is Not Associated with Hemorrhage in Cranial Vault Remodeling for Craniosynostosis

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Background: Nonsteroidal anti-inflammatory drugs have been used as part of multimodal postoperative analgesic regimens to reduce the necessity of opioids. However, due to its effect on platelet function, there is a hesitation to utilize ketorolac postoperatively. The goal of this study is to analyze our experience utilizing ketorolac in patients who underwent major cranial vault remodeling (CVR) for craniosynostosis with an emphasis on postoperative hemorrhage and complications.

Methods: A retrospective review was performed for all patients undergoing CVR for craniosynostosis from 2013 to 2017. Primary outcomes were hemorrhagic complications. Secondary outcomes included length of stay, emesis, and doses of pain medication.

Results: Seventy-four consecutive patients met inclusion criteria. Forty-three (58.1%) received ketorolac. Seven in the ketorolac group (16%) and 9 in the control group (29%) received intraoperative blood transfusion ($P = 0.25$). One in the ketorolac group (2.3%) and 2 in the control group (3.1%) necessitated postoperative transfusion ($P = 0.56$). Patients who received ketorolac required less morphine doses (2.1 versus 3.3 doses; $P = 0.02$) and had a reduced length of stay (2.1 versus 2.6 nights; $P = 0.04$).

Conclusions: This is the first study to demonstrate that postoperative ketorolac is not associated with an increase in hemorrhagic complications or transfusion risk in children who underwent CVR for craniosynostosis. Patients administered ketorolac required less morphine and had a hospital length of stay. We hope this study stimulates more well-done prospective trials analyzing the role that ketorolac can play in an effective and safe postoperative analgesia regimen. *(Plast Reconstr Surg Glob Open 2019;7:e2401; doi: 10.1097/GOX.0000000000002401; Published online 19 August 2019.)*

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) offer analgesic efficacy similar to that of morphine and meperidine[1,2] and have been used as part of multimodal postoperative analgesic regimens to reduce the necessity of opioids and their associated side effects, and hospital length of stay.[3–11] The incorporation of NSAIDs in the postoperative period has shown to reduce opioid consumption by 30%–50%[12] with an associated decrease in postoperative nausea, vomiting, and sedation.[13] Ketorolac tromethamine (ketorolac) is an NSAID that can be administered parenterally and is not associated with central nervous system or cardiorespiratory depression or postoperative nausea and vomiting.[1,14]

NSAIDs and ketorolac, due to their nonselective inhibition of Cyclooxygenase (COX)-1 and COX-2 enzymes on platelets, gastrointestinal mucosa, and kidneys, have been associated with a variety of adverse events.[15] Most pertinent to surgery, inhibition of COX by NSAIDs has shown to alter platelet function and prolong bleeding times in healthy volunteers[2,15–17] even though bleeding times generally remain within normal limits.[16] Due to this impact on the coagulation cascade and potential to result in hemorrhagic complications, there is a hesitation to utilize ketor-

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olac postoperatively and there are conflicting results over its use and increased risk of bleeding in the literature.[18–22]

The rate of allogenic blood transfusion in cranial vault remodeling (CVR) for craniosynostosis has been reported to be as high as 80%–100%.[23–27] Many surgeons have been reluctant to use ketorolac after major cranial procedures to avoid postoperative bleeding and the necessity for additional transfusions. However, a recent study by Richardson et al[21] showed that routine ketorolac administration was not associated with hemorrhage in children undergoing a wide range of neurosurgical procedures. At our institution, the rate of intraoperative hemorrhage requiring transfusion is 21%, and postoperative transfusions are only required by 4% of patients. As a result, we have incorporated ketorolac into our postoperative pathway for children undergoing CVR. The goal of this study is to analyze our experience utilizing ketorolac in patients who underwent major CVR for craniosynostosis at our institution with an emphasis on postoperative hemorrhage and complications.

PATIENTS AND METHODS

Following approval from our Institutional Review Board, a retrospective review was performed for all patients undergoing CVR for craniosynostosis from December 2013 to September 2017. Patients undergoing limited craniectomies (strip or Pi procedures) were excluded. All patients were placed on a perioperative blood management protocol that was instituted in December 2013. No routine postoperative drains or head wrap was utilized, and no postoperative imaging was performed. Routine neurologic examinations were performed during the hospitalization to monitor for the signs of intracranial bleeding.

Nonsteroidal anti-inflammatory medications, ibuprofen or ibuprofen/ketorolac, were written for all patients postoperatively. Ibuprofen was ordered at 10 mg/kg per dose and intravenous ketorolac at 0.25 mg/kg at a frequency of every 6 hours as needed. When both were ordered, the decision to administer ibuprofen or ketorolac was made by the bedside nurse, typically based on the patient's ability to take medications orally. The surgical team did not influence the use or administration of ketorolac. Patients who received ibuprofen only served as the control group for this study.

Demographic data (age at the time of surgery and sex), type of synostosis based on involved sutures (simple versus complex), type of CVR (anterior CVR [ACVR] or posterior CVR [PCVR]), primary or secondary surgery, procedural time, crystalloid and colloid use during the surgery (ml/kg), recycled autologous red cell volume (ml/kg), estimated blood loss (ml), the rate of intraoperative transfusion, the rate of postoperative transfusion, and follow-up time (in days) were collected. Postoperative hemoglobin trend was evaluated by comparing hemoglobin values drawn at 3 scheduled time points (occasionally more) after the procedure. The percent change in hemoglobin was calculated ([discharge hemoglobin – the first postoperative hemoglobin]/the first postoperative hemoglobin × 100). For the 3 patients who received postoperative blood transfusions, the discharge hemoglobin was substituted by pretransfusion hemoglobin to better reflect the decrease in hemoglobin. Confounding variables, such as comorbidities with increased bleeding risk (eg, factor deficiencies, von Willebrand disease) or home medications with potential anticoagulation properties (eg, aspirin, valproic acid), were also analyzed.

Primary outcomes were postoperative hemorrhagic complications such as postoperative transfusion rate, change in hemoglobin over the postoperative period, and hematoma and intracranial hemorrhage rates. Hematomas were defined as a sanguineous fluid collection that required intervention in the postoperative period. Secondary outcomes included the development of renal insufficiency/failure and gastrointestinal bleeding, which are measures related to the safety profile of ketorolac. Renal insufficiency/failure was defined as decreased urine output or increased serum creatinine in the postoperative period. Gastrointestinal bleeding was defined as the presence of hematemesis or melena. Other variables were length of hospitalization (measured as number of nights spent in the hospital after the procedure), episodes of emesis, and doses of morphine, oxycodone, ketorolac, and ibuprofen administered during the hospitalization.

Categorical variables are presented as prevalence and percentages. Continuous variables are presented as means ± SD, range. Categorical variables were examined using the chi-square or Fisher's exact test as appropriate. Continuous variables were examined using a Student's t test. Statistical significance was set at $P < 0.05$. GraphPad Prism 7.0 (GraphPad Software, La Jolla, Calif.) was used for all analyses.

RESULTS

Demographics and Clinical Characteristics

Seventy-four consecutive patients who underwent CVR for craniosynostosis were identified during the study period. The median age of patients was 0.9 years (range, 0.6–16.1 years). Thirty patients (40.5%) were female and 44 (59.4%) were males. The types of synostoses included 24 (32%) sagittal, 15 (20%) metopic, 10 (13%) unilateral coronal, 3 (4%) lambdoid, and 22 (30%) multisuture or complex synostosis patients. Forty-three patients (58%) underwent ACVR, and 31 patients (42%) underwent PCVR. Thirteen patients (17%) underwent CVR as a secondary CVR procedure. The mean procedural time was 319 ± 76 minutes (range, 201–580 minutes). No patients had comorbidities that would increase bleeding risk or were on any blood thinning medication at the time of the procedure (Table 1).

Of the 74 consecutive patients included in the study, 43 (58.1%) patients received at least 1 dose of ketorolac and the remaining 31 (41.9%) patients did not receive any ketorolac, making up the control group. There was no significant difference between the groups in regard to age (2.0 versus 3.1; $P = 0.21$), type of synostosis (complex versus simple: 13/30 versus 8/23; $P = 0.6$), or sex (male/female: 30/13 versus 14/17; $P = 0.05$) (Table 2).

Table 1. Demographics of Patient Cohort

Demographic	N (%)
Total no. patients	74
Age at surgery, median (range in years)	0.9 (0.6–16.1)
Sex, n (%)	
Female	30 (40.5)
Male	44 (59.4)
Synostoses, n (%)	
Sagittal	24 (32)
Metopic	15 (20)
Unilateral coronal	10 (13)
Sagittal	24 (32)
Lambdoid	3 (4)
Multisuture or complex	22 (30)
Remodeling, n (%)	22 (30)
Anterior cranial vault	43 (58)
Posterior cranial vault	31 (42)
Procedure time, mean (range in minutes)	319 (201–580)

Table 2. Demographic and Clinical Characteristics of Ketorolac and Control Patients

	Ketorolac (n = 43)	Control (n = 31)	*P*
Mean age at surgery in years	2.0 ± 1.9	3.1 ± 4.6	0.21
Male-to-female ratio	30/13	14/17	0.05
Type of synostosis (simple/complex)	30/13	23/8	0.6

Perioperative Findings

The only significant difference between the ketorolac and control groups was a higher ratio of ACVR to PCVR in the control group (24/7 versus 19/24; $P < 0.01$). Operative time, intraoperative crystalloid use, autologous red cell recycling volume, and estimated blood loss were not different between the groups. When calculated per body weight, the amount of colloid administered intraoperatively was higher in the ketorolac group (9.5 ± 2.7 versus 5.1 ± 6 ml/kg; $P = 0.01$). Seven patients in the ketorolac group (16%) and 9 patients in the control group (29%) received intraoperative transfusion ($P = 0.25$). One patient in the ketorolac group (2.3%) and 2 patients in the control group (3.1%) necessitated postoperative transfusion ($P = 0.56$). For the ketorolac group, the mean first postoperative hemoglobin was lower than the control group at 9.2 versus 9.7 g/dl, respectively, but this difference was not statistically significant ($P = 0.21$). Although the discharge hemoglobin was lower in the ketorolac group (8.2 versus 9.1 g/dl; $P = 0.02$), the postoperative change in hemoglobin was similar between the 2 groups (10% versus 6.7% decrease in hemoglobin; $P = 0.1$) (Table 3).

Table 4. Analgesic Use, Oral Intake, and Emesis During Postoperative Hospital Stay

	Ketorolac (n = 43)	Control (n = 31)	*P*
Ibuprofen, doses	3.8	6.1	<0.01*
Oxycodone, doses	2.1	2.9	0.21
Ketorolac, doses	3.2	N/A	
Morphine, doses	2.1	3.3	0.02*
Emesis, no. episodes	1.2	1.6	0.33
Length of stay, nights	2.1	2.6	0.04*

*$P < 0.05$.
N/A, not applicable.

Postoperative Outcomes

The average time between the end of the procedure and ketorolac administration was 4 hours ± 19 minutes (range, 40 minutes to 24 hours). The mean number of ketorolac doses given during hospitalization was 3.2 ± 1.8 (range, 1–11). Patients in the ketorolac group required less morphine than the control group (2.1 versus 3.3 doses; $P = 0.02$), whereas oxycodone doses were similar between the 2 groups ($P = 0.21$). In the ketorolac group, less doses of ibuprofen were administered as it was substituted by ketorolac (3.8 versus 6.1; $P < 0.01$). Emesis rates were similar between the 2 groups. The hospital length of stay was shorter in the ketorolac group (2.1 nights) than in the control group (2.6 days) ($P < 0.05$). No patients experienced postoperative hematoma, oliguria or increase in creatinine levels that would indicate renal insufficiency/failure or hematemesis, melena, or other suggestion of gastrointestinal hemorrhage (Table 4).

DISCUSSION

Effective postsurgical analgesia is a critical aspect of the patient recovery because it can contribute to faster patient mobilization, shorter hospital stays, and reduced health care costs. NSAIDs can be an effective component of the multimodal postoperative pathway and can result in improved postoperative analgesia[28] with decreased opioid utilization.[16] This is associated with a more rapid return of gastrointestinal function,[2] shortened hospital length of

Table 3. Transfusion Rates and Hemoglobin Changes

	Ketorolac (n = 43)	Control (n = 31)	*P*
ACVR/PCVR ratio	19/24	24/7	<0.01*
Operative time (min)	320	319	0.96
Crystalloid use (ml/kg)	95 ± 27	87 ± 27	0.19
Colloid use (ml/kg)	9.5 ± 7.8	5.1 ± 6	0.01*
Recycled autologous cell volume (ml/kg)	8.8 ± 6.7	6.7 ± 4.2	0.13
Estimated blood loss (ml)	308	304	0.95
Intraoperative transfusion rate	16% (7/43)	29% (9/31)	0.25
Postoperative transfusion rate	1/43 (2%)	2/31 (6%)	0.56
Mean first postoperative Hgb value (g/dl)	9.2	9.7	0.21
Mean discharge Hgb value (g/dl)	8.2	9.1	0.02*
Decrease in Hgb	10%	6.7%	0.1

*$P < 0.05$.
Hgb, hemoglobin.

stay,[20] and decreased emesis.[29] A randomized control trial demonstrated that an intravenous nonnarcotic postoperative pain regimen including ketorolac and acetaminophen was superior at reducing nausea and emesis compared with oral ibuprofen and acetaminophen for patients undergoing craniosynostosis correction.[30] Numerous clinical trials have demonstrated that the NSAID ketorolac is as effective as morphine and even more effective than codeine in the pediatric population.[1,16,31] Specific to patients undergoing craniotomies, scheduled doses of NSAIDs have shown to improve analgesia and decrease opioid requirement.[32,33] Additionally, the use of nonsedating analgesics is particularly advantageous after cranial procedures to monitor the central nervous system with postoperative serial neurologic examinations.[34] In our study, we also corroborated prior studies that patients receiving ketorolac required less morphine in the postoperative period.[32,33] By utilizing nonopioid analgesics, there may be early return to daily activities. Although we cannot argue causality, there seems to be an association among ketorolac use, decreased opioid requirement, and shorter hospital length of stay.

However, concerns over the potential of NSAIDs, including toradol and ibuprofen, to cause postoperative hemorrhage have prevented widespread utilization. The risk of bleeding is of greater importance in procedures where postoperative hemorrhage may lead to catastrophic complications. For this reason, some neurosurgeons are reluctant to use ketorolac and other NSAIDs in the acute postoperative period.[21] Although early studies raised concerns for an increased risk of bleeding with the use of NSAIDs and ketorolac in pediatric and adult populations,[19,20,29,35] this was not corroborated in further studies.[20,28,36] A meta-analysis published in 2014 which analyzed 27 studies with 2,314 patients who underwent a variety of surgical procedures found that postoperative bleeding was not increased with ketorolac administration and that ketorolac resulted in superior pain control.[36] Additionally, a case-control study was able to demonstrate no increased risk in the occurrence of symptomatic postoperative intracranial hemorrhage with the administration of ketorolac after elective intracranial procedures in adults.[34]

In our study, we were able to demonstrate in a pediatric patient population undergoing major CVR for craniosynostosis that the administration of ketorolac as part of the postoperative analgesia regimen did not result in hemorrhagic complications or need for transfusion. Despite there being a significant difference in postoperative hemoglobin between the ketorolac and control groups, the percent decrease in hemoglobin was not significant and it typically did not result in physical manifestations warranting transfusion. Additionally, others have proposed that the threshold for transfusion in the pediatric population after CVR should be 7.5–8 g/dl[37,38] and the mean discharge hemoglobin was 8.2 g/dl in the ketorolac group. Patients who received ketorolac also required less morphine doses and had decreased hospital length of stay. A similar study by Richardson et al[21] found that routine perioperative ketorolac administration was not associated with a significant increase in the risk of bleeding in pediatric neurosurgery patients. This study analyzed patient outcomes by type of surgical procedure and found that hemorrhage on examination or demonstrated through imaging was associated with craniosynostosis repair or Chiari malformation decompression as compared to intradural placement of a catheter or endoscope.[21] This might be explained by the amount of dissection required for a craniectomy in CVR and the potential for increased blood loss and accumulation of blood and serous fluids in the surgical site. However, our study was specific to CVR and we did not demonstrate an increased risk of hemorrhagic complications or need for transfusion. Additionally, as patients had a major cranial procedure, it was expected that all would have a serosanguinous fluid collection in the first week postoperatively. However, all fluid collections resolved without any intervention and no patients in our series required drainage or intervention. Thus, we can make the conclusion that ketorolac was not associated with an increased rate of clinically significant hematoma. Although some patients receiving toradol may have had a more sanguinous than serous collection, postoperative transfusion rates were not increased and vitals signed remained stable.

The optimal timing of ketorolac delivery is an area of research and contention. Some have proposed that administration before incision or before primary hemostasis might be responsible for the observed increased bleeding in some of the studies.[11,34,39] In our cohort, we did not administer ketorolac before or during the surgery and the median time between the end of surgery and the time of ketorolac administration was about 3 hours. Of note, we used ketorolac at the lowest pharmacologic dose (0.25 mg/kg/dose, up to 15 mg/dose), whereas others have used 0.5–1 mg/kg in children and 30–50 mg/d in adults.[1,18,20,28,31,34] Importantly in our patient population, our application of a formalized, well-established, and effective blood management protocol and strategic hemostasis allowed us to have a 4% postoperative transfusion rate over the study period. This can be compared with postoperative transfusion rates in the literature as high as 34%–42%.[24,37] Our low transfusion rate represents a single-center experience, and, thus, our results may not be translatable to all centers.

Our study is not without limitations. This study is a retrospective and nonrandomized cohort study. In a series of consecutive patients, results will typically improve over time and our strategies for blood management and hemostasis continue to evolve. Thus, although there is some degree of experience bias, importantly, the ketorolac group was not isolated to the most recent patients. Also, the ketorolac group had a higher proportion of ACVR. These are typically associated with higher rates of blood loss and transfusion, so the difference although significant further supports the safety of ketorolac. Although concerns have been raised that selective/nonselective COX inhibitor use may adversely affect osteogenic activity,[40,41] our goal was not to evaluate cranial defects. Although we do not believe that there is an increase in cranial defect rate with ketorolac utilization, we will continue to follow our patients to critically analyze our outcomes.

CONCLUSIONS

In conclusion, this is the first study to demonstrate that postoperative ketorolac is not associated with increased bleeding or transfusion risk in children who underwent CVR for craniosynostosis. Additionally, patients administered ketorolac required less morphine for pain control and had a shorter hospital length of stay. We hope that this study stimulates more well-done prospective trials analyzing the role that ketorolac can play in an effective and safe postoperative analgesia regimen.

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