Original Investigation

Nonsteroidal Anti-inflammatory Drugs and the Risk for Anastomotic Failure

A Report From Washington State's Surgical Care and Outcomes Assessment Program (SCOAP)

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IMPORTANCE Nonsteroidal anti-inflammatory drugs (NSAIDs) have many physiologic effects and are being used more commonly to treat postoperative pain, but recent small studies have suggested that NSAIDs may impair anastomotic healing in the gastrointestinal tract.

OBJECTIVE To evaluate the relationship between postoperative NSAID administration and anastomotic complications.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 13 082 patients undergoing bariatric or colorectal surgery at 47 hospitals in Washington State from January 1, 2006, through December 31, 2010, using data from the Surgical Care and Outcomes Assessment Program linked to the Washington State Comprehensive Abstract Reporting System.

EXPOSURE NSAID administration beginning within 24 hours after surgery.

MAIN OUTCOMES AND MEASURES We used multivariate logistic regression modeling to assess the risk for anastomotic complications (reoperation, rescue stoma, revision of an anastomosis, and percutaneous drainage of an abscess) through 90 days after bariatric and colorectal surgery involving anastomoses.

RESULTS Of the 13 082 patients (mean [SD] age, 58.1 [15.8] years; 60.7% women), 3158 (24.1%) received NSAIDs. The overall 90-day rate of anastomotic leaks was 4.3% for all patients (151 patients [4.8%] in the NSAID group and 417 patients [4.2%] in the non-NSAID group; $P = .16$). After risk adjustment, NSAIDs were associated with a 24% increased risk for anastomotic leak (odds ratio, 1.24 [95% CI, 1.01-1.56]; $P = .04$). This association was isolated to nonelective colorectal surgery, for which the leak rate was 12.3% in the NSAID group and 8.3% in the non-NSAID group (odds ratio, 1.70 [95% CI, 1.11-2.68]; $P = .01$).

CONCLUSIONS AND RELEVANCE Postoperative NSAIDs were associated with a significantly increased risk for anastomotic complications among patients undergoing nonelective colorectal resection. To determine the role of NSAIDs in colorectal surgery, future evaluations should consider specific formulations, the dose effect, mechanism, and other relevant outcome domains, including pain control, cardiac complications, and overall recovery.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a broad class of drugs that are commonly used for their anti-inflammatory and analgesic properties. NSAIDs have long been used to treat postoperative pain, but until recently, they were used primarily in oral formulations once the patient tolerated an oral diet. With the recent development of intravenous formulations, the postoperative use of NSAIDs has expanded primarily because of their benefit in avoiding adverse effects associated with opioid analgesia, including respiratory depression, sedation, euphoria, and impaired motility of the gastrointestinal tract. However, within the past decade, several small and single-institution studies[1-5] have suggested that NSAIDs may have a detrimental effect on anastomotic healing of the gastrointestinal tract and may increase rates of anastomotic leak. We aimed to evaluate the association between postoperative NSAID administration and anastomotic complication rates using a large cohort of patients in a statewide collaborative study.

Methods

Study Design

This research project was reviewed and approved by the human subject division of the institutional review board at the University of Washington. Informed consent was waived, and deidentified patient data were used. The Comparative Effectiveness Translational Network (CERTAIN) is an Agency for Healthcare Research and Quality–funded research platform directed from the Surgical Outcomes Research Center of the University of Washington, Seattle. CERTAIN applies skills in comparative evaluation to prospective data collection activities for the purpose of quality improvement across Washington State. This quality improvement activity is directed by a statewide program called the Surgical Care and Outcomes Assessment Program (SCOAP), which is a physician-led surveillance and response system for surgical quality. The mission of SCOAP is to improve the quality of surgical care by reducing variations in outcomes and processes of care through measurement and data sharing between participants. The SCOAP system monitors the incidence of various surgical complications, including anastomotic leak, at participating hospitals. Data are captured for specific procedures performed at participating hospitals. This clinical registry includes more than 50 hospitals in Washington State. For this research question, CERTAIN assembled a retrospective cohort of patients with prospectively collected data who underwent bariatric and colorectal surgery involving an anastomosis from January 1, 2006, through December 31, 2010, in Washington State. We excluded 206 patients (1.6%) for whom postoperative NSAID administration data were missing. For this study, data from 47 SCOAP hospitals were available during the evaluation period. We used SCOAP records to obtain demographic, laboratory, anthropometric, and clinical characteristics, procedures, laboratory values, operative type, operative level, operative urgency, and perioperative information deemed to be relevant to the risk for anastomotic failure. The SCOAP data were linked to the Washington State Comprehensive Hospital Abstract Reporting System to assess for 90-day complications, including rehospitalization, operative reintervention, and percutaneous reintervention. The Comprehensive Hospital Abstract Reporting System is a data set administered by the Washington State Department of Health that captures the diagnostic, demographic, and billing data from inpatient hospital stays and allows longitudinal assessment of multiple hospital admissions for the same patient.

Definitions

Data definitions for SCOAP variables are publically available (http://www.scoap.org). Beginning in 2006, SCOAP added a postoperative NSAID administration data metric, and abstracters were trained to review the medical record for the administration of NSAIDs (including ibuprofen, naproxen sodium, ketorolac tromethamine, caldolor, celecoxib, and diclofenac) starting within 24 hours of surgery. Information about preoperative NSAID use is not available. For the purposes of this study, a patient was considered to have an anastomotic failure if operative reintervention was performed and indicated a leak or if percutaneous reintervention was performed for a fluid collection at the site of the anastomosis. Radiographic evidence of leak without intervention was not captured in the SCOAP database at the time of this study. The decision not to surveil actively for radiographic leaks not requiring reintervention within the SCOAP platform was made for the following 2 reasons: (1) different institutions and surgeons may have different postoperative imaging practices that would introduce a surveillance bias, and (2) SCOAP is primarily concerned with outcomes that have clinically noticeable effects and that affect the use of health care resources. Study deaths were determined by in-hospital deaths reported through SCOAP or by the Comprehensive Hospital Abstract Reporting System, which links to the Department of Health vital statistics for 90-day deaths in Washington State. For comorbid conditions, we calculated a score modeled on the Charlson Comorbidity Index[6] on the basis of health conditions identified from the medical record.

Statistical Analysis

The primary outcome in our study was anastomotic complications requiring reintervention within 90 days. The primary exposure was NSAID administration beginning within 24 hours after surgery. Patient characteristics were summarized using frequency distributions for categorical variables and means and SDs for continuous variables. To evaluate for differences in categorical and continuous variables, we performed χ^2 and multiple paired 2-tailed *t* tests, respectively.

We developed logistic regression models, adjusting for clustering at the hospital level, to evaluate the association between postoperative NSAID administration and anastomotic failure after adjusting for patient, clinical, and operative characteristics. Covariates were selected if they were associated with anastomotic failure ($P < .05$) in univariate analyses or if they were found to be important in previous studies. A priori selected covariates included patient age, sex, procedure type (bariatric or colorectal), operative approach (open, laparoscopic, or laparoscopic converted to open), protective os-

Table 1. Demographic and Clinical Characteristics by Assignment Group

Characteristic	NSAID Group	Non-NSAID Group	*P* Value
Total, No. (%) of patients	3158 (24.1)	9924 (75.9)	NA
Age, mean (SD), y	54.9 (15.4)	59.1 (15.8)	<.001
Female sex, No. (%)	1926 (61.0)	6014 (60.6)	.66
Charlson Comorbidity Index, No. (%)			
0	1631 (51.7)	4387 (44.2)	<.001
1	478 (15.1)	1832 (18.5)	
2	557 (17.6)	1795 (18.1)	
≥3	492 (15.6)	1910 (19.2)	
Cardiac risk index, No. (%)			
0	2874 (91.0)	8305 (83.7)	<.001
1	227 (7.2)	1241 (12.5)	
2	54 (1.7)	328 (3.3)	
≥3	3 (0.1)	50 (0.5)	
Albumin level <3 g/dL, No. (%)	152 (4.8)	685 (6.9)	<.001
Admission priority, No. (%)			
Emergency/urgent	300 (9.5)	1280 (12.9)	<.001
Elective	2858 (90.5)	8644 (87.1)	<.001
Procedure type, No. (%)			
Bariatric	656 (20.8)	2562 (25.8)	<.001
Colectomy			
Nonelective	308 (9.8)	1313 (13.2)	<.001
Elective	2194 (69.5)	6049 (61.0)	<.001
Anastomosis tested, No. (%)	1740 (55.1)	5567 (56.1)	.34
Diverting ostomy, No. (%)[a]	319 (12.7)	850 (11.5)	.29
Open procedure or conversion to open procedure, No. (%)	1794 (56.8)	5706 (57.5)	.47
Time to oral intake, mean (SD), d[a]	3.6 (3.0)	4.7 (3.7)	<.001
Epidural, No. (%)	666 (21.1)	1856 (18.7)	.003
Patient-controlled analgesia, No. (%)	2564 (81.2)	8296 (83.6)	.002

Abbreviations: NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug.

SI conversion factor: To convert albumin to grams per liter, multiply by 10.

[a] Includes patients undergoing colorectal procedures only.

tomy, comorbid conditions, body mass index, and a low serum albumin level. Because protective ostomies are used only in colorectal procedures, patients undergoing bariatric procedures are not at risk for protective stoma, and this variable was used in the analysis of patients undergoing colorectal procedures only. The revised cardiac risk index[7] was used in addition to these covariates for the analysis of 90-day mortality. In addition to adjusting for procedure type and priority in the full model, planned subpopulation analyses among patients undergoing bariatric and elective and nonelective colorectal procedures were performed because of known differences in complication rates. Because NSAIDs are used primarily as part of the analgesic regimen, we also controlled for other (patient-controlled and epidural) methods of postoperative analgesia.

We used commercially available software (STATA, version 12; StataCorp) for all statistical analyses. Results of 2-sided tests with $P < .05$ were considered significant.

Results

We identified 13 082 patients (mean [SD] age, 58.1 [15.8] years; 60.7% women) who underwent surgery of the gastrointestinal tract with anastomosis (63.0% elective colorectal, 24.6% bariatric, and 12.4% nonelective colorectal) at SCOAP hospitals. NSAIDS were used in 24.1% of patients (25.4% undergoing colorectal and 20.4% undergoing bariatric procedures). Baseline clinical and demographic characteristics of the groups that did and did not receive NSAIDS differed considerably. Patients who received NSAIDs were younger, had lower levels of comorbidities and a lower cardiac risk index, and underwent elective procedures more frequently than patients not receiving NSAIDs (**Table 1**). The overall rate of anastomotic complication was 4.3% (151 patients [4.8%] in the NSAID group and 417 patients [4.2%] in the non-NSAID group; $P = .16$). The overall 90-day mortality was 2.4% (41 patients [1.3%] in the NSAID group and 278 patients [2.8%] in the non-NSAID group; $P < .001$). Exploratory analysis revealed associations between anastomotic leak and complications, including urinary tract infection (odds ratio [OR], 1.17 [95% CI, 1.02-1.32]; $P = .04$) and acute kidney injury (OR, 1.34 [95% CI, 1.11-1.57]; $P = .02$), but these associations were independent of whether patients received NSAIDs.

After controlling for important covariates, NSAID administration was associated with an increased risk for anastomotic leak (OR, 1.24 [95% CI, 1.01-1.56]; $P = .04$) (**Table 2**). Planned subgroup analysis showed that this relationship was largely isolated to patients undergoing nonelective colorectal procedures, in whom the association was greater (OR, 1.70 [95% CI, 1.11-2.68]; $P = .01$) (**Table 3**), and no effect was identified

Table 2. Risk for Anastomotic Leak Among All Patients

Variable	OR (95% CI)	
	Unadjusted	Adjusted
Age	1.00 (1.00-1.01)	0.99 (0.99-1.00)
Male sex	1.56 (1.27-1.93)	1.50 (1.27-1.75)
Charlson Comorbidity Index		
0	1 [Reference]	1 [Reference]
1	0.74 (0.60-0.93)	0.91 (0.69-1.21)
2	0.93 (0.65-1.34)	0.99 (0.60-1.63)
≥3	1.05 (0.82-1.34)	0.97 (0.63-1.52)
BMI ≥30	0.74 (0.57-0.96)	1.04 (0.71-1.41)
Albumin level <3 g/dL	2.73 (2.01-3.70)	2.20 (1.63-2.96)
Procedure type		
Bariatric	1 [Reference]	1 [Reference]
Colorectal	2.01 (1.08-3.72)	1.20 (0.67-2.11)
Nonelective colorectal	4.04 (2.17-7.47)	1.44 (0.97-3.04)
Anastomosis tested	0.76 (0.59-0.97)	1.10 (0.90-1.35)
Postoperative NSAID administration	1.15 (0.92-1.42)	1.24 (1.01-1.56)
Epidural	1.07 (0.70-1.63)	1.05 (0.74-1.50)
Patient-controlled analgesia	0.94 (0.60-1.46)	0.95 (0.60-1.50)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

SI conversion factor: To convert albumin to grams per liter, multiply by 10.

Table 3. Risk for Anastomotic Leak Among 1621 Patients Undergoing Nonelective Colorectal Procedures

Variable	OR (95% CI)	
	Unadjusted	Adjusted
Age	1.00 (0.99-1.01)	0.98 (0.97-1.00)
Male sex	1.32 (0.87-2.00)	1.42 (0.88-2.30)
Charlson Comorbidity Index		
0	1 [Reference]	1 [Reference]
1	1.35 (0.82-2.24)	1.43 (0.82-2.51)
2	1.04 (0.70-1.55)	1.61 (0.86-2.99)
≥3	0.80 (0.55-1.17)	1.15 (0.59-2.23)
Cancer diagnosis	0.73 (0.51-1.05)	0.82 (0.43-1.55)
BMI ≥30	1.19 (0.93-1.54)	0.97 (0.67-1.41)
Albumin level <3 g/dL	1.61 (1.11-2.32)	1.74 (1.22-2.47)
Open procedure	1.53 (0.91-2.58)	1.57 (0.81-3.01)
Anastomosis tested	0.92 (0.66-1.28)	1.03 (0.63-1.69)
Protective ostomy	1.51 (0.77-2.25)	0.89 (0.76-1.02)
Postoperative NSAID administration	1.57 (1.08-2.27)	1.70 (1.11-2.68)
Epidural	0.78 (0.42-1.45)	0.68 (0.32-1.45)
Patient-controlled analgesia	0.70 (0.43-1.14)	0.54 (0.31-0.95)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

SI conversion factor: To convert albumin to grams per liter, multiply by 10.

among patients undergoing elective colorectal (OR, 1.13 [95% CI, 0.87-1.49]; $P = .36$) or bariatric (OR, 1.04 [95% CI, 0.53-2.06]; $P = .89$) procedures. Among patients undergoing nonelective colorectal surgery, the 90-day rate of anastomotic leak was 12.3% among those receiving NSAIDs compared with 8.3% among those who did not receive NSAIDs ($P = .03$).

Because of the significantly different crude 90-day mortality observed among patients receiving NSAIDs, a post hoc analysis evaluated the association between 90-day mortality and NSAID administration, cardiac events, and the cardiac risk index. We observed no significant association between NSAID administration and the risk for 90-day death (OR, 0.89 [95% CI, 0.64-1.14]; $P = .25$). We found a strong association between increasing cardiac risk index and the risk for 90-day death (OR, 2.41 [95% CI, 1.79-3.03]; $P < .001$) and between cardiac events and the risk for 90-day mortality (OR, 3.01 [95% CI, 2.22-3.82]; $P < .001$). This finding suggests that differences in cardiac risk profiles between groups were responsible for differences in observed crude mortality.

Discussion

Postoperative NSAID administration in patients undergoing nonelective colorectal surgery was associated with a 60% higher risk-adjusted rate of anastomotic complications. We found no significant difference in risk-adjusted 90-day mortality between the NSAID and non-NSAID groups. The observed difference in crude 90-day mortality is likely attributable to the higher degree of cardiac risk and the associated increase in cardiac events among patients in the non-NSAID group.

Results of animal studies suggest that NSAIDs can impair healing and anastomotic strength in the gastrointestinal tract.[8-10] Two small series[2,3] suggested an increased risk for anastomotic leak among patients undergoing colorectal procedures who receive postoperative NSAIDs, but the results have been mixed and the mechanism has been uncertain. A case-control study by Klein et al[2] and a retrospective cohort using a time-sequence method by Holte et al[3] found an increased risk for anastomotic leak associated with selective cyclooxygenase 2 (COX2) inhibitors among patients undergoing elective laparoscopic colorectal surgery. However, a larger cohort study by Gorissen et al[5] found an increased risk associated with nonselective NSAIDs but no specifically increased risk associated with COX2-seletive NSAIDs. The work by Gorissen and colleagues[5] included nonelective cases, but whether the investigators controlled for this factor in their analysis remains unclear.

We found an association of NSAIDs and anastomotic complications isolated to patients undergoing nonelective colorectal surgery. These procedures likely take place in the settings of infection, inflammation, and hemodynamic instability or shock. NSAIDs work by inhibiting the conversion of arachidonic acid via COX1 or COX2 into thromboxane or other prostaglandins, respectively. COX1 is expressed constitutively at significantly higher levels than COX2, but in times of inflammation, expression of COX2 is increased to levels significantly higher than those of COX1. Therapeutically, NSAIDs inhibit conversion of arachidonic acid by COX2 into prostaglandin E_2, which is thought to be responsible for pain and fever associated with inflammation. Various other prostaglandins produced via COX2 have been shown to be involved in epithelial cell migration in the gastrointestinal tract

in animal models, to modulate activity of myofibroblasts and collagen deposition in wounds, and to have immunomodulatory effects on leukocyte adhesion and granulocyte functions, including chemotaxis, oxidative burst, and bactericidal activity.[11-18] The increased risk for anastomotic leak observed among patients undergoing nonelective colorectal procedures and receiving NSAIDs may represent differential downstream effects of COX2 inhibition in the setting of antecedent physiologic stress and inflammation or some other mechanism that has yet to be determined.

Our present study has several limitations. SCOAP data do not specify which NSAID was administered or provide data on dose and duration. Therefore, we cannot evaluate the relative risk among different NSAIDs for anastomotic leak or evaluate for a dose-response relationship between NSAIDs and the risk for anastomotic leak. However, given practice patterns among SCOAP hospitals and the requirements that NSAID administration began within 24 hours before most patients would have transitioned to oral diets, intravenous NSAIDs (eg, ketorolac or caldolor) were likely the most common. Ketorolac and caldolor are relatively nonselective NSAIDs, which bind to COX1 and COX2. Thus, our study likely supports the findings of prior cohorts showing an increased risk for anastomotic leak with nonselective NSAIDs.[5] Second, we do not have information on preoperative NSAID use. Practice patterns vary significantly, and some surgeons allow patients to continue taking NSAIDs until surgery, whereas others recommend discontinuation a week or more before surgery. The half-lives of most NSAIDs are very short, on the order of a few hours; thus, we can expect that most NSAIDs would have cleared fully even if taken until the day before surgery. However, we cannot estimate how this prior exposure might alter the physiologic response to further NSAID administration or to surgical stress. As such, information about the preoperative use of NSAIDs warrants inclusion in further investigation of the relationship between NSAIDs and anastomotic complications. We also lack information about the timing of complications in the current SCOAP platform, and we cannot comment on what fraction of leaks occurred early (<1 week) or later. We therefore cannot evaluate the specific effect of limited perioperative NSAID use compared with ongoing postoperative and postdischarge NSAID use; this information also warrants further investigation. We were not able to exclude patients who had an NSAID allergy or other contraindication. We are unaware of any suggested association between NSAID allergy and impaired tissue healing; because NSAID allergies are estimated to affect only 0.3% to 1.5% of the general population, we do not believe this failure to exclude these patients would significantly alter the results.[19] Despite these limitations, we believe that the results of the present study are sufficient to suggest caution in the use of NSAIDs in the postoperative treatment of patients undergoing nonelective colorectal surgery and highlight the importance of further evaluation of this association, including investigation into rates of anastomotic complication inclusive of those radiographically identified, regardless of reintervention.

Conclusions

The results of this large statewide cohort study show that, among patients undergoing nonelective colorectal resection, postoperative NSAID administration is associated with a significantly increased risk for anastomotic complications. Given that other analgesic regimens are effective and well tolerated, these data may be enough for some surgeons to alter practice patterns. Future work should explore the mechanism of action and assess for formulation and dose effects of NSAIDs, including preoperative use, on the risk for anastomotic complications while further evaluating other outcome domains, including pain control, cardiac complications, and overall outcomes. These results, taken in the context of prior literature, emphasize the importance of a learning health care system to determine the proper role of drugs, devices, and interventions. The SCOAP-CERTAIN process of comparative effectiveness evaluation with translation of evidence into practice will work to disseminate this information about added risk to better inform clinicians and patients about the apparent risks of NSAIDs in this population.

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Correction: This article was corrected on April 10, 2015, to fix the number of patients in Table 3's title.

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