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NSAID administration post colorectal surgery increases anastomotic leak rate: systematic review/meta-analysis

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Abstract

Background Current enhanced recovery guidelines suggest that opioid sparing medications should be used for analgesia whenever possible following colorectal surgery. The present study aims to assess whether post-operative NSAID use is associated with an increased anastomotic leak rate after a colonic or rectal anastomosis.

Methods A systematic review was performed for studies investigating anastomotic leak rate following NSAID use vs control after colonic or rectal anastomosis. Meta-analysis was performed to assess for overall risk of anastomotic leak with NSAID use, as well as sub-group analysis to compare selective vs non-selective NSAIDs and drug-specific NSAID safety profiles.

Results Seven studies were included in the final review. Use of an NSAID post-operatively was associated with an overall increased risk of anastomotic leakage [OR 1.58 (1.23, 2.03), $P=0.0003$]. Non-selective NSAIDs were associated with an increased risk [OR 1.79 (1.47, 2.18), $P<0.00001$], but selective NSAIDs were not. The non-selective NSAID diclofenac was associated with an increased leak rate [OR 2.79 (1.96, 3.96), $P<0.00001$], but ketorolac was not [OR 1.36 (0.89, 2.06), $P=0.16$].

Conclusions Great caution must be taken when prescribing NSAIDs following colonic or rectal anastomotic creation. The safety profile varies within the NSAID class and further research is needed to clarify which NSAIDs are safe for use and which are not.

Keywords Early recovery after surgery (ERAS) · Non-steroidal anti-inflammatory drugs (NSAIDs) · Colorectal anastomosis · Anastomotic leak

It can be argued that no domain within general surgery has undergone as much scrutiny and refinement within the last decade as the post-operative management of colorectal patients. With increasing acceptance and implementation of Early Recovery after Surgery (ERAS) protocols, much focus has been placed on decreasing the length of hospital stay post-operatively without compromising patient safety. Given the myriad of complications associated with opioid use, a multi-modality approach using non-steroidal anti-inflammatories (NSAIDs) for pain control has increasingly become an integral component of patient care in many centers. However, questions still remain regarding the impact that NSAIDs have on anastomotic healing. The implications of a clinically significant association between NSAIDs and post-operative anastomotic leakage would be far-reaching, requiring significant reassessment of our current post-operative management regime.

The discussion surrounding NSAIDs and anastomotic leak risk is a complicated one, with several important considerations. A recent meta-analysis by Pang et al. [1] demonstrated that there may be a class-dependent effect associated with NSAID use, with non-selective NSAIDs being associated with a greater incidence of leakage compared to selective NSAIDs. Furthermore, animal studies performed by Yauw et al. [2], de Hingh et al. [3], and van der Vijver et al. [4] all demonstrated that NSAIDs have a location-dependent

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effect on anastomotic healing within the GI tract, with small bowel to small bowel anastomosis demonstrating a greater effect (higher association between NSAIDs and leakage) than colon to colon anastomoses.

This study aims to determine if NSAID administration given post-operatively after performing an anastomosis involving the colon or rectum increases the incidence of anastomotic leakage. Given data from the animal studies performed within this field, a decision was made to exclude small bowel to small bowel anastomoses as these anastomoses may harbor a different risk profile altogether.

Materials and methods

Search strategy and selection criteria

The following systematic review and meta-analysis was completed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were placed on language. It was decided that if foreign papers were identified they would be translated and included in the article review. The databases searched included MEDLINE, EMBASE, and CINAHL.

Studies were included if the following criteria were met: (1) The primary outcome assessed was the anastomotic leak rate. (2) Patients underwent a colonic or rectal resection with an anastomosis. (3) Administration of an NSAID post-operatively (within the first 7 days) was compared to a control group without NSAID administration. As there is currently limited research available that is designed and powered to assess anastomotic leakage after NSAID use as its primary outcome, a decision was made to use both randomized control trials and non-randomized observational studies.

Colonic anastomoses were defined as any anastomosis in which at least one limb involved colonic tissue (i.e., ileocolic anastomoses involving small bowel and colon were classified as a colonic anastomosis). Similarly, rectal anastomoses were defined as an anastomosis whereby at least one limb included rectal tissue (i.e., colorectal anastomosis following proximal rectal resection). Studies were excluded if they were animal based, did not involve a colonic or rectal anastomosis, were editorials or case reports, did not look at anastomotic leak rates as a primary outcome, or involved an additional intervention in addition to NSAID analgesia in the treatment arm (i.e., NSAIDs plus steroids vs. placebo). Studies that included small bowel anastomoses were not included.

A broad search strategy was employed to ensure that any and all relevant articles were assessed. The following two search terms were used with all 3 databases: "anastomosis" and "NSAIDs." Given that the search term "NSAIDs" is synonymous with the term "non-steroidal anti-inflammatory" and the singular form—"NSAID," these three terms were grouped together using the "OR" function. As an example, our database search consisted of the following inquiry: "Anastomosis AND (NSAID OR NSAIDs OR non-steroidal anti-inflammatory)." Study eligibility was evaluated in an un-blinded standardized manner by two independent physicians/authors. Any disagreements between reviewers were resolved by consensus. Initial screening was performed by analysis of article titles/abstracts. Articles were then read in full to assess for final inclusion/exclusion into the systematic review and meta-analysis.

Risk of bias assessment

A risk of bias assessment was performed using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [6]. Studies were graded on risk of bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported units. A final overall risk of bias was then determined. Overall risk of bias was placed into one of five categories:

1: *Low risk of bias*—the study is comparable to a well-performed RCT.
2: *Medium risk of bias*—the study provides sound evidence for an RCT, but cannot be considered comparable to a well-performed RCT.
3: *Serious risk of bias*—the study has some important problems.
4: *Critical risk of bias*—the study is too problematic to provide any useful evidence and should not be included in any synthesis.
5: *No information* on which to base a judgment about risk.

Data analysis

Meta-analysis was performed by computing the odds ratio (OR) from the original data using the Cochran–Mantel–Haenszel method (with a 95% confidence interval). A P value of 0.05 was considered significant for all analyses. Synthesis and graphical representation of the meta-analysis was performed with the Review Manager (Rev-Man) 5.3 software, using a random-effects model. Inter-study heterogeneity was assessed using the I^2 statistic. Publication bias was assessed via a graphical representation of precision vs effect estimate (i.e., a funnel plot).

Given the hypothesis that there may be a drug-specific effect that NSAIDs have on the healing of colorectal

anastomoses, further sub-group analysis was performed to stratify patients based on the type of NSAID they received (selective vs. non-selective). Furthermore, we examined the drug-specific effects of ketorolac and diclofenac, non-selective NSAIDs.

Results

Study selection/characteristics

A database search and review of reference lists of relevant papers yielded a total of 432 articles. After adjusting for duplicates, we were left with a total of 373 non-duplicate articles (Fig. 1). These 373 articles were then screened and we were then left with 31 articles remaining for full-text review. Of these remaining articles, 24 were excluded because they did not meet our inclusion/exclusion criteria.

In total, 9835 participants were involved in the seven selected studies (Table 1). All studies were published in English with three originating from North America, and four from Europe. Three were single-centered studies and four were multi-centered. With respect to their study methodology, 6 of the selected studies were of a retrospective cohort design, while one was a nested, matched case–control study.

Risk of bias within studies

All studies were graded using the official ROBINS-I scoring guidelines [6]. Four studies were deemed Moderate Risk based on baseline differences in potential confounding variables between the control and intervention groups. Interestingly, in three of those four studies (Bakker et al. [7], Klein et al. [9], and Saleh et al. [12]) patients in the control group began with poorer baseline health, while in the end it was the NSAID group that was found to have a significantly higher leak rate. The three other studies were rated as Serious Risk because important confounding variables were not mentioned and taken account of in the analysis.

NSAID use and anastomotic leak rate

NSAIDs were associated with a significantly higher anastomotic leak rate in four of the seven studies, with an overall leak rate of 300/3555 (8.44%) compared to 302/6280 (4.81%) (Fig. 2). When synthesized using our pre-ordained parameters (M–H analysis, OR with random-effects model), the overall anastomotic leak rate was found to be significantly higher in the NSAID group [OR 1.58 (1.23, 2.03), $P=0.0003$]. Heterogeneity as defined by our I^2 statistics was classified as moderate (38%).

Of the 7 included studies, documentation of NSAID type was provided by 6 (the exception being Paulasir et al. [11]). All 6 studies included non-selective NSAIDs in their intervention group, while 1 (Gorrisen et al. [8]) included both

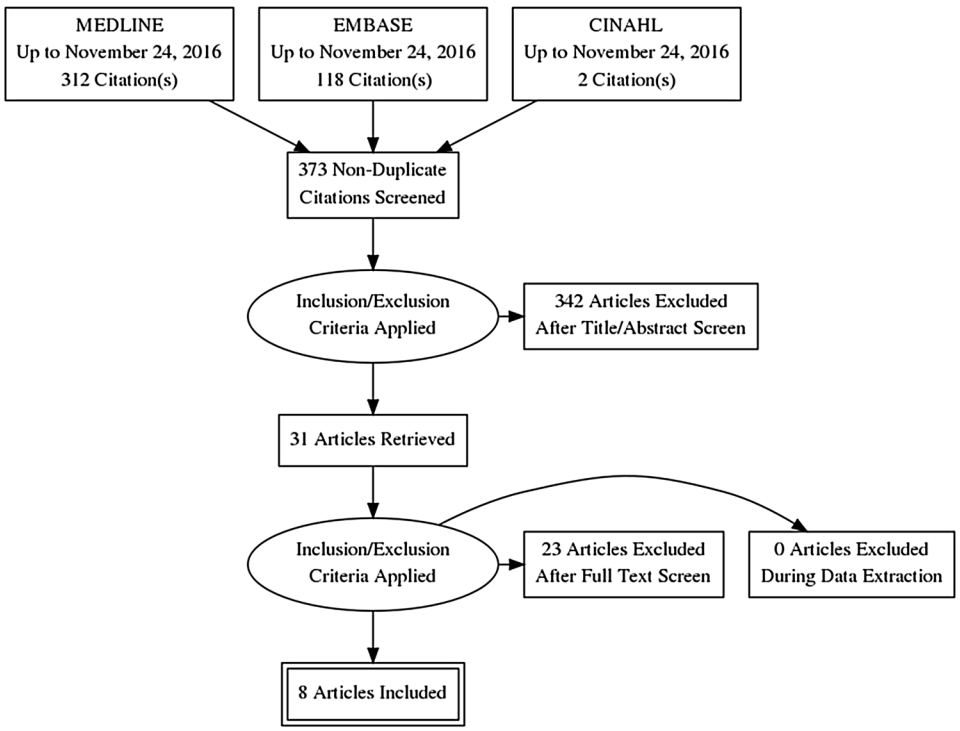

Fig. 1 PRISMA flowchart of included studies

Table 1 Characteristics of included studies

Study	Year/country	Risk of bias	Design	*N*	Intervention	Result (leak rate)
Bakker et al. [7]	2016, Netherlands	Moderate	Retrospective cohort	856	NSAID starting POD 2 until resumption of oral diet	Intervention: 9.2% Control: 5.3% ***P* < 0.05** **Odds ratio: 1.81 [1.03, 3.21]**
Gorrisen et al. [8]	2012, Netherlands	Moderate	Retrospective cohort	795	Any NSAID use within the first 5 days post-operatively	Intervention: 13.2% Control: 7.6% ***P* < 0.05** **Odds ratio: 1.85 [1.16, 2.95]**
Klein et al. [9]	2009, Denmark	Moderate	Retrospective cohort	75	Oral diclofenac (150 mg/day) starting POD #1	Intervention: 21.2% Control: 2.4% ***P* < 0.05** **Odds ratio: 11.04 [1.28, 94.97]**
Klein et al. [10]	2012, Denmark	Serious	Retrospective cohort	2756	NSAID taken post-operatively within the first 7 days	Intervention: 9.4% Control: 5.1% ***P* < 0.05** **Odds ratio: 1.93 [1.42, 2.63]**
Paulasir et al. [11]	2015, United States	Serious	Retrospective cohort	4360	NSAID (not specified) taken on post-op day 1	Intervention: 2.9% Control: 2.6% ***P* > 0.05** **Odds ratio: 1.11 [0.75, 1.65]**
Saleh et al. [12]	2015, Canada	Moderate	Retrospective cohort	731	Ketorolac administered within 5 days of surgery	Intervention: 3.4% Control: 3.2% ***P* > 0.05** **Odds ratio: 1.06 [0.47, 2.39]**
Subendran et al. [13]	2014, Canada	Serious	Nested matched case–control study	262	Any post-operative NSAID use within the first 5 days post-surgery	Cases: 52.7% exposed to NSAIDs Control: 44.3% exposed to NSAIDs ***P* > 0.05** **Odds ratio: 1.40 [0.86, 2.28]**

P values and odds ratio are bolded

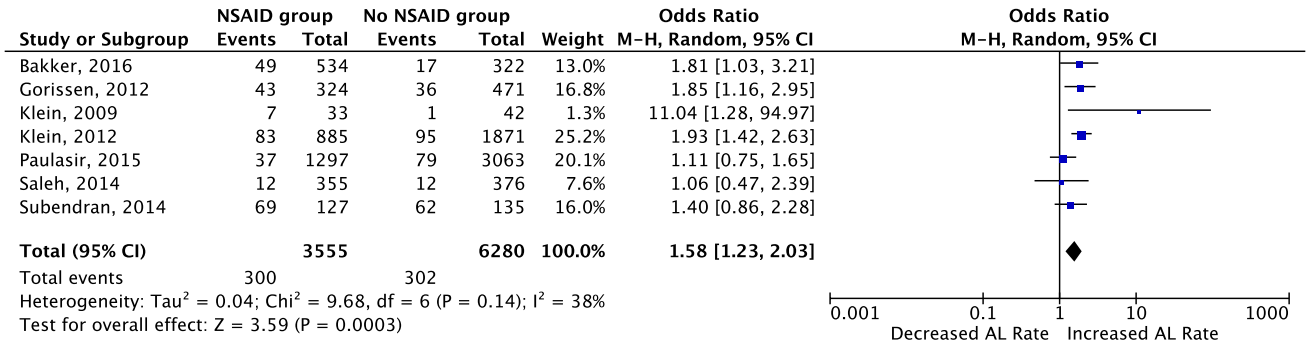

Fig. 2 NSAIDs post colorectal surgery and anastomotic leak rate

selective and non-selective NSAIDs. When looked at in isolation, Gorrisen et al. [8] found an increased anastomotic leak rate with non-selective NSAIDs compared to selective NSAIDs [OR 2.13 (1.24, 3.65); $P=0.006$]. Selective COX-2 inhibitors were not associated with an increased risk of anastomotic leak when compared to controls [OR 1.17 (0.50, 2.74), $P=0.7$]. Sub-group analysis was then performed on the 6 studies comparing non-selective NSAID use to controls. Of this patient group, a significantly elevated anastomotic leak rate was found following non-selective NSAID use in four of the six studies (Fig. 3). The overall leak rate in the non-selective NSAID group was found to be 248/2310 (11.64%), compared to 240/3499 (6.86%) in the control group (OR 1.77 [1.43, 2.20], $P<0.00001$). Heterogeneity between groups was low ($I^2=8\%$).

Diclofenac was the most commonly used medication across studies. The second most commonly used medication was ketorolac. Of the four studies in which diclofenac was used, three provided isolated anastomotic leak rates for patients taking diclofenac (Fig. 4). In all three studies, diclofenac was associated with a statistically significant increased anastomotic leak rate [OR 2.74 (1.94, 3.88), $P<0.00001$]. The overall leak rate in patients taking diclofenac across these studies was 81/631 (12.84%) compared to 113/2235 (5.06%) in controls. The one study that did not include specific numbers for diclofenac (Gorrisen et al. [8]) did however indicate that diclofenac was the most commonly used non-selective NSAID among their study population, and non-selective NSAIDs as a class were found to be associated with a significantly increased post-operative leak rate [14.5% leak rate; OR 2.13 (1.24, 3.65); $P=0.006$]. Ketorolac-specific leak rates were documented in two studies (Fig. 5), with neither finding ketorolac to be associated with a significant change in the post-operative

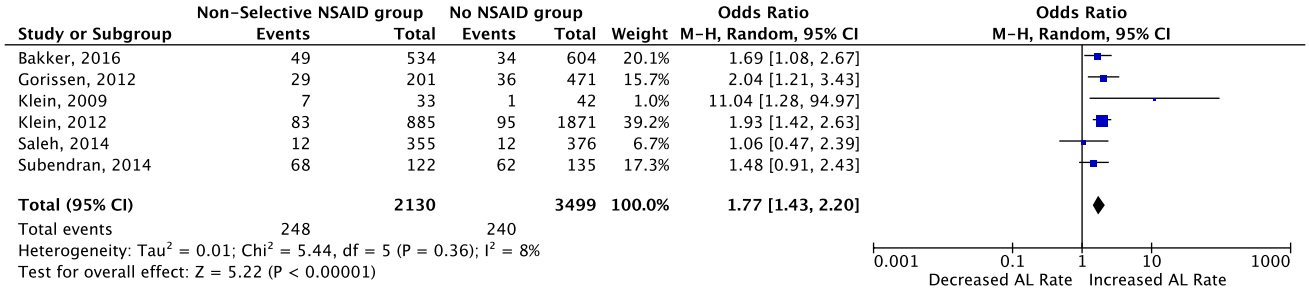

Fig. 3 Non-selective NSAIDs post colorectal surgery and anastomotic leak rate

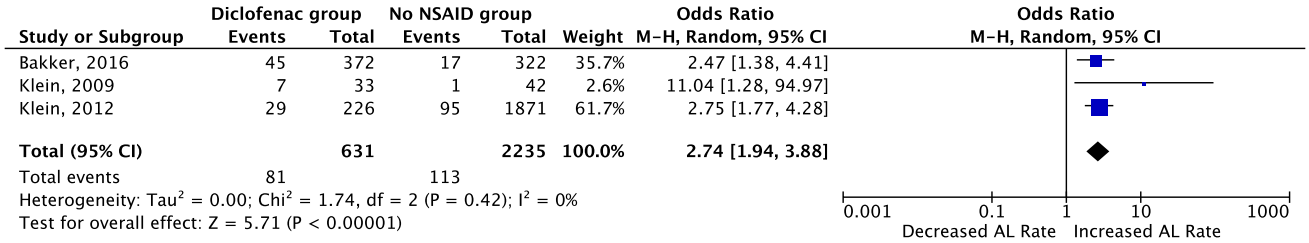

Fig. 4 Diclofenac post colorectal surgery and anastomotic leak rate

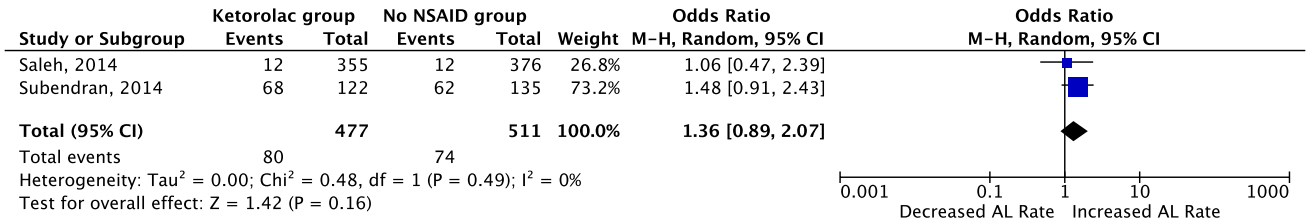

Fig. 5 Ketorolac post colorectal surgery and anastomotic leak rate

leak rate [OR 1.36 (0.89, 2.06), $P = 0.16$]. Heterogeneity was absent ($I^2 = 0\%$) in both the diclofenac and ketorolac sub-group analyses.

Risk of bias across studies

Moderate heterogeneity was found in the overall NSAID versus control group analysis ($I^2 = 38\%$). This heterogeneity was further assessed using a funnel plot (Fig. 6). Given the relatively low number of studies accounted for in this analysis, the general shape of our funnel plot remained fairly symmetrical.

Discussion

Overall, the evidence in this study indicates that NSAIDs are associated with an increased risk of anastomotic leakage following colorectal surgery. With further sub-group analysis however, this effect was not found to be consistent across all NSAIDs, with medications within the same class demonstrating conflicting risk profiles.

This meta-analysis is the first to look at isolated colonic and rectal anastomotic leak rate associated with NSAID use. As demonstrated in several animal studies, the effect that NSAIDs have on anastomotic healing varies based on the location within the gastrointestinal tract [2–4]. Small bowel anastomoses have been shown to be affected by postoperative NSAID use to a greater extent than distal colonic anastomoses. As to why NSAIDs impair anastomotic healing and why different segments of the gastrointestinal tract are affected differently, the pathophysiological mechanism still remains up for debate. Histological factors associated with the healing process certainly seem to be affected following NSAID use. These medications appear to decrease fibroblast infiltration, decrease granulation tissue formation, decrease re-epithelialization, and increase microscopic necrosis [14].

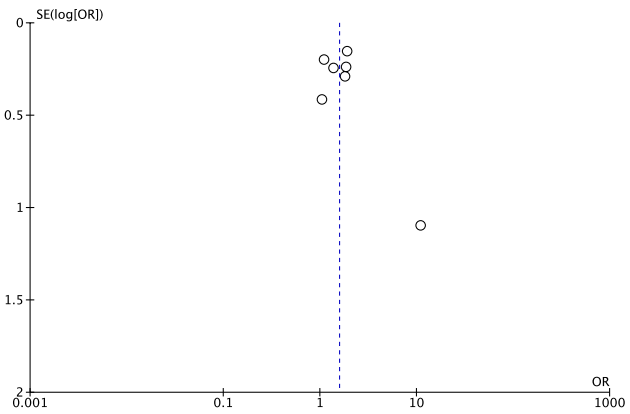

Fig. 6 Funnel plot (NSAID use vs. No NSAID use)

Taken all together, this can certainly lead to impaired wound healing and tissue regeneration. Furthermore, NSAIDs appear to have an effect on collagen deposition and cross-linking, although this effect is not yet clear [15].

Although it is unclear what the overall effect is on intestinal collagen structure/function, studies have shown that COX-2 expression is greatest in the ileum and that this expression decreases after NSAID use [4, 16]. This has led to theories that the increased leak rate associated with NSAIDs may in fact be a COX-2-specific inhibitory effect. When tested clinically however, this has not been proven to be the case. Bhangu et al. [17] performed sub-group analysis in their meta-analysis to stratify selective vs non-selective NSAIDs. They found that only the non-selective NSAID group was associated with an increased anastomotic leak rate post-operatively, while the selective COX-2 inhibitor group did not demonstrate any significant change in leak rate. A more recent meta-analysis by Pang et al. [1] demonstrated similar results, with significantly increased leak rates with non-selective NSAIDs, but not with selective NSAID use. These findings are in line with our own results, in which we found that when patient data were analyzed based on class of NSAID received, only the non-selective NSAID group demonstrated an increased risk of anastomotic leakage.

In our study, we found the association between postoperative leak rate and medication use inconsistent when two non-selective NSAIDs, ketorolac and diclofenac, were compared to controls. While both are categorized within the same class of medication, only diclofenac was associated with an increased leak rate. This would indicate that the question regarding NSAID safety is much more complicated than once believed, and there may be drug-specific effects.

There are limitations that must be taken into account when interpreting these data. In comparison to previous meta-analyses performed on this topic, we narrowed our focus to only colonic and rectal anastomoses, and only on studies that had been designed and powered with anastomotic leak rate as their primary outcome. Because we narrowed down our research question, the number of studies present within this meta-analysis is relatively low. This is especially important when considering the sub-group analysis that was performed. Only one study included selective NSAID medications in their published data, and when performing our medication-specific analysis only 3 studies were included in the diclofenac group, and two in the ketorolac group. Given the limitations of these sub-group analyses, further research is needed to truly clarify these class and drug-specific risk profiles. Another limitation of this review is the reliance on non-randomized data. Within this paper, nearly half of the studies examined posed potential bias secondary to confounding factors that were unaccounted for by the study authors. Of the remaining studies that measured these confounding factors, they all contained baseline

differences between intervention and control groups that made final size effect interpretations difficult. As with any study reliant on observational data, it is difficult to differentiate association with causation. While some studies did show an increased leak rate with NSAID usage, there also remains the possibility that those patients with a post-operative leak required greater pain control in the immediate post-operative setting, necessitating the addition of an NSAID to their management plan. Finally, while this study has taken a first step towards stratifying the impact that NSAIDs have based on anastomotic location, our study grouped all colonic and rectal anastomoses as one category. We did not analyze patients based on proximal or distal colonic anastomoses, nor did we stratify them based on colonic versus rectal anastomoses. This was in large part due to limited data available in this regard.

In conclusion, our findings indicate that the use of NSAIDs in the immediate post-operative period (within 7 days) in these patients may increase the risk of a post-operative anastomotic leak. Going forward significant efforts will need to be made to confidently identify which individual NSAIDs increase the risk of anastomotic leakage and which do not. Where no conclusive recommendation currently exists regarding post-operative NSAID use, we advise great caution when prescribing NSAIDs following colonic or rectal anastomotic creation.

Compliance with ethical standards

Disclosures Drs. Aryan Modasi, David Pace, Marshall Godwin, Chris Smith, and Bryan Curtis have no conflicts of interest or financial ties to disclose.

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