Postoperative non-steroidal anti-inflammatory drugs and anastomotic leakage after gastrointestinal anastomoses: Systematic review and meta-analysis

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Abstract
Aim: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to control postoperative pain; however, their postoperative use has been associated with anastomotic leakage after gastrointestinal surgery. This systematic review and meta-analysis aimed to determine the correlation between the use of NSAIDs and anastomotic leakage.

Methods: We conducted a comprehensive electronic literature search up to August 2018 to identify studies comparing anastomotic leakage in patients with and without postoperative NSAID use following gastrointestinal surgery. We then carried out a meta-analysis using random-effects models to calculate odds ratios (OR) with 95% confidence intervals (CI).

Results: Twenty-four studies were included in this meta-analysis, including a total of 31,877 patients. Meta-analysis showed a significant association between NSAID use and anastomotic leakage (OR 1.73; 95% CI = 1.31-2.29, \( P < 0.0001 \)). Subgroup analyses showed that non-selective NSAIDs, but not selective cyclooxygenase-2 inhibitors, were significantly associated with anastomotic leakage. However there was no significant subgroup difference between selective and non-selective NSAIDs.

Conclusion: Results of this meta-analysis indicate that postoperative NSAID use is associated with anastomotic leakage following gastrointestinal surgeries. Caution is warranted when using NSAIDs for postoperative analgesic control in patients with gastrointestinal anastomoses.

KEYWORDS
anastomotic leakage, cyclooxygenase inhibitor, gastrointestinal surgery, meta-analysis, non-steroidal anti-inflammatory drugs
1 | INTRODUCTION

Anastomotic leakage has long been a concern among gastrointestinal surgeons. Its occurrence not only causes postoperative morbidity and mortality, but also lengthens hospital stay and increases hospital costs.\(^1\)\(^,\)\(^2\) Importantly, anastomotic leakage worsens oncological outcomes in patients with resectable and curable malignancies, leading to poorer disease-free survival, overall survival, and functional outcome.\(^3\)\(^,\)\(^4\)

Multiple factors contribute to anastomotic leakage, and its incidence varies depending on the location of the anastomosis. Esophageal anastomoses have the highest incidence of leakage, and gastric anastomoses the lowest incidence, whereas the incidence of colorectal anastomotic leakage differs among publications and anastomosis sites, ranging from 1% to 20\%.\(^5\)

The early recovery after surgery protocol has been proposed to reduce postoperative stress. The protocol aims to promote postoperative recovery, reduce hospital stay and, most importantly, reduce postoperative complications, especially cardiovascular and pulmonary complications.\(^6\) Non-steroidal anti-inflammatory drugs (NSAIDs) play a major part in this protocol as a means of postoperative pain control. However, application of the early recovery after surgery protocol has been associated with an increased incidence of anastomotic leakage,\(^7\) and it has been suggested that NSAIDs may be a causative factor in impaired anastomotic healing.

Many potential mechanisms have been proposed to explain how postoperative NSAID use may cause anastomotic leakage. NSAIDs decreased protective prostaglandins, and inhibited mucosal cyclooxygenase (COX)-1, intestinal epithelial cell migration, and mucosal restitution in animal models\(^8\) which, in turn, reduced anastomotic tensile strength and collagen deposition causing delayed anastomotic healing.\(^9\)\(^-\)\(^11\)

Previous reviews have examined the correlation between postoperative NSAID use and anastomotic leakage, but most have considered colorectal anastomoses only.\(^7\)\(^,\)\(^12\) However, we suggest that the mechanisms shown in animal models may be applicable to all gastrointestinal anastomoses. Furthermore, it is also possible that selective COX-2 inhibitors may be safer than non-selective NSAIDs in terms of preventing anastomotic leakage based on the above-mentioned mechanism.

The primary objective of this systematic review and meta-analysis was to determine the effect of postoperative NSAID use on gastrointestinal anastomotic leakage, regardless of the site of anastomosis. The secondary objective was to compare the anastomotic leakage risk between non-selective NSAIDs and selective COX-2 inhibitors.

2 | METHODS

2.1 | Search strategy

We conducted a literature search of the Medline, PubMed, Cochrane Library, clinicaltrials.gov, and Web of Science databases up to August 2018. The search was limited to English language and human studies. The search terms used were “Anastomosis or anastomotic leakage” AND “NSAIDs” [Mesh term]. Additional articles were retrieved by manually searching the reference lists of the included studies and other reviews.

2.2 | Selection criteria

Studies were included if they met the following criteria: (i) study with anastomosis of the gastrointestinal tract; (ii) study compared postoperative NSAID use with non-use; and (iii) investigations reported anastomotic leakage. Case reports or reports with incomplete data were excluded.

2.3 | Data extraction

The studies were independently and critically assessed by two authors using a standard protocol and discrepancies were resolved by consensus. Extracted data included study design, number of institutions, definition of anastomotic leakage, operative diagnosis, location of anastomosis, urgency of surgery, type of NSAIDs, sample size, and numbers of anastomotic leakage per group.

2.4 | Quality assessment

Qualities of the included studies were assessed using the Jadad score\(^13\) and the Newcastle-Ottawa scale (NOS)\(^14\) for randomized controlled trials (RCT) and observational studies, respectively. Studies were considered to be high quality if they had a Jadad score ≥3 or NOS ≥7.

2.5 | Data synthesis and meta-analysis

Meta-analysis was done by computing the OR from the original data using the Cochrane-Mantel-Haenszel method, with 95% CI. \(P < .05\) was considered significant in all analyses. Data analysis was carried out using Review Manager (RevMan) v5.3 software (Cochrane Collaboration) and a random-effect model was used for graphical presentation. Statistical heterogeneity was quantified using \(I^2\) statistics and Cochrane Q tests. \(I^2\) values >50% indicated heterogeneity.\(^15\) In the presence of heterogeneity, we conducted subgroup and meta-regression analyses to determine if the inter-study variation could be explained by certain co-variates, including type of study, NSAID class, NSAID administration, urgency of surgery, location of anastomosis, and operative diagnosis. Sensitivity analyses were done to assess the impact of individual potential confounding variables. Publication bias was assessed visually by funnel plot, and asymmetry was assessed formally by rank correlation test (Begg’s test).\(^16\) Publication bias was analyzed using WINPEPI software.\(^17\)
3 | RESULTS

3.1 | Study selection

The initial systematic search identified 430 studies and an additional search for reviews identified a further five studies. After adjusting for duplicates and critical assessment, a total of six RCT and 18 observational studies were included in the meta-analysis. The PRISMA flow diagram of the detailed literature search and selection process is shown in Figure 1. Of 27 full-text article reviews, three were excluded from the quantitative analysis because we could not extract the original data from two, and the other study compared multimodal interventions in which NSAIDs were also distributed to the control group.

3.2 | Characteristics of included studies

Six RCT and 18 observational studies were included in this meta-analysis. Sample sizes varied from 40 to 220 for the RCT and from 75 to 13 082 for the observational studies. Most studies included the anastomotic location as colorectal anastomoses (four RCT, 13 observational studies), a diagnosis of malignancy (three RCT, six observational studies), and surgery carried out as an elective procedure.

3.3 | Association of NSAIDs with anastomotic leakage

Overall anastomotic leakage rate in this study was 6.0% (1922/31 877). Patients who received NSAIDs postoperatively had a higher leakage rate (7.5%; 777/10 318) than those without NSAIDs (5.3%; 1145/21 558). Meta-analysis showed a significantly higher rate of anastomotic leakage after postoperative NSAID use (pooled OR 1.73, 95% CI 1.31-2.29, \( P < .001 \)), but with evidence of heterogeneity across the included studies (\( I^2 = 80% \), Cochrane Q test \( P < .00001 \)) (Figure 2). The funnel plot appeared relatively symmetrical, suggesting no publication bias, as confirmed by Begg's test (\( P = .444 \)) (Figure 3). There was some heterogeneity in the included studies (\( I^2 = 80% \)).

**Figure 1** PRISMA flow shows study selection process. NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial
**Table 1** Characteristics of included studies to determine the correlation between the use of NSAIDs and anastomotic leakage

| Author, year, Country, Institute | Study design | Recruitment period | Definition of AL | Diagnosis | Location of anastomosis | Urgency of surgery | N | NSAIDs administration | Quality assessment |
|----------------------------------|--------------|--------------------|------------------|-----------|------------------------|-------------------|----|-----------------------|-------------------|
| Chen, 2005 Taiwan, single        | RCT, Double-blind | 2003 | NR               | Mixed     | Colorectal             | Elective         | 74 | PCA: ketolorac 1.2 g/mL + morphine 1 mg/mL 2 mL bolus and 10 min lockout until pain score <3 | 5 |
| Schlachta, 2007 Canada, single   | RCT, Double-blind | 2002-2005 | NR   | Mixed (Cancer 50%) | Colorectal | Elective | 44 | Ketolorac 30 mg IV every 6 h for 2 d after operation | 3 |
| Sim, 2007 Singapore, single      | RCT, Double-blind | 2002-2004 | NR | Mixed (Cancer 94.9%) | Mixed (Colorectal 94.9%) | Elective | 79 | Valdecoxib 40 mg orally once pre-operation and once daily for 5 d after operation | 2 |
| Xu, 2008 China, single           | RCT, Double-blind | 2006-2007 | NR | Cancer | Colorectal | Elective | 40 | Flurbiprofen 1 mg/kg IV 30 min before and 6 h after skin incision | 5 |
| Chen, 2009 Taiwan, single        | RCT, Double-blind | 2006-2007 | NR | Mixed | Colorectal | Elective | 102 | PCA: ketolorac 1.2 g/mL + morphine 1 mg/mL 2 mL bolus and 10 min lockout until pain score <3 | 4 |
| Wattchow, 2009 Australia, 2 institutes | RCT, Double-blind | 2003-2006 | NR | Mixed | Mixed (Colorectal 99%, Small intestine 1%) | Elective | 220 | Celecoxib 100 mg or Diclofenac 50 mg orally twice daily for 7 d or until discharge | 4 |
| Rosenberg, 2007 Denmark, Single  | Retrospective cohort | 2004-2006 | NR | Cancer | Colorectal | Elective | 310 | Diclofenac 75 mg twice daily, Not reported duration | 5 |
| Klein, 2009 Denmark, Single      | Retrospective case-control | 2004-2007 | Leak requiring reoperation | Mixed (Cancer 96%) | Colorectal | Elective | 75 | Diclofenac 150 mg/d, Not reported duration | 7 |
| Holte, 2009 Denmark, Single      | Retrospective cohort | 1997-2006 | Radiologic finding or intra-operative finding or clinical finding | NR | Colon | Elective | 502 | Ibuprofen 600 mg every 8 h or Celecoxib 200 mg every 12 h at POD 2-8 | 7 |
| Gorissen, 2012 Netherlands, 2 institutes | Retrospective cohort | 2008-2010 | Radiologic finding or intra-operative finding or clinical finding | Mixed (Cancer 72%) | Colorectal | Elective | 795 | NSAIDs use within POD 5 | 8 |
| Klein, 2012 Denmark, 6 institutes | Retrospective cohort | 2006-2009 | Leak requiring reoperation | Cancer | Colorectal | Elective | 2752 | NSAIDs use at least 2 d within POD 7 | 9 |
| Zittel, 2013 Sweden, single      | Retrospective cohort | 2008-2009 | NR | Mixed (Cancer 57.6%) | Colorectal | Elective | 205 | Etoricoxib 120 mg once daily, Not reported duration | 8 |
| Subendran, 2014 Canada, single   | Retrospective case-control | 2001-2012 | Radiologic finding or intra-operative finding | Mixed (IBD 65.6%, cancer 34.4%) | Colorectal | Elective | 262 | NSAIDs use within POD 5 | 8 |

(Continues)
| Author, year | Study design | Country, Institute | Recruitment period | Definition of AL | Diagnosis | Location of anastomosis | Urgency of surgery | N | NSAIDs administration | Quality assessment |
|-------------|-------------|--------------------|--------------------|----------------|-----------|-------------------------|------------------|----|----------------------|------------------|
| Saleh, 2014 | Retrospective cohort | Canada, single | 2004-2011 | Document at reoperation or Radiological finding | Mixed (Cancer 65.5%) | Colorectal | Elective | 731 | NSAIDs use within POD 5 | 8 |
| STARSurg UK, 2014 | Prospective cohort | UK, multi-institutes | 2013 | Radiologic finding or intra-operative finding or clinical finding | Mixed (Cancer 62.1%) | Mixed (Colorectal 75.9%) | Mixed (Elective 72.1%) | 1503 | NSAIDs use within POD 2 | 8 |
| Paulsir, 2015 | Retrospective cohort | USA, multi-institutes | 2012-2014 | Leaks requiring antibiotic or intervention or reoperation | NR | Colorectal | Mixed (Elective 78.6%) | 4360 | NSAIDs use within POD 1 | 9 |
| Hakkarainen, 2015 | Retrospective cohort | USA, 47 institutes | 2006-2010 | Leak requiring percutaneous drainage or reoperation | NR | Bariatic, Colorectal | Mixed (Elective 87.6%) | 13082 | NSAIDs use within POD 1 | 9 |
| Raju, 2015 | Retrospective cohort | Australia, 2 institutes | 2008-2014 | Leak requiring percutaneous drainage or reoperation | Mixed (Cancer 70.6%) | Colorectal | Elective | 267 | Celecoxib 100 mg twice daily start at 2 h before operation to POD 7 | 6 |
| Bakker, 2016 | Retrospective cohort | Netherlands, single | 2006-2013 | Leak requiring percutaneous drainage or reoperation | Cancer | Colorectal | Elective | 856 | NSAIDs use at least 2 d until discharge | 8 |
| Rutegard, 2016 | Retrospective cohort | Sweden, multi-institutes | 2007-2012 | Leak requiring percutaneous drainage or reoperation | Cancer | Rectum | Elective | 2605 | NSAIDs use within POD 10 | 8 |
| Rushfeldt, 2016 | Retrospective cohort with propensity score analysis | Norway, Single | 2007-2009 | NR | Mixed (Cancer 52.8%) | Mixed (Colorectal 73.4%) | Mixed (Elective 88%) | 428 | NSAIDs use within POD 5 | 8 |
| Haddad, 2017 | Retrospective cohort | USA, multi-institutes | 2013-2015 | NR | Trauma | Mixed (Small intestine 93.4%, Colorectal 6.6%) | Emergency | 533 | NSAIDs use 7 d prior to operation up to POD 14 | 7 |
| Fjederholt, 2018 | Retrospective cohort | Denmark, 2 institutes | 2003-2012 | Radiologic finding or endoscopic finding | Cancer | Esophagojejunostomy | Elective | 556 | NSAIDs use within POD 7 | 9 |
| Hultberg, 2017 | Retrospective cohort | Sweden, 15 institutes | 2007-2013 | Radiologic finding or intra-operative finding or clinical finding or Endoscopic finding | Cancer | Rectal | Elective | 1495 | NSAIDs use at least 2 d within POD 7 | 9 |

Abbreviations: AL, anastomotic leakage; IBD, inflammatory bowel disease; NR, not reported; NSAIDs, non-steroidal anti-inflammatory drugs; PCA, patient controlled analgesia; POD, postoperative day; RCT, randomised controlled trial.

Quality assessment for RCT and observational studies using Jadad score and Newcastle-Ottawa scale (NOS) for randomised controlled trials (RCTs) and observational studies, respectively.
FIGURE 2 Forrest plot of meta-analysis between randomized controlled trials (RCT) and observational studies. NSAIDs, non-steroidal anti-inflammatory drugs

FIGURE 3 Funnel plot with pseudo 95% CI (random-effect model). OR, odds ratio; SE, study effect
discrepancy in the results between the study types: RCT showed a non-significant difference in anastomotic leakage between the NSAID and placebo groups (pooled OR 1.91, 95%CI 0.69-5.35, P = .67) without heterogeneity ($I^2 = 0\%$, Cochrane Q test $P = .67$), whereas observational studies found a significantly higher leakage rate after postoperative NSAID use (OR 1.72, 95%CI 1.28-2.31, $P < .001$) with evidence of heterogeneity ($I^2 = 84\%$, Cochrane Q test $P < .001$) (Figure 2).

### 3.4 Protocol-based versus non-systematic NSAIDs use

To investigate the effect of NSAID dose on anastomotic leakage, we categorized NSAID use in the included studies into protocol-based and non-systematic use. In the protocol-based group, NSAIDs were given according to the institutional protocol (11 studies; n = 1918), whereas in the non-systematic group, NSAIDs were given at any given time during the postoperative period (13 studies; n = 30 140). Details of NSAID use are shown in Table 1. The protocol-based group had a significantly higher anastomotic leakage rate compared with non-users (pooled OR 4.67, 95% CI 2.84-7.67, $P < .001$) without evidence of heterogeneity ($I^2 = 5\%$, Cochrane Q test $P = .40$), whereas the non-systematic group also had a significantly increased risk for anastomotic leakage compared with non-users (pooled OR 1.38, 95% CI 1.06-1.81, $P = .02$), but with evidence of heterogeneity ($I^2 = 82\%$, Cochrane Q test $P < .001$). However, there was a statistically significant subgroup difference between the protocol-based group and the non-systematic group ($P < .001$) (Figure 4).

### 3.5 Non-selective NSAIDs versus selective COX-2 inhibitors

Among all the included studies, we extracted information on non-selective NSAID use from 15 (n = 4110) and on selective COX-2 inhibitor use from eight (n = 1063) studies. Subgroup analysis showed that patients who received postoperative non-selective NSAIDs had a significantly higher rate of anastomotic leakage than patients who did not receive NSAIDs (pooled OR 1.80, 95% CI 1.12-2.91,

| Study or Subgroup | NSAIDs Events | Control Events | Total Events | Weight | M-H, Random, 95% CI |
|-------------------|---------------|----------------|--------------|--------|---------------------|
| **1.2.1 Protocol-based** | | | | | |
| Chen et al, 2005  | 1 39 | 1 35 | 0.9% | 0.89 [0.05, 14.86] |
| Chen et al, 2009  | 3 52 | 1 50 | 1.2% | 3.00 [0.30, 29.85] |
| Holte et al, 2009 | 18 119 | 10 383 | 4.7% | 6.65 [2.98, 14.85] |
| Klein et al, 2009 | 7 33 | 1 42 | 1.4% | 11.04 [1.28, 94.97] |
| Raju et al, 2015  | 2 221 | 0 46 | 0.7% | 1.06 [0.05, 22.43] |
| Rosenberg et al, 2007 | 16 78 | 7 232 | 4.1% | 8.29 [3.27, 21.06] |
| Schlachter et al, 2007 | 5 22 | 1 22 | 1.3% | 6.18 [0.66, 58.03] |
| Sim et al, 2007    | 1 40 | 0 39 | 0.7% | 3.00 [0.12, 75.90] |
| Wattchow et al, 2009 | 4 153 | 2 67 | 1.9% | 0.87 [0.16, 4.88] |
| Xu et al, 2008     | 0 20 | 0 20 | Not estimable |
| Zittel et al, 2013 | 8 102 | 3 104 | 2.7% | 2.90 [0.75, 11.24] |
| **Subtotal (95% CI)** | 878 | 1040 | 19.6% | 4.67 [2.84, 7.67] |
| **Total events** | 65 | 26 | | | |
| **Heterogeneity:** Tau² = 0.03; Chi² = 9.46, df = 9 ($P = .40$); $I^2 = 5\%$ |
| Test for overall effect: Z = 6.07 ($P < .00001$) |

| Study or Subgroup | NSAIDs Events | Control Events | Total Events | Weight | M-H, Random, 95% CI |
|-------------------|---------------|----------------|--------------|--------|---------------------|
| **1.2.2 Unsystematic NSAID use** | | | | | |
| Bakker et al, 2016 | 49 534 | 17 322 | 5.8% | 1.81 [1.03, 3.21] |
| Fiedereholt et al, 2017 | 20 98 | 22 458 | 5.4% | 5.08 [2.65, 9.75] |
| Gorissen et al, 2012 | 43 324 | 36 471 | 6.3% | 1.85 [1.16, 2.95] |
| Haddad et al, 2017 | 34 244 | 31 289 | 6.0% | 1.35 [0.80, 2.27] |
| Hakkarainen et al, 2015 | 151 3158 | 417 9924 | 7.4% | 1.14 [0.95, 1.39] |
| Huitberg et al, 2017 | 47 411 | 156 1084 | 6.8% | 0.77 [0.54, 1.09] |
| Klein et al, 2012 | 83 881 | 95 1871 | 7.0% | 1.94 [1.43, 2.64] |
| Pauls et al, 2015 | 37 1297 | 79 3063 | 6.6% | 1.11 [0.75, 1.65] |
| Rushfeldt et al, 2016 | 52 311 | 15 117 | 5.6% | 1.37 [0.74, 2.53] |
| Rutgert et al, 2016 | 102 1458 | 124 1147 | 7.1% | 0.62 [0.47, 0.82] |
| Saleh et al, 2014 | 12 355 | 12 376 | 4.6% | 1.06 [0.47, 2.39] |
| STAARSurg UK, 2014 | 13 247 | 53 1261 | 5.5% | 1.29 [0.69, 2.41] |
| Subendran et al, 2014 | 69 127 | 62 113 | 6.2% | 1.40 [0.86, 2.28] |
| **Subtotal (95% CI)** | 9440 | 20518 | 80.4% | 1.34 [1.03, 1.75] |
| **Total events** | 712 | 1119 | | | |
| **Heterogeneity:** Tau² = 0.17; Chi² = 61.48, df = 12 ($P < .00001$); $I^2 = 81\%$ |
| Test for overall effect: Z = 2.20 ($P = .03$) |

**FIGURE 4** Forrest plot of meta-analysis between protocol-based non-steroidal anti-inflammatory drugs (NSAIDs) use and non-systematic NSAIDs use
with evidence of heterogeneity ($I^2 = 85\%$, Cochrane Q test $P < .00001$). In contrast, the anastomotic leakage rate in patients taking selective COX-2 inhibitors was not significantly higher than in those not taking NSAIDs (pooled OR = 1.67, 95% CI 0.90-3.13, $P = .11$), with evidence of heterogeneity ($I^2 = 67\%$, Cochrane Q test $P = .004$). However, comparison between users of non-selective and selective NSAIDs showed no significant subgroup difference ($P = .85$) (Figure 5).

### 3.6 Colorectal anastomoses versus other gastrointestinal anastomoses

We carried out subgroup analyses between studies restricted to colorectal anastomoses (17 studies; n = 15 475) and studies with anastomoses not limited to colorectal (seven studies; n = 16 538). Studies with colorectal anastomoses had significantly increased anastomotic leakage rates when perioperative NSAIDs were used (pooled OR 1.80, 95% CI 1.22-2.66, $P = .003$), with evidence of heterogeneity ($I^2 = 83\%$, Cochrane Q test $P < .00001$). Studies of anastomoses of all sites also showed significantly higher rates of anastomotic leakage (pooled OR 1.61, 95% CI 1.25-2.66, $P = .02$), with evidence of heterogeneity ($I^2 = 72\%$, Cochrane Q test $P = .002$). There were no subgroup differences between the two groups of studies ($P = .85$) (Figure S1).

### 3.7 Meta-regression and sensitivity analyses

Meta-regression analysis stratified by location of anastomoses showed pooled OR for anastomatic leakage of 1.80 (95% CI 1.22-2.66, $I^2 = 83\%$) for colorectal anastomoses and 1.70 (95% CI 1.09-2.66, $I^2 = 72\%$) for studies that were not limited to colorectal anastomoses. Meta-regression analysis showed no significant difference between various anastomotic sites ($P = .85$). Furthermore, separate stratified and meta-regression analyses showed no significant differences in the OR of anastomotic leakage rates after postoperative NSAID use in relation to the type of study, NSAID class, urgency of surgery, or operative diagnosis (Table 2).

| Study or Subgroup | NSAIDs Events | NSAIDs Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------------|--------------|----------------|--------------|--------|--------------------------------|--------------------------------|
| 1.3.1 Non-selective | Bakker et al, 2016 | 49 | 534 | 17 | 322 | 6.5% | 1.81 [1.03, 3.21] |  |
| | Chen et al, 2005 | 1 | 39 | 1 | 35 | 1.4% | 0.89 [0.05, 14.86] |  |
| | Chen et al, 2009 | 3 | 52 | 1 | 50 | 1.9% | 3.00 [0.30, 29.85] |  |
| | Fjederholt et al, 2017 | 13 | 66 | 22 | 458 | 5.8% | 4.86 [2.31, 10.21] |  |
| | Gorissen et al, 2012 | 29 | 201 | 36 | 471 | 6.6% | 2.04 [1.21, 3.43] |  |
| | Hultberg et al, 2017 | 36 | 344 | 156 | 1084 | 7.1% | 0.70 [0.47, 1.02] |  |
| | Klein et al, 2009 | 7 | 33 | 1 | 42 | 2.1% | 11.04 [1.28, 94.97] |  |
| | Klein et al, 2012 | 83 | 881 | 95 | 1871 | 7.3% | 1.94 [1.43, 2.64] |  |
| | Rosenberg et al, 2007 | 16 | 78 | 7 | 232 | 5.1% | 8.29 [3.27, 21.06] |  |
| | Rusfeldt et al, 2016 | 52 | 311 | 15 | 117 | 6.3% | 1.37 [0.74, 2.53] |  |
| | Rutegard et al, 2016 | 66 | 1095 | 124 | 1147 | 7.2% | 0.53 [0.39, 0.72] |  |
| | Sadeh et al, 2017 | 12 | 355 | 12 | 376 | 5.6% | 1.06 [0.47, 2.39] |  |
| | Schlachte et al, 2007 | 5 | 22 | 1 | 22 | 2.0% | 6.18 [0.66, 58.03] |  |
| | Watchow et al, 2009 | 2 | 79 | 2 | 67 | 2.4% | 0.84 [0.12, 6.16] |  |
| | Xu et al, 2008 | 20 | 20 | 0 | 20 |  | Not estimable |  |
| Total (95% CI) | 4110 | 6314 | 67.3% | 1.80 [1.12, 2.91] |  |

**FIGURE 5** Forrest plot of meta-analysis between non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 NSAIDs

**TABLE 2**

- **Heterogeneity:** $I^2 = 0.54$; $Chi^2 = 87.04$, df = 13 ($P < .00001$); $I^2 = 85\%$
- **Test for overall effect:** $Z = 2.42$ ($P = .02$)

**1.3.2 Selective COX-2**

| Study or Subgroup | NSAIDs Events | NSAIDs Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------------|--------------|----------------|--------------|--------|--------------------------------|--------------------------------|
| Gorissen et al, 2012 | 7 | 79 | 36 | 471 | 5.4% | 1.17 [0.50, 2.74] |  |
| Hoite et al, 2009 | 18 | 119 | 10 | 384 | 5.6% | 6.65 [2.98, 14.85] |  |
| Hultberg et al, 2017 | 11 | 66 | 156 | 1084 | 6.1% | 1.19 [0.61, 2.32] |  |
| Raju et al, 2015 | 2 | 221 | 0 | 46 | 1.2% | 1.06 [0.05, 22.43] |  |
| Rutegard et al, 2016 | 36 | 363 | 124 | 1247 | 7.0% | 0.91 [0.61, 1.34] |  |
| Sim et al, 2007 | 1 | 40 | 0 | 39 | 1.1% | 3.00 [0.12, 75.90] |  |
| Watchow et al, 2009 | 2 | 74 | 2 | 67 | 2.4% | 0.90 [0.12, 6.59] |  |
| Zittel et al, 2013 | 8 | 101 | 3 | 104 | 3.8% | 2.90 [0.75, 11.24] |  |
| Total (95% CI) | 1063 | 3341 | 32.7% | 1.67 [0.90, 3.13] |  |

**Total events**: 85

**Heterogeneity:** $I^2 = 0.42$; $Chi^2 = 20.91$, df = 7 ($P = .004$); $I^2 = 67\%$

**Test for overall effect:** $Z = 1.62$ ($P = .11$)

| Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|--------------------------------|--------------------------------|

**TABLE 3**

- **Heterogeneity:** $I^2 = 0.46$; $Chi^2 = 108.04$, df = 21 ($P < .00001$); $I^2 = 81\%$
- **Test for overall effect:** $Z = 2.97$ ($P = .003$)

**Test for subgroup differences:** $Chi^2 = 0.03$, df = 1 ($P = .85$), $I^2 = 0\%$
Sensitivity analyses were carried out to assess the impact of low-quality studies (Table 1). Exclusion of the two low-quality studies did not affect the significance of the results (pooled OR 1.61, 95% CI 1.22-2.11, \( P < .001 \)).

### 4 | DISCUSSION

Numerous mechanisms have shown how NSAIDs can damage human intestines, although some remain controversial. Non-selective NSAIDs have been associated with enterocyte mitochondrial dysfunction leading to increased epithelial permeability, invasion of luminal bacteria, neutrophil infiltration, and free radical production.\(^{42-44}\) Inhibition of COX by NSAIDs also decreases protective prostaglandins.\(^{45}\) Non-selective NSAIDs and their acidic compounds can cause topical mucosal injury.\(^{7}\) However, most COX in the intestinal mucosal layer are COX-1, and selective COX-2 inhibitors may thus be more tolerable in the normal gastrointestinal tract.

Selective COX-2 inhibitors and non-selective NSAIDs confound the anastomotic healing process. Submucosal collagen fibers provide a core structure that determines tensile strength, and both selective COX-2 inhibitors and non-selective NSAIDs adversely affected this structure in an animal model which, in turn, led to decreased tensile strength of the anastomoses and reduced bursting pressure.\(^{46-48}\) NSAIDs also inhibited epithelial cell migration and mucosal restitution by depolarization and decreased surface expression of potassium channels.\(^{8}\) However, unlike in normal tissue, enterocytes express high levels of COX-2 during inflammation, which catalyzes prostaglandin E2, resulting in increased vascular endothelial growth factor expression and angiogenesis.\(^{49}\)

The above results and hypotheses shed doubt on the safety of postoperative NSAID use for analgesic control. Numerous previous meta-analyses have shown significantly higher anastomotic leakage rates in patients given NSAIDs.\(^{7,12,50}\) The current systematic review and meta-analysis confirmed the association between postoperative NSAID use and higher anastomotic leakage (pooled OR 1.73, 95% CI 1.31-2.29, \( P < .001 \)). However, our analysis of RCT did not show a significant effect of postoperative NSAIDs on anastomotic leakage rate compared with placebo. This meta-analysis included only six RCT. Furthermore, the primary outcome of all RCT were not anastomotic leakage; therefore, we extracted corresponding data from each RCT. Finally, the sample size from RCT was very small compared to observational studies (n = 559 vs 31,499), which makes it relatively reasonable to integrate both study designs in order to make a conclusion from current evidence. From the result of no significant subgroup difference between studies, RCT and all designs, we believe that the controversial result may be explainable by the small sample sizes of the RCT, thus limiting their statistical power, rather than by the absence of a relationship between NSAIDs use and anastomotic leakage.

Subgroup analysis showed that patients taking NSAIDs according to hospital protocol had significantly higher rates of anastomotic leakage than those not taking NSAIDs (pooled OR 4.67, 95%

### TABLE 2 Stratified analysis and meta-regression of included studies

|                          | Studies | N    | OR (95% CI) | \( I^2 \) | \( P \) value |
|--------------------------|---------|------|-------------|----------|--------------|
| 1. Type of studies       |         |      |             |          |              |
| RCTS                     | 6       | 559  | 1.91 (0.69-5.35) | 0        | 0.06         | 0.81         |
| Cohort studies           | 18      | 31,317 | 1.68 (1.25-2.24) | 83       |              |              |
| 2. NSAIDs class          |         |      |             |          |              |
| Non selective            | 15      | 10,424 | 1.80 (1.12-2.91) | 85       | 0.03         | 0.85         |
| Selective COX-2          | 8       | 4,404 | 1.67 (0.90-3.13) | 67       |              |              |
| 3. Urgency of surgery    |         |      |             |          |              |
| Elective                 | 18      | 11,175 | 2.08 (1.31-3.29) | 84       | 4.55         | 72           | 0.03         |
| Not limit to elective    | 6       | 20,701 | 1.23 (1.06-1.42) | 0        |              |              |
| 4. Location of anastomoses|         |      |             |          |              |
| Colorectal               | 17      | 15,475 | 1.80 (1.22-2.66) | 83       | 0.20         | 0.66         |
| Not limit to colorectal  | 7       | 16,401 | 1.58 (1.04-2.42) | 72       |              |              |
| 5. Diagnosis             |         |      |             |          |              |
| Cancer                   | 7       | 8,614  | 1.88 (0.96-3.69) | 93       | 0.31         | 0.58         |
| Not limit to cancer      | 17      | 23,262 | 1.54 (1.21-1.96) | 44       |              |              |
| 6. NSAIDs administration |         |      |             |          |              |
| Protocol based           | 11      | 19,18  | 4.67 (2.84-7.67) | 5        | 18.78        | 94.7         | <.0001       |
| Unsystematic             | 13      | 29,958 | 1.34 (1.03-1.75) | 81       |              |              |

Abbreviations: CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; RCT, randomized controlled trial.
In conclusion, postoperative NSAID use appears to be associated with an increased incidence of anastomotic leakage following gastrointestinal surgery. Selective COX-2 inhibitors might be safer than non-selective NSAIDs, although the results were inconclusive. Caution is warranted when using NSAIDs for postoperative analgesic control in patients with gastrointestinal anastomoses.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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