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Ketorolac Use and Postoperative Complications in Gastrointestinal Surgery

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Abstract

Objective—To study the association between ketorolac use and postoperative complications.

Background—Nonsteroidal anti-inflammatory drugs may impair wound healing and increase the risk of anastomotic leak in colon surgery. Studies to date have been limited by sample size, inability to identify confounding, and a focus limited to colon surgery.

Methods—Ketorolac use, reinterventions, emergency department (ED) visits, and readmissions in adults (> 18 years) undergoing gastrointestinal (GI) operations was assessed in a nationwide cohort using the MarketScan Database (2008–2012).

Results—Among 398,752 patients (median age 52, 45% male), 55% underwent colorectal surgery, whereas 45% had noncolorectal GI surgery. Five percent of patients received ketorolac. Adjusting for demographic characteristics, comorbidities, surgery type/indication, and preoperative medications, patients receiving ketorolac had higher odds of reintervention (odds ratio [OR] 1.20, 95% confidence interval [CI] 1.08–1.32), ED visit (OR 1.44, 95% CI 1.37–1.51), and readmission within 30 days (OR 1.11, 95% CI 1.05–1.18) compared to those who did not receive ketorolac. Ketorolac use was associated with readmissions related to anastomotic complications (OR 1.20, 95% CI 1.06–1.36). Evaluating only admissions with > 3 days duration to exclude cases where ketorolac might have been used for complication-related pain relief, the odds of complications associated with ketorolac were even greater.

Conclusions—Use of intravenous ketorolac was associated with greater odds of reintervention, ED visit, and readmission in both colorectal and noncolorectal GI surgery. Given this confirmatory evaluation of other reports of a negative association and the large size of this cohort, clinicians should exercise caution when using ketorolac in patients undergoing GI surgery.

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Keywords

adverse events; gastrointestinal surgery; ketorolac; medication use; post-operative complications

Operations on the gastrointestinal (GI) tract, including colon resections and appendectomies, are among the most common procedures conducted in the United States.¹ Pain management is an important component of peri- and postoperative care, and opi-oids are commonly prescribed as the mainstay of postoperative pain management in the United States.^{2–4} Increasingly, the side effects of opioids—including nausea, sedation, dependence, constipation, and paralytic ileus—are being recognized as burdensome to patients and as a barrier to more effective and efficient care. With this focus on opioid minimization, nonsteroidal anti-inflammatory drugs (NSAIDs) have become a common component of pain management regimens.^{3,5} NSAIDs effectively treat postoperative pain, leading to reductions in opioid use, time to first ambulation, and time to first bowel movement.^{6,7} Injectable NSAIDs, such as ketorolac, have been shown to have an equivalent analgesic effect to morphine in major abdominal surgery and reduce the use of opioid medications.^{6–11}

Recent reports from small observational cohorts, however, have questioned the impact of NSAIDs on anastomotic healing. Several case series, including one statewide cohort study from our group,¹² suggest that patients receiving postoperative NSAIDs—including diclofenac and celecoxib—may have an increased rate of anastomotic leak, particularly in those undergoing colorectal surgery.^{13–16} Prospective studies addressing this question have not substantiated the association between NSAID use and anastomotic leak, but have been underpowered to address this outcome.^{17–19}

Among NSAIDs, ketorolac has gained particular popularity in postoperative pain management because it can be given intravenously.²⁰ Given its ease of administration, understanding the impact of ketorolac on anastomotic healing is important for safe peri-operative pain management. To address the gap in current knowledge, we evaluated the association between ketorolac use and adverse events in patients undergoing GI surgery using a national claims database. The purpose of this study was to determine if ketorolac use was associated with higher rates of reinterventions, emergency department (ED) visits, and readmissions.

METHODS

Study Population and Setting

We identified and included adult patients (≥ 18 years old) who underwent a GI surgery, between 2008 and 2012, using the Truven Health MarketScan Commercial Claims Database. This national database contains individual-level, de-identified healthcare claims from employers, health plans, and hospitals. The database includes health insurance claims as well as enrollment data on over 40 million patients per year, including a variety of fee-for-service, preferred provider organizations, and capitated health plans. The database does not include Medicare or Medicaid claims, representing only patients with private insurance.

We included all patients with a continuous enrollment of 12 months prior to the index operation and 6 months after. Patients in the study cohort did not have another GI operation in the 12 months prior to what we defined as the index operation. We excluded any patients less than 18 years old, patients who did not have a GI operation during the study period, and patients without the necessary continuous enrollment period.

Data Characteristics

Demographic information, insurance type, comorbidities, procedure and diagnosis codes, outpatient pharmacy claims, and inpatient medication use were abstracted from claims and verified by Thomson Reuters. Preoperative medication use was identified from the outpatient pharmacy claims. Patients were classified as taking a medication preoperatively if they had a claim for that medication within 90 days of their index surgery date. Current Procedural Terminology (CPT) codes were used to identify patients undergoing a GI operation during the study period (see Appendix A). Operations were classified as either colorectal or noncolorectal GI tract. Index operations were divided into emergent versus nonemergent based on whether or not the patient had a CPT code for any ED visit during the 48 hours prior to the date of the operation. The primary diagnosis was identified using the International Classification of Diseases, 9th modification (ICD-9) codes. Comorbidities were identified from ICD-9 diagnostic codes utilized in the 6 months before the operation—in either outpatient or inpatient claims—and the Quan modification of the Charlson Comorbidity Index (CCI) was determined.²¹

Exposure

Use of ketorolac was identified from hospital claims. Patients were classified as having received ketorolac if they had a claim for ketorolac on or after the day of surgery during the index hospitalization. Dose and frequency were not identifiable from the claims.

Outcome Measures

Three outcome measures were evaluated: ED visit within 30 days of index operation, readmission within 30 days, and reintervention within 30 days. Reinterventions were specified, using CPT codes, as reopening of recent laparotomy, exploratory laparotomy, diagnostic laparoscopy, operative drainage of an abscess, and drain placement (Appendix B).

Analytical Methods

Demographic and clinical characteristics were compared among patients who did and did not receive ketorolac during their index hospitalization. Characteristics were summarized using frequency distributions for categorical variables and means and standard deviations for continuous variables. Categorical variable comparisons were evaluated for significance using the Pearson χ^2 test. Continuous variables were evaluated for significance using *t* tests or Wilcoxon rank sum test for nonparametric data.

The rate of ED visits, readmissions, and reinterventions within 30 days of index operation were compared between patients who did and did not receive ketorolac. The association between ketorolac use and ED visits, readmissions, and reinterventions was then evaluated,

adjusting for potential confounders, using multivariable logistic regression. Potential confounders included age, sex, insurance type, geographic region, type of surgery (colorectal vs noncolorectal GI tract), emergent versus nonemergent, health status using Quan's modification of the CCI, primary diagnosis, and preoperative medication use. A sensitivity analysis looking only at readmissions related to anastomotic complications—sepsis, peritonitis, complications of anastomosis, abscess, dehiscence, or postoperative complication—was conducted. These were identified using the ICD-9 code associated with the readmission. A second sensitivity analysis, looking only at reinterventions in patients with index hospitalization ≥ 3 days, to exclude cases where ketorolac might be used for complication-related pain relief, was also conducted. This project was deemed exempt from review by the University of Washington Institutional Review Board.

RESULTS

A total of 398,752 patients who underwent GI surgery between 2008 and 2012 were identified and included in the analysis. The median age was 52 years (interquartile range [IQR] 41–59) and 55.4% were female. Over half of the patients underwent colorectal surgery (55.8%) while the remaining patients had noncolorectal GI surgery. Nearly half of the patients had a CCI of 0 (49.1%), with another 27.4% had an index of 1, and 23.5% had an index of 2 or greater. Clinical and demographic characteristics of the cohort are described in Table 1.

Peri- or Postoperative Ketorolac Use

Five percent of patients had a claim for ketorolac during their index hospitalization (Table 1). These patients were younger, more likely to undergo emergent surgery and colorectal surgery, and more likely to have diverticulitis or diverticulosis as their primary diagnosis. Patients receiving ketorolac had higher rates of preoperative steroid (31.8% vs 25.7%, $P < 0.001$), other NSAID (31.0% vs 20.4%, $P < 0.001$), and opioid (14.0% vs 9.0%, $P < 0.001$) use. They had lower rates of immunosuppressant and anticoagulant use preoperatively.

ED Visits, Readmissions, and Reinterventions

Patients receiving ketorolac had higher rates of ED visits (11.4% vs 7.5%, $P < 0.001$), readmissions (8.0% vs 7.3%, $P < 0.001$), and reintervention (2.3% vs 2.0%, $P = 0.004$) within 30 days of the index operation (Figure 1). After controlling for confounders, patients receiving ketorolac were more likely to have an ED visit within 30 days (odds ratio [OR] 1.44, 95% CI 1.37–1.51). Patients receiving ketorolac also had higher odds of readmission (OR 1.11, 95% CI 1.05–1.18) and reintervention (OR 1.20, 95% CI 1.08–1.32) within 30 days of the index operation (Figure 2). Other factors associated with higher odds of ED visits included female sex, emergent surgery, higher CCI, and preoperative use of steroids, other NSAIDs, anticoagulants, and opiates (Table 2). Factors associated with higher odds of readmission were male sex, emergent surgery, higher CCI, and preoperative use of immunosuppressants, anticoagulants, and opiates. Factors associated with reintervention were emergent surgery, lower CCI, and preoperative opiate use.

In an effort to ensure that ketorolac was not being given in response to complication-related pain, we conducted a sensitivity analysis looking exclusively at patients with hospital length of stay of 3 days or less. The odds of a reintervention (OR 1.29, 95% CI 1.07–1.55) were higher in this subgroup of patients. Additionally, looking just at readmissions that could plausibly be related to concerns about wound or intestinal healing, we also found higher odds of readmission in patients receiving ketorolac postoperatively (OR 1.20, 95% CI 1.06–1.36).

DISCUSSION

In this large nationwide cohort, we found that ketorolac use in patients undergoing GI operations was associated with a greater risk of complications. After adjusting for important differences at baseline, these complications included higher odds of ED visits, readmissions, and reintervention within 30 days of admission. In this study, we extended the analysis from colorectal procedures to other GI operations involving staple lines and anastomoses where healing could be affected by the use of ketorolac. The finding of increased ED visits, readmissions, and reinterventions in this more inclusive population argues in favor of a detrimental impact of ketorolac in GI surgery.

These results reinforce the findings of an increased rate of adverse events from 5 previous observational studies (including a Washington State analysis of over 13,000 patients)¹² but stand in distinction to a meta-analysis of 6 randomized controlled studies with 480 patients suggesting no increased risk of anastomotic dehiscence in patients receiving NSAIDs.^{13,14,16,19} The OR in that meta-analysis was 2.16 (95% CI 0.83–5.53), and the authors concluded that they may have been underpowered to detect an association, given the size of the OR.¹⁹ The observational studies have also been supported by the experimental literature. In animal studies, diclofenac use has been associated with reductions in anastomotic tensile strength, bursting pressure, and hydroxyproline deposition.^{22–24}

Anastomotic leak is a serious complication of GI surgery, resulting in significantly increased morbidity and mortality.^{25–30} NSAIDs such as ketorolac may influence intestinal healing through their action inhibiting cyclo-oxygenase. Through this pathway, and downstream effects, NSAIDs have been shown to attenuate granulocyte function—an important component of the acute phase of wound healing.^{31,32} NSAIDs may also inhibit epithelial cell migration and mucosal restitution, a factor that has been shown to be important in the pathophysiology of intestinal ulcer healing.³³ Collectively, these factors may help explain why use of NSAIDs, such as ketorolac, around the time of surgery is associated with higher rates of reoperative complications, although these mechanisms of action may not all be generalizable to ketorolac itself.

This study must be interpreted in the context of its limitations. First, we analyze the relationship between ketorolac and GI surgery complications using claims data, which depend on submission of claims to identify treatment and interventions and, therefore, may contribute to misclassification. Although claims data are more reliable than other forms of administrative data that rely on discharge abstracts, we are only able to identify the exposure and outcomes if there is a claim submitted.^{34,35} However, there is no reason to believe that

there might be differential misclassification among those who do and do not receive ketorolac, leading to bias. We are, however, not able to identify whether patients may have received oral NSAIDs before their hospitalization if they were purchased over the counter, or during their hospitalization, as there are no inpatient claims for oral medications in MarketScan. This may present confounding that cannot be addressed in our analysis. Second, we are not able to specifically identify the outcome of anastomotic leak as there is no diagnostic or CPT code that would accurately identify it. As such, our study looks at healthcare utilization that might be associated with an anastomotic leak—ED visits, readmissions, and reinterventions. Our sensitivity analysis looking solely at readmissions with diagnostic codes such as those for sepsis, peritonitis, complication of anastomosis, and postoperative abscess that are common with anastomotic complications found an even greater association with ketorolac use, suggesting that the increased ED visits and readmissions are not due to some unmeasured confounder. Third, we are not able to determine the timing of ketorolac administration, and its relation to any reinterventions that might have occurred. In an effort to exclude cases where ketorolac might be used for complication-related pain relief, we conducted a sensitivity analysis looking only at admissions 3 days and found even greater odds of complications in this subgroup. Fourth, there are a number of other factors involved in a patient's care that might influence outcomes, including the type of anesthesia used. We are unable to identify whether epidural anesthesia was used in this study, and this may represent a potential confounder. Additionally, we are not able to identify specific hospitals or surgeons in our study, and these factors may have influenced the outcomes that we studied. This represents a potential confounder that we could not address. We are also not able to specifically identify whether an operation is emergent, but used a proxy of an ED visit in the previous 48 hours, which may not identify all emergent operations. Lastly, given that this is a retrospective analysis, we were unable to identify clinical decision-making that might have influenced the use of ketorolac in patients undergoing GI surgery.

In conclusion, in this large cohort study, we found that the use of intravenous ketorolac was associated with a greater risk of reintervention, ED visit, and readmission in GI surgery. There is biological plausibility that NSAIDs may impair anastomotic healing, and this finding has been reproduced in 5 studies of sufficient size and now in a very large national cohort with an expanded set of clinical procedures. The only reports that have failed to identify this effect have been underpowered. These characteristics of an association support a cause and effect relationship, but only a prospective study with an acceptable control can address what may be residual confounding that could be influencing this finding. In the absence of evidence of other confounding factors, clinicians should exercise caution when using ketorolac during and after GI surgery.

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APPENDIX A

CPT Codes Used to Identify Gastrointestinal Operations: 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44155, 44157, 44158, 44160, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212, 44213, 44950, 44955, 44960, 44970, 44979, 45110, 45111, 45112, 45113, 45114, 45116, 45119, 45120, 45121, 45123, 45126, 45136, 45160, 43100, 43101, 43107, 43108, 43112, 43113, 43116, 43117, 43118, 43121, 43122, 43123, 43124, 43130, 43135, 43279, 43280, 43281, 43282, 43305, 43312, 43314, 43324, 43325, 43326, 43330, 43331, 43340, 43341, 43360, 43361, 43401, 43405, 43620, 43621, 43622, 43631, 43632, 43633, 43634, 43644, 43645, 43770, 43773, 43775, 43810, 43820, 43825, 43840, 43842, 43843, 43845, 43846, 43847, 43848, 43850, 43855, 43860, 43865, 44050, 44055, 44120, 44121, 44125, 44126, 44127, 44128, 44130, 44135, 44186, 44188, 44202, 44203, 44800, 44820

APPENDIX B

CPT Codes for Reintervention: 49002, 49000, 49320, 49020, 75989, 44901

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FIGURE 1.
Unadjusted rate of ED visit, readmission, and re-intervention within 30 days by ketorolac use.

FIGURE 2.

Forest plot of odds of ED visit, readmission, and reintervention within 30 days associated with receiving ketorolac during index admission.

*Adjusted for age, sex, geographic region, insurance plan type, surgery type, diagnosis, emergent vs. elective operation, comorbidities and pre-operative medication use. Dots represent odds ratios; bars represent confidence intervals.

TABLE 1

Cohort Demographic Characteristics

	All	Received Ketorolac	Did Not Receive Ketorolac	P
N (%)	398,752	19,780 (5.0)	378,972 (95.0)	
Median age (IQR)	52 (41,59)	48 (39,56)	52 (41,59)	<0.001
Sex (%)				<0.001
Male	177,999 (44.6)	6489 (32.8)	171,510 (45.3)	
Female	220,753 (55.4)	13,291 (67.2)	207,462 (54.7)	
Plan type (%)				<0.001
Fee-for-service	331,867(86.0)	16,470 (87.6)	315,397 (85.9)	
Capitation	54,071 (14.0)	2375 (12.4)	51,696 (14.1)	
Region (%)				<0.001
Northeast	61,012 (15.3)	2531 (12.8)	58,481 (15.4)	
North Central	101,895 (25.5)	4805 (24.3)	97,090 (25.6)	
South	164,673 (41.3)	9030 (45.7)	155,643 (41.1)	
West	62,936 (15.8)	3114 (15.7)	59,822 (15.8)	
Unknown	8236 (2.1)	300 (1.5)	7936 (2.1)	
Type of Surgery (%)				<0.001
Colorectal	322,581 (55.8)	11,622 (58.8)	310,959 (55.7)	
Noncolorectal GI Tract	176,171 (44.2)	8158 (41.2)	168,013 (44.3)	
Emergent (%)	20769 (5.2)	1655 (8.4)	19114 (5.0)	<0.001
Charlson comorbidity index (%)				<0.001
0	183,490 (49.1)	9009 (46.4)	174,481 (49.2)	
1	102,620 (27.4)	5753 (29.6)	96,867 (27.3)	
2	87,895 (23.5)	4654 (24.0)	83,241 (23.5)	
Primary diagnosis (%)				<0.001
Neoplasm	22,530 (21.6)	718 (16.6)	21,812 (21.8)	
Appendicitis	52,304 (50.2)	1894 (43.9)	50,410 (50.5)	
Inflammatory bowel disease	2368 (2.3)	110 (2.5)	2258 (2.3)	
Hernia	2981 (2.9)	154 (3.6)	2827 (2.8)	
Obstruction/perforation	4146 (4.0)	240 (5.6)	3906 (3.9)	
Meckel	440 (0.4)	26 (0.6)	414 (0.4)	
Volvulus	1083 (1.0)	48 (1.1)	1035 (1.0)	
Diverticulitis/diverticulosis	18,373 (17.6)	1127 (26.1)	17,246 (17.3)	
Preoperative medication use (%)				
Steroids	103,738 (26.0)	6294 (31.8)	97,444 (25.7)	<0.001
NSAIDs	83,429 (20.9)	6124 (31.0)	77,305 (20.4)	<0.001
ASA	855 (0.2)	27 (0.1)	828 (0.2)	0.02
Immunosuppressants	12,228 (3.1)	532 (2.7)	11,696 (3.1)	0.002
Anticoagulants	35,276 (8.9)	1474 (7.5)	33,802 (8.9)	<0.001
Other antiplatelet agents	2824 (0.7)	86 (0.4)	2738 (0.7)	<0.001
Opiates	36,957 (9.3)	2764 (14.0)	34,193 (9.0)	<0.001

IQR, interquartile range; plan type, insurance plan type; region, geographic region of the United States; NSAIDs, nonsteroidal anti-inflammatory drugs; ASA, acetylsalicylic acid (aspirin).

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TABLE 2

Odds of ED Visit, Reintervention, and Readmission, After Adjustment*

	ED Visit	Reintervention	Readmission	Anastomosis-related Readmission
Age	0.99 (0.98–0.99)	0.99 (0.99–1.00)	1.00 (1.00–1.01)	1.00 (0.99–1.00)
Female sex	1.07 (1.04–1.10)	0.95 (0.91–1.00)	0.88 (0.85–0.90)	0.96 (0.90–1.01)
Type of surgery				
Noncolorectal GI Tract	Ref	Ref	Ref	Ref
Colorectal	0.94 (0.92–0.97)	0.81 (0.77–0.86)	1.01 (0.98–1.04)	0.81 (0.75–0.87)
Emergent	1.41 (1.35–1.48)	1.15 (1.04–1.27)	1.07 (1.02–1.13)	0.89 (0.77–1.02)
Charlson comorbidity index				
0	Ref	Ref	Ref	Ref
1	1.18 (1.14–1.21)	0.85 (0.80–0.90)	1.13 (1.09–1.16)	1.02 (0.95–1.10)
2	1.60 (1.55–1.65)	0.67 (0.63–0.72)	1.71 (1.66–1.77)	1.16 (1.07–1.25)
Preoperative medication				
Steroids	1.05 (1.02–1.08)	0.80 (0.76–0.85)	0.96 (0.93–0.99)	0.81 (0.75–0.87)
NSAIDs	1.10 (1.07–1.14)	1.01 (0.95–1.07)	0.89 (0.86–0.92)	1.04 (0.97–1.11)
Immunosuppressants	0.94 (0.88–1.00)	1.04 (0.91–1.19)	1.13 (1.06–1.20)	1.01 (0.86–1.19)
Anticoagulants	1.32 (1.27–1.37)	1.00 (0.92–1.09)	1.78 (1.71–1.84)	1.31 (1.19–1.43)
Opiates	1.50 (1.45–1.56)	1.60 (1.49–1.72)	1.70 (1.64–1.76)	1.89 (1.74–2.04)
Ketorolac use	1.44 (1.37–1.51)	1.20 (1.08–1.32)	1.11 (1.05–1.18)	1.20 (1.06–1.36)

* Outcomes are adjusted for all of the factors included in the table above, as well as for geographic region, insurance type, and primary diagnosis.