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Ketorolac after colectomy for ulcerative colitis in children: An analysis of opioid utilization and postoperative complications

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ABSTRACT

Introduction: Enhanced recovery protocols include multimodal perioperative pain control and frequently include use of NSAIDs. There is conflicting evidence that ketorolac use in inflammatory bowel disease (IBD) may precipitate disease flares and postoperative complications. The outcomes of children who receive ketorolac in this setting are not well known. We sought to evaluate ketorolac utilization in children following colectomy for ulcerative colitis.

Methods: All patients undergoing colectomy for ulcerative colitis between 2007 and 2017 at a tertiary children's hospital were reviewed. We collected patient age, duration of symptoms, operative details, medication utilization, length of stay, and postoperative complications. We performed a cohort comparison of these variables across patients who did vs. did not receive postoperative ketorolac.

Results: Sixty children were identified with median age at diagnosis of 12.6 years (IQR: 9.9–14.5). At colectomy, patients had a median PUCAI score of 60 (45–70), ESR 34 mm/h (15–50), hemoglobin 10.9 g/dL (9.3–12.9), and albumin 3.1 g/dL (2.4–3.8). Postoperatively, 45% ($n = 27$) received ketorolac. Patients in both cohorts had a similar length of stay, duration of opioid exposure, total morphine equivalents utilized, readmission rate, and unexpected return to the operating room. There were no documented cases of postoperative bleeding, acute kidney injury, or disease related flares among children receiving ketorolac.

Conclusions: Administration of ketorolac after colectomy in IBD was not associated with an increase in any postoperative complications, though the study was underpowered to detect these differences. However, ketorolac administration did not lead to a decreased utilization of opioid analgesia. Further prospective research is necessary to understand whether ketorolac in this population is safe and offers benefit.

Type of study: Retrospective study.

Level of evidence: III

Enhanced recovery protocols (ERPs) have been shown to improve outcomes including postoperative length of stay, frequency of complications, and financial costs of care. These ERPs are aimed at reducing the stress of surgery on the body to enhance recovery through preoperative interventions, such as surgical "prehabilitation", intraoperative interventions, such as optimizing fluid administration and body temperature and utilizing minimally invasive techniques, and postoperative interventions, such as early enteral feeding. Multimodal pain management is a crucial component of ERPs and can be utilized in all three perioperative phases [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a major component of multimodal perioperative pain management and have been shown to reduce opioid use in the postoperative period [2–5]. This is particularly important given that opioid abuse has become a significant public health crisis in the U.S with deaths from opioid overdose increasing by 157% in the last decade [6]. In addition, there is a known link between postoperative opioid utilization and chronic opioid abuse [7,8]. Therefore, in the midst of the ongoing opioid epidemic, many institutions are placing emphasis on reducing or eliminating opioid prescribing with increasing use of these adjunctive analgesics.

Despite the emphasis on utilizing multimodal pain regimens postoperatively, an area of considerable controversy is the utilization of NSAIDs in the setting of inflammatory bowel disease (IBD). Prior studies suggest that NSAID use can lead to disease flairs in IBD, and many clinicians prohibit their use despite conflicting results in the literature [9–16]. Outcomes of children with IBD who receive NSAIDS in the postoperative setting are not well known.

The aim of this study was to evaluate ketorolac utilization in children following colectomy for ulcerative colitis (UC). We hypothesized that

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the use of ketorolac would be safe in this population and offer pain control with diminished opioid consumption.

1. Methods

A retrospective cohort study was performed of all patients undergoing laparoscopic or open total abdominal colectomy or proctocolectomy for ulcerative colitis during the 10-year period from 2007 to 2017 at a free standing, tertiary referral children's hospital. We included all children with ICD-9 and ICD-10 codes associated with a diagnosis of ulcerative colitis (ICD-9556, 556.1, 556.5, 556.6, 556.8, 556.9, ICD-10 (K51–K51.9). We excluded all children with Crohn's disease, those with an alternate diagnosis on pathology, and those with incomplete data regarding NSAID and opioid use. Demographic data were collected on all patients including age, gender, comorbidities, duration of symptoms, medication exposure including UC specific medications, antibiotics, and antidepressants/anxiolytics, Pediatric Ulcerative Colitis Activity Index (PUCAI) score, erythrocyte sedimentation rate (ESR), hemoglobin, and albumin. Perioperative data collected included operative approach, duration of opioid exposure, total morphine equivalents given during postoperative period, and length of stay. Data on complications, including postoperative bleeding, acute kidney injury, unexpected return to the operating room, disease related flares in the remnant rectum, and readmission were collected at 30 days postoperatively via manual chart review by two independent authors (S.S. and W.W.).

There were no defined pain management protocols in place during the study period, and postoperative pain management was left to the discretion of the operative surgeon and/or the anesthesia lead inpatient pain service. Intraoperative pain management, including ketorolac use, was determined by the operative surgeon and the anesthesia team. Ketorolac dosing was 0.5 mg/kg up to a total dose of 30 mg and was given up to every 6 h. Dosing and duration of ketorolac exposure were variable and not standardized, but the maximum allowable duration of a course of ketorolac was 3 days. If patients had received a course of ketorolac and a sufficient period of time had passed after as determined by the operative surgeon, a second course of ketorolac was occasionally given. Ketorolac was not given in the preoperative setting. In patients who were admitted to the hospital prior to surgery, preoperative data on opiate use were not included in the analysis.

The cohort of patients with postoperative ketorolac exposure was compared to that without exposure on the above variables. A subgroup analysis was performed excluding patients that required an unexpected return to the OR with the hypothesis that these patients may have higher MME requirements based on the underlying reason for the patients' return to the OR. In addition, a subgroup analysis was performed comparing the group of patients that received scheduled ketorolac to those that received nonscheduled ketorolac. Scheduled ketorolac exposure was defined as a patient receiving greater than 2 days of routine dosing (i.e. eight or more doses consecutively).

Cohort characteristics were summarized using percentages for nominal variables and using the median and interquartile range (IQR) for interval variables. Continuous variables were analyzed using Wilcoxon rank sum, and dichotomous variables were analyzed using Fisher's Exact Text with a significance level of $p < 0.05$. This was performed using JMP v 14.0 software. This study was approved by the University of Utah Institutional Review Board.

2. Results

Sixty children were identified during the study period. The median age at diagnosis was 12.6 years with an IQR of 9.9 to 14.5 years. At colectomy, patients had a median PUCAI score of 60 with an IQR of 45 to 70, ESR of 34 mm/h (15–50), hemoglobin of 10.9 g/dL (9.3–12.9), and albumin of 3.1 g/dL (2.4–3.8). All patients required preoperative immunosuppression with 63% taking steroids and 64% taking biologics within 30 days of surgery. Median time to surgery from diagnosis was 19 months (8–45), and 53.3% had a laparoscopic surgical approach. The median length of stay was 7 days (5–9.5) (Table 1).

In the postop period, 45% received ketorolac with a median duration of 2 days. The median opioid consumption was 121 mg (IQR 47.9–211) with a median duration of 5 days. Postoperative complications were common with 17% requiring an unexpected return to the operating room, 5% experiencing an ileostomy related complication, and 30% having an unplanned readmission to the hospital within 30 days (Table 2).

Comparing the ketorolac exposed cohort to the nonexposed cohort, there were no differences between the two groups with regard to age, gender, PUCAI score, laboratory data, use of chronic antidepressants/anxiolytics, use of antibiotics, and use of steroids, immunomodulators, or biologics. Patients receiving ketorolac had no differences compared to those who did not receive ketorolac regarding frequency of laparoscopic approach, duration of opioid exposure in the postoperative period, total morphine equivalents received in the postoperative period, or length of stay (Table 2). This lack of opioid sparing effect with ketorolac use was present regardless of the operative approach (Fig. 1). With regards to complications, there were no differences between the two cohorts in unexpected return to the operating room, readmissions, or ileostomy complications (Tables 2 and 3). During our study period, there were no documented cases of postoperative bleeding, acute kidney injury, or disease related flares in the remnant rectum among children receiving ketorolac.

A subgroup analysis was done excluding patients that required an unexpected return to the OR, and there was no statistical difference in median MME consumed by the ketorolac exposed cohort and the unexposed cohort (121 mg vs. 111 mg; $p = 0.58$). In addition, a subgroup analysis was done comparing the group of patients that received scheduled ketorolac to those that received nonscheduled ketorolac. Of the 27 patients that received postoperative ketorolac, 21 (78%) received scheduled ketorolac as defined above. There was no difference between the cohort with scheduled ketorolac and that with nonscheduled ketorolac with regards to median duration of opioid use [4 days (IQR 2.5–7.5) vs. 6.5 days (IQR 5–8.3); $p = 0.13$] or median MME consumed [114 mg (IQR 44.3–229.5) vs. 122 mg (IQR 78–320); $p = 0.7$].

3. Discussion

To our knowledge, this is the largest study investigating the utility of ketorolac after colectomy in children with UC. Although underpowered, we found that the fears of many surgeons may be unfounded as we did not identify any ketorolac-related complications or disease flares in the cohort of patients receiving ketorolac. However, use of ketorolac postoperatively did not reduce opioid use in our study.

The literature is conflicting on the safety of NSAIDs in patients with UC. It has been suggested that NSAIDs play a role in inducing flares of inflammatory bowel disease owing to their negative immune modulatory effects, thereby increasing inflammatory cytokines and exacerbating mucosal injury in bowel that is already prone to injury [17]. However,

Table 1
Clinical and laboratory characteristics of patients.

Clinical variable	$N = 60$
Median age at diagnosis in years (IQR)	12.6 (9.9–14.5)
Male	58.3%
Median PUCAI score (IQR)	60 (45–70)
Median albumin (IQR)	3.1 (2.4–3.8)
Median hemoglobin (IQR)	10.9 (9.3–12.9)
ESR (IQR)	34 (15–50)
Steroid use	63.3%
Immunomodulator use	20.8%
Biologic use	63.8%
Antidepressant/anxiolytic use	23.4%
Antibiotic use	42.4%
Median months to surgery from diagnosis (IQR)	19 (8–45)

Table 2
Comparison of pre- and postoperative variables in pediatric patients with ulcerative colitis with and without ketorolac exposure after colectomy.

Clinical variable	No ketorolac exposure $N = 33$	Ketorolac exposure $N = 27$	p-value
Median age at diagnosis in years (IQR)	12.6 (10.5–14.2)	12.5 (9.9–14.9)	0.34
Male	65%	34%	0.06
Median PUCAI score (IQR)	60 (45–70)	55 (45–70)	0.98
Median albumin (IQR)	2.7 (2.4–3.7)	3.2 (2.7–3.8)	0.36
Median hemoglobin (IQR)	10.9 (9.5–12.9)	10.9 (9.2–12.9)	0.85
ESR (IQR)	24 (13–44)	40 (25–55)	0.12
Steroid use	67%	61%	0.79
Immunomodulator use	33%	26%	0.58
Biologic use	71%	56%	0.27
Antidepressant/anxiolytic use	35%	10%	0.08
Antibiotic use	56%	31%	0.07
Median months to surgery from diagnosis (IQR)	16.0 (6–46.6)	19.4 (9.5–44.6)	0.68
Laparoscopic procedure	58%	48%	0.60
Median ketorolac doses given (IQR)	-	12 (8–12)	-
Median morphine milligram equivalents(IQR)	133 (51–210)	114 (45–264)	0.47
Median days of opioid exposure (IQR)	5 (2.5–6)	5 (3–8)	0.67
Ketorolac-related complications	-	0	-
IBD flare	4%	0%	0.43
Ileostomy complication	3%	7.4%	0.59
Median length of stay in days (IQR)	7 (5–11)	6 (5–8)	0.46
Readmission	28%	33%	0.78
Unexpected return to OR	12.5%	22%	0.48

our study supports the notion that NSAIDs may be safe for use in children after colectomy for UC. The population in our study is different from most of the studies published investigating the safety of NSAIDs in patients with UC. First, our patients are immediately postoperative from colectomy for UC. Surgery is a unique treatment for UC in that it extirpates the diseased intestine, thus, theoretically, eliminating the vulnerable tissue upon which the aforementioned pathologic pathway acts and explaining the possible safety of NSAIDs seen in our study. Second, the patients in our study are children, which are different than most of the previous literature. UC often has a different phenotype based on the age of the patient, which may affect the interaction between NSAIDs and UC [18–20]. These unique aspects of this study give insights into this specific patient population that previous literature has not.

Despite the demonstrated safety of ketorolac, our study did not demonstrate decreased opioid consumption with ketorolac utilization. While it is possible that ketorolac does not have opioid sparing effects in this population, given the abundant literature demonstrating the opioid sparing effects of NSAIDs and their role in ERPs, our findings likely reflect our lack of standardized protocols at our institution during this time period as well as variable bias among providers [2–5]. Some of our providers only utilized ketorolac in the setting where opioids failed to provide adequate pain control in order to avoid NSAID-related morbidity unless they were absolutely required for adjunctive pain control. This inherently biases the data towards increased opioid consumption among some of the patients receiving NSAIDs. We believe this likely drives our lack of improved opioid consumption in the NSAID population and argues for reevaluation of this population with enhanced recovery protocols as outlined by Heiss and colleagues [5,21].

Our study has several limitations. We are tertiary referral center, which may limit the generalizability of our data. Further, despite having a large number of pediatric patients, our data are underpowered to identify clinically significant differences among children receiving differential postoperative pain regimens. Thus, the safety of ketorolac in postcolectomy UC patients cannot be established until further studies are performed. Moreover, there was not consistent utilization of adjuvant pain medications and modalities, such as acetaminophen, gabapentin, and epidural analgesia. Use of these pain adjuncts could significantly affect the opioid requirements for these patients and cloud the data presented above. Finally, our institution did not employ a

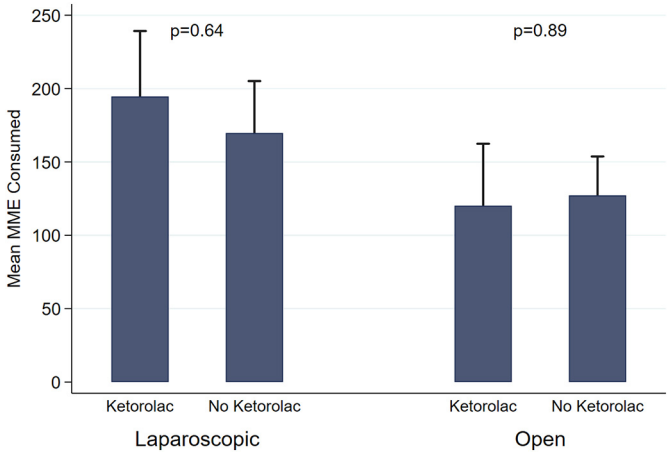

Fig. 1. Comparison of mean morphine milligram equivalents consumed between those who utilized ketorolac and those who did not by operative approach. Error bars represent standard error of the mean.

Table 3
Detailed analysis of reasons for readmissions and unexpected return to the OR and of ileostomy complications.

Complication	No ketorolac exposure $N = 33$	Ketorolac exposure $N = 27$
Readmission[a]	**9**	**9**
Dehydration	3	0
Superficial or deep SSI	1	1
Ileus/small bowel obstruction	3	1
Pancreatitis	0	1
Clostridium difficile infection	2	1
Gastroenteritis	0	2
Organ space SSI	1	4
Nonspecific abdominal pain	0	1
Unexpected return to OR	**4**	**6**
Washout for SSI	1	4
Volvulized ostomy	1	1
Postoperative small bowel obstruction	2	0
Reduction of prolapsed ileostomy	0	1
Ileostomy complications	**1**	**2**
Volvulized ileostomy	1	1
Ileostomy prolapse	0	1

[a] Patients may have been readmitted for multiple diagnoses.

standardized pain protocol in the postoperative period and allowed for provider bias to drive pain regimens. The lack of a comprehensive protocol and relatively small sample size may reflect the inability of our data to demonstrate an opioid sparing effect of ketorolac. A future prospective study of a standard postoperative multimodal pain protocol is needed to better understand utilization of ketorolac in this setting.

4. Conclusion

Although our study is underpowered to detect differences in incidence of complications, we did not identify any clinically relevant morbidity with utilization of ketorolac after colectomy for UC in pediatric patients. However, the use of ketorolac was not associated with reduction of opioid requirements in the postoperative setting. Owing to a lack of defined morbidity and the lack of power in our study to adequately detect differences in NSAID-related complications, we feel additional future research is needed to better understand the role of NSAIDs in this setting to diminish opioid utilization.

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