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ORIGINAL ARTICLE

NSAID Use and Anastomotic Leaks Following Elective Colorectal Surgery: a Matched Case-Control Study

Jhananiee Subendran · Naveed Siddiqui · J. Charles Victor · Robin S. McLeod · Anand Govindarajan

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Abstract
Introduction Non-steroidal anti-inflammatory drugs (NSAIDs) decrease postoperative pain and opioid consumption. The objective of the study was to determine if postoperative NSAIDs were associated with anastomotic leaks following elective colorectal surgery.
Materials and Methods We used a matched nested case-control study design. Using a prospectively collected database, we identified all patients having elective colorectal surgery between January 2001 and June 2012. Cases and matched controls were identified based on the occurrence of a postoperative anastomotic leak. The primary and secondary exposure variables were, respectively, use of any NSAID and use of ketorolac specifically. Conditional logistic regression was used to determine the unadjusted and adjusted odds ratio.
Results A total of 262 patients were included (65.6 % inflammatory bowel disease, 34.4 % cancer). Use of any NSAID was associated with a non-significant increase in anastomotic leaks (odds ratio (OR) 1.81, 95 % confidence interval (CI) 0.98–3.37, p=0.06). Use of ketorolac was associated with a significant increase in anastomotic leaks (OR 2.09, 95 % CI 1.12–3.89, p=0.021). There was no significant association between anastomotic leaks and cumulative NSAID dose.
Conclusion These data suggest that there may be an association between NSAIDs and risk of anastomotic leaks after colorectal surgery. Further research is needed to better elucidate this relationship to clarify the implications for patients.

Keywords NSAIDs · Anastomotic leaks · Colorectal surgery

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J. Subendran · R. S. McLeod · A. Govindarajan (✉)
Division of General Surgery, Department of Surgery, Mount Sinai Hospital, University of Toronto, 600 University Avenue, Suite 1220, Toronto, ON M5G 1X5, Canada
e-mail: agovindarajan@mtsinai.on.ca

N. Siddiqui
Department of Anesthesia, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

J. C. Victor
Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

R. S. McLeod
Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

Introduction

In the current practice of multimodal pain management, non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be an integral part of postoperative analgesia after major surgery. Their use has also been promoted in various guidelines on enhanced recovery after surgery or fast-track surgery programs.[1,2]

NSAIDs act through inhibition of the cyclooxygenase (COX) pathways, which are important in the development of inflammation and pain. A broad array of NSAIDs is available with differential inhibitory effects on the COX-1 and COX-2 isoenzymes. Clinically, the addition of NSAIDs to postoperative pain protocols has been shown to significantly reduce the amount of opioids required, with attendant benefits on pain scores, duration of ileus, length of hospital stay, and patient satisfaction.[3–7]

However, the inhibitory effects of NSAIDs on inflammation may also have an impact on normal wound healing processes and thus may adversely affect the healing of intestinal anastomoses. A few animal studies have suggested higher rates of anastomotic failure associated with the use of NSAIDs.[8–10] Some retrospective studies and a small randomized trial have also questioned an association between anastomotic leaks and use of NSAIDs.[4,6,11–13] However, these studies frequently have a relatively small number of events, inconsistent definitions of anastomotic leaks, and a patient population largely comprising colorectal malignancy. In this study, we sought to determine the association between use of postoperative NSAIDs and anastomotic leaks in a group of patients undergoing colorectal surgery for benign and malignant diseases.

Material and Methods

We used a nested matched case-control study design. The study population was selected from a cohort of patients prospectively entered into colorectal cancer and inflammatory bowel disease databases at Mount Sinai Hospital, a tertiary-care academic hospital. The cohorts of patients in these databases, including anastomotic leak rate, have been previously described by our group in different patient subgroups (2.1 % for colorectal cancer patients, 4.8 % for Crohn's patients, and 6.8 % for ileal pouch-anal anastomosis patients).[14–16] Using these databases, all patients who had elective colorectal surgery at Mount Sinai Hospital between January 2001 and June 2012 were identified. Cases were defined as those who had an anastomotic leak postoperatively. Anastomotic leaks were identified by radiologic investigations and/or direct confirmation at the time of reoperation, and thus, this definition included all clinically relevant anastomotic leaks, regardless of whether they were severe enough to warrant reoperation. Findings on imaging signifying anastomotic leaks included extravasation of oral or rectal contrast and abscesses associated with the anastomosis. Controls were chosen using 1:1 matching with cases based on underlying disease, type of surgery, age (within 5 years), sex, and year of surgery (within 5 years). The study was approved by the institutional research ethics board.

The primary exposure was use of any postoperative NSAID within the first five postoperative days. The secondary exposure was use of the non-selective NSAID, ketorolac, which was the most common NSAID used during the study period. During the study period, the dose of ketorolac used was 10–30 mg every 6 h as needed, and patients receiving ketorolac did not receive other NSAIDs concurrently. The following variables were also recorded: age, sex, year of surgery, type of surgery, underlying disease, use of preoperative steroids, smoking status, other comorbidities, total ketorolac dose, and method of detection of the anastomotic leak. Exposures and covariates were identified through the database and from the patient's medical record. Comorbidity was not recorded in the database.

All operations were performed by subspecialty-trained surgeons in colorectal surgery or surgical oncology. The technique for anastomosis and use of a diverting stoma were at the discretion of the individual surgeon. Use of postoperative NSAIDs and other analgesic modalities was at the discretion of the surgical and the pain management team. Over the period of the study, the presence of an intestinal anastomosis and the presence of an ostomy were not considerations in the decision to use NSAIDs postoperatively.

Statistical Analysis

Baseline patient characteristics were recorded and tabulated. To examine the association between postoperative NSAID use and anastomotic leaks, conditional logistic regression was used to compare the distribution of the primary (any NSAID) and secondary exposures (ketorolac) between cases and controls. Conditional logistic regression accounts for the paired nature of the data. Simple analyses were performed as well as multivariable regression analyses to determine adjusted odds ratios (OR) and 95 % confidence intervals. Covariates included in the multivariable model were those that differed between cases and controls in univariate analysis at a significance level of $p<0.50$. Use of proton pump inhibitors or histamine blockers was tested as an interaction term in the multivariable models. A secondary analysis was performed examining differences in the cumulative dose of ketorolac between cases and controls. Exploratory analyses were also performed to examine the association of NSAIDs with anastomotic leaks in three disease subgroups—ulcerative colitis patients treated with ileal pouch-anal anastomosis (IPAA), Crohn's patients, and cancer patients. All analyses were performed using SAS v9.3 (Cary, NC).

Results

A total of 270 patients (135 case-control pairs) were identified for inclusion in the study. Of these, we excluded four pairs because the anastomotic leak occurred more than 12 months after their initial surgery and are likely unrelated to their exposure to NSAIDs. Thus, the final study population comprised 262 patients (131 cases with an anastomotic leak, 131 controls without an anastomotic leak). Of the 262 patients, 90 patients had surgery for cancer and 172 had surgery for ulcerative colitis or Crohn's disease. The mean age at surgery was 46.8 and 55.3 % of the sample was male. Baseline characteristics for the study sample are outlined in Table 1.

Table 1 Description of study population

	Cases (n=131)	Controls (n=131)	p value
Age at surgery, mean (SD)	47.0 (17.9)	46.5 (17.8)	0.40
Sex, % male	55.0 %	55.7 %	0.90
Indication for surgery			1.00
Cancer	34.4 %	34.4 %	
Ulcerative colitis	45.8 %	45.8 %	
Crohn's disease	19.8 %	19.8 %	
Type/location of anastomosis			1.00
Ileal pouch-anal anastomosis	46.6 %	46.6 %	
Coloanal	1.5 %	1.5 %	
Anterior resection	15.3 %	15.3 %	
Ileorectal	3.8 %	3.8 %	
Left hemicolectomy	3.8 %	3.8 %	
Ileocolic	24.4 %	24.4 %	
Other colocolic anastomosis (e.g., segmental resection)	4.6 %	4.6 %	
Laparoscopic surgery	14.5 %	17.9 %	0.46
Year of surgery			0.74
2001–2003	16.0 %	16.8 %	
2004–2006	21.4 %	26.7 %	
2007–2009	36.6 %	32.8 %	
2010–2012	26.0 %	23.7 %	
Preoperative steroids	17.6 %	9.9 %	0.073
Current smoker	18.4 %	14.2 %	0.40
Neoadjuvant chemoradiation[a]	22.2 %	22.2 %	1.00
Diverting ileostomy	32.1 %	31.3 %	0.89
Use of NSAID			
Any NSAID	52.7 %	44.3 %	0.13
Ketorolac	51.9 %	41.2 %	0.06
Cumulative ketorolac dose, mean (SD) (mg)	96.4 (34.1)	92.4 (37.3)	0.89
Use of proton pump inhibitor or H2 blocker	35.9 %	42.7 %	0.24

[a] Cancer cases only

Postoperative NSAIDs were used in 48.5 % of the patients, with ketorolac being used in over 90 % of the patients that received NSAIDs. Other NSAIDs used included celecoxib, ketoprofen, and ibuprofen. Among patients who received ketorolac, the cumulative dose of ketorolac ranged from 20 to 170 mg, with a mean cumulative dose of 94.6 mg. A total of 13.7 % of the patients were on prednisone or equivalent preoperatively, with 17.6 % of the cases and 9.9 % of the controls being on preoperative steroids (p=0.11). By subgroup, the proportion of patients on preoperative steroids was 1.1 % in the cancer subgroup, 19.7 % in the ulcerative colitis subgroup, and 21.2 % in the Crohn's subgroup. Overall, 16.2 % of the patients smoked at the time of surgery (18.4 % cases, 14.2 % controls, p=0.40). By subgroup, the proportion of the patients who were smokers was 18.8 % in the cancer subgroup, 9.9 % in the ulcerative colitis subgroup, and 26.9 % in the Crohn's subgroup. There was no clinically or statistically significant difference between cases and controls in the use of neoadjuvant chemoradiation (p=1.00) or diverting ostomies (p=0.89). Based on these univariate analyses, smoking and preoperative steroid use were included in the final multivariable model. Information on smoking history was unavailable for either the case or control in 14 of the matched pairs. Therefore, all multivariable analyses controlling for smoking status were performed on the 117 matched pairs where complete information was available. Anastomoses performed included an IPAA in 46.6 %, a rectal anastomosis in 23.8 %, and colonic anastomosis in 29.9 %. Of the 131 cases with anastomotic leaks, 41 patients (31.3 %) required reoperation, while the remainder was managed nonoperatively with antibiotics and percutaneous drainage.

In unadjusted analysis, there was no significant association between anastomotic leaks and use of any NSAID (OR 1.55, 95 % confidence interval (CI) 0.88–2.72, p=0.13, Table 2).

Table 2 Association of NSAIDs with anastomotic leak in entire population

	Unadjusted analysis		Adjusted analysis[a]	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Any NSAID	1.55 (0.88, 2.72)	0.13	1.81 (0.98, 3.37)	0.060
Ketorolac	1.70 (0.98, 2.95)	0.060	2.09 (1.12, 3.89)	0.021
Cumulative dose of ketorolac	1.001 (0.99, 1.02)	0.89	1.00 (0.98, 1.01)	0.66

[a] Patients with complete covariate information (n=234)

There was an increased risk of anastomotic leaks when use of ketorolac specifically was analyzed, but this did not reach statistical significance (OR 1.70, 95 % CI 0.98–2.95, p=0.06). In adjusted analysis, use of any NSAID was associated with a non-significant increase in leaks (OR 1.81, 95 % CI 0.98–3.37, p=0.06), while use of ketorolac was associated with a significantly higher risk of anastomotic leaks (OR 2.09, 95 % CI 1.12–3.89, p=0.021). There was no significant association between cumulative ketorolac dose and anastomotic leaks in unadjusted (OR 1.00, 95 % CI 0.98–1.01, p=0.73) and adjusted analyses (OR 1.00, 95 % CI 0.98–1.01, p=0.66). There was no significant association between anastomotic leaks and the number of days of NSAID (p=0.23) or ketorolac use (p=0.97). There was no significant interaction between NSAIDs and use of antacids (proton pump inhibitors, H2 blockers) on anastomotic leaks.

Subgroup Analyses

In unadjusted analysis, use of any NSAID was not significantly associated with an increased risk of anastomotic leaks in the three subgroups (ulcerative colitis: OR 1.33, 95 % CI 0.56–3.16; Crohn's: OR 2.67, 95 % CI 0.71–10.05; colorectal cancer: OR 1.38, 95 % CI 0.55–3.42; see Table 3). Similar results were observed with ketorolac. In adjusted analysis, use of NSAIDs was not significantly associated with leaks in ulcerative colitis patients (adjusted OR 1.31, 95 % CI 0.49–3.51, p=0.59), Crohn's patients (adjusted OR 2.51, 95 % CI 0.64–9.93, p=0.19), or cancer patients (adjusted OR 2.84, 95 % CI 0.86–9.34, p=0.086). Use of ketorolac was not significantly associated with leaks in ulcerative colitis patients (adjusted OR 1.57, 95 % CI 0.56–4.36, p=0.39) or in Crohn's patients (adjusted OR 2.51, 95 % CI 0.64–9.93, p=0.19), but was significantly associated with leaks in cancer patients (adjusted OR of 3.23, 95 % CI 1.02–10.28, p=0.047).

Discussion

NSAIDs are frequently used in the perioperative setting to improve pain control and reduce the use of opioids. Their use after elective colorectal surgery can have significant benefits on perioperative pain control by abrogating inflammatory and nociceptive pathways, but may have an adverse effect on wound healing and intestinal anastomoses.[6·12·13] Although we found a higher odds ratio associated with the use of any perioperative NSAID, these results did not reach statistical significance. In this study, ketorolac, a non-selective NSAID, was the most common NSAID used. We found that use of ketorolac specifically was associated with a statistically significant twofold increase in the adjusted odds of anastomotic leak.

These results extend the work from previous studies that have examined the association between anastomotic leaks and NSAIDs and have found conflicting results. A recent meta-analysis of randomized trials found a meta-analytic odds ratio of 2.16, which did not reach statistical significance likely due to the small number of events in both study groups (14 cumulative leaks in the NSAID group, 5 cumulative leaks in the non-NSAID group).[6] To date, there have been five non-randomized studies examining this issue, reporting twofold to tenfold increases in the risk of anastomotic leaks. Holte et al. reported an anastomotic leak rate of 15.1 % in a period where celecoxib, a selective COX-2 inhibitor, was used as part of an enhanced recovery after surgery protocol, compared to leak rates of 3.3 % in historical controls.[17] Using a similar study design, Rosenberg et al. reported a change in anastomotic leak rate from 3.9 to 20.5 % during a period when diclofenac was used.[11] The same group also reported similar findings when laparoscopic colorectal surgeries were examined with anastomotic leak rates increasing from 2.4 to 21.2 % when diclofenac was used.[18] These studies are limited by small sample sizes and event rates (68 total patients with anastomotic leaks combined across the three studies). In addition, all three studies rely on comparison of patients from a time period when NSAIDs were used to historical controls when NSAIDs were not, rather than a true comparison of patients receiving NSAIDs with contemporaneous controls. This limits the conclusions that can be drawn as there may be myriad other factors that differ across time periods.

Only two studies to date have used contemporaneous controls. Gorissen et al. conducted a retrospective cohort study of patients undergoing colorectal surgery at two hospitals in the

Table 3 Association of NSAIDs with anastomotic leaks by disease subgroup

	Unadjusted analysis		Adjusted analysis[a]	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Ulcerative colitis				
Any NSAID	1.33 (0.56, 3.16)	0.51	1.31 (0.49, 3.51)	0.59
Ketorolac	1.44 (0.62, 3.38)	0.39	1.57 (0.56, 4.36)	0.39
Cumulative dose of ketorolac	1.00 (0.98, 1.02)	0.78	1.00 (0.97, 1.02)	0.89
Crohn's disease				
Any NSAID	2.67 (0.71, 10.05)	0.15	2.51 (0.64, 9.93)	0.19
Ketorolac	2.67 (0.71, 10.05)	0.15	2.51 (0.64, 9.93)	0.19
Cumulative dose of ketorolac	1.00 (0.98, 1.02)	0.86	1.01 (0.98, 1.05)	0.50
Cancer				
Any NSAID	1.38 (0.55, 3.42)	0.49	2.84 (0.86, 9.34)	0.086
Ketorolac	1.63 (0.67, 3.92)	0.67	3.23 (1.02, 10.28)	0.047
Cumulative dose of ketorolac	1.00 (0.95, 1.06)	0.89	1.03 (0.96, 1.12)	0.42

[a] Patients with complete covariate information

Netherlands.[12] Although there were 795 patients in the study, the event rate was relatively low with only 79 patients with anastomotic leaks, and only 28 % of patients had benign disease. In this population, there was 2.13-fold increase in the risk of anastomotic leak in patients treated with non-selective NSAIDs but no significant increase in patients treated with selective COX-2 inhibitors. The analyses were also not controlled for emergent versus elective surgery, which could significantly impact the findings, given the increased risk of leaks in emergent operations. In the largest study to date, Klein et al. examined data from six Danish hospitals performing surgery on colorectal cancer, comprising 2,766 patients and 179 leaks.[13] They found a 7.2-fold increase in the risk of anastomotic leak with the use of diclofenac, a COX-2 inhibitor, but no significant increase with the use of a non-selective NSAID. This is in contrast to the findings of Gorissen et al. and the present study. The study by Klein et al. also considered only patients with malignant disease and included only anastomotic leaks that required reoperation, which excludes clinically significant but less severe anastomotic leaks.[13] In addition, the threshold to reoperate on patients for an anastomotic leak is subjective and may be surgeon- and/or hospital-dependent, thus introducing another potential source of bias in a study that spanned six hospitals. In our study, a minority of patients with anastomotic leaks required reoperation, and therefore, restricting the inclusion criteria in the present study to only these patients could introduce bias.

The present case-control study is one of the larger studies in the literature with respect to the number of events analyzed and has an 80 % power to detect the clinically significant odds ratio of 2.16 found in the meta-analysis (with a type I error rate of 5 %). In addition, a strength of the present study is the inclusion of leaks of all severity (not only those requiring reoperation), the inclusion of only elective patients, and the enriching of the study population with patients with inflammatory bowel disease, a group that is relatively underrepresented in the literature on this topic. At our institution, we have not prospectively collected data on patients undergoing surgery for other benign diseases such as diverticular disease and thus did not include them in this study.

The mechanisms by which NSAIDs may contribute to poor healing of an intestinal anastomosis are unclear. NSAIDs interfere with inflammatory and nociceptive responses through inhibition of the COX-1 and/or COX-2 pathways. As inflammation is a key part of normal wound healing, the inhibition of inflammation by NSAIDs may be one contributing factor. Studies have also suggested that NSAIDs may inhibit collagen production and cross-linking, thus impairing wound healing.[9,10,19,20] Finally, NSAIDs may interfere with angiogenesis, with COX-2 inhibitors increasing the risk of microvascular thrombosis,[21,22] processes that may further contribute to impaired wound healing. Furthermore, there is increasing evidence that approximately 50 % of patients who take NSAIDS may have some intestinal mucosal damage, which can manifest as ulcers and strictures,[23] thus leading to impaired anastomotic healing. Some small studies have suggested that mucoprotective agents may abrogate the impact of NSAIDs on intestinal mucosa; in the present study, we did not find a significant protective effect of perioperative proton pump inhibitors or H2 blockers, although the study was not powered to analyze this interaction.

In subgroup analyses, we found variation in the adjusted odds ratios based on underlying disease with ulcerative colitis patients having lower odds ratios than patients with Crohn's disease and those with colorectal malignancy. However, these

subgroup analyses are exploratory and are intended for hypothesis generation only. Our study was not designed or powered to demonstrate differential effects of NSAIDs on anastomotic leaks between disease groups. We know of no literature to date that has explored the biological mechanisms by which NSAIDs may exert differential effects in different intestinal disease processes. Should these findings be confirmed by other studies, further research to elucidate possible underlying mechanisms for these differences may be warranted.

The current literature provides conflicting data on the relative roles of different NSAIDs. We found a significant odds ratio with ketorolac, a non-selective NSAID, but not when all NSAIDs were combined. The difference in odds ratios between ketorolac and all NSAIDs was relatively small (2.09 vs. 1.81), and the odds ratio for all NSAIDs bordered on statistical significance in multivariable analysis (p=0.06). In our study population, ketorolac was used in over 90 % of the patients, and as a result, we were unable to make definitive conclusions on the differential effects of different perioperative NSAIDs. This difference could, therefore, represent a type II error but may indeed reflect a lower odds ratio with some NSAIDs than with the non-selective NSAID ketorolac.

Our study has some important limitations. Although nested in a prospectively collected database, our study was retrospective in nature and is thus subject to potential biases related to unknown confounders. We have attempted to control for this bias somewhat by using both a matched design and adjusting the final analyses for two important known confounders that were unbalanced in this population (smoking and preoperative steroids). We were not able to control for the duration of preoperative steroids and did not control for the preoperative dose of steroids as the general institutional practice is to not perform intestinal anastomoses in the setting of moderate to high dose steroids (e.g., higher than 20 mg prednisone), thus resulting in minimal variation in steroid doses for statistical analyses. We also did not control for the use of preoperative biological agents (e.g., anti-TNF agents), as previous work from our group and others has not shown their use to be linked to the outcome (anastomotic leak)[24,25] and are not plausibly associated with the exposure (NSAIDs). We did not observe any clinically or statistically significant imbalance between cases and controls in the use of neoadjuvant chemoradiation or diverting ostomies. Moreover, the impact of neoadjuvant chemoradiation on anastomotic leaks is controversial with the two large randomized trials on neoadjuvant chemoradiation in rectal cancer demonstrating no significantly increased risk (25.0 vs. 22.6 % overall complication rate in NSABP R-03[26] and 11 vs. 12 % anastomotic leak rate in the German Rectal Cancer Study[27]). Nonetheless, there may be other unmeasured confounding variables that may influence the results, including poor nutritional status and comorbidities. However, over the time frame of this study, the presence of intestinal anastomoses, diverting ostomies, poor nutrition, or preoperative treatment with radiation or steroids was not a consideration in the decision to prescribe postoperative NSAIDs, thus minimizing the potential effect of confounding by indication from these factors. Estimating the potential effect of unmeasured confounding, only confounders with a very strong association (i.e., OR>2) with anastomotic leak would be likely to alter the findings regarding ketorolac.[28] Our study is also not powered to detect differences in the odds ratio of anastomotic leak between disease groups; therefore, the subgroup analyses performed are exploratory and are intended to be hypothesis-generating.

Conclusion

In summary, we found a non-significant increase in anastomotic leaks with the use of postoperative NSAIDs overall, but a significant increase in anastomotic leaks with the use of ketorolac specifically, suggesting that postoperative NSAID use may be associated with an increased risk of anastomotic leaks after elective colorectal surgery. These findings, taken together with the existing literature, lead us to recommend caution in the use of postoperative NSAIDs in the presence of a colorectal anastomosis but stress the importance of weighing the potential risks of NSAIDs against their benefits in terms of reduced opioid-related side effects. These findings may potentially impact a large number of patients as NSAIDs are frequently used in the postoperative setting after colorectal surgery. Although a randomized controlled trial would be the optimal method of testing this association, the feasibility of such a trial is questionable given sample size considerations and the ethical considerations associated with the primary endpoint being one of harm. However, further study is warranted to better elucidate these issues including the differential effect of non-selective NSAIDs versus COX-2 inhibitors, to identify high-risk subgroups, and to study the impact of NSAIDs on non-colorectal anastomoses.

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