World J Surg (2014) 38:2247–2257
DOI 10.1007/s00268-014-2531-1

World Journal of Surgery

Postoperative Nonsteroidal Anti-inflammatory Drugs and Risk of Anastomotic Leak: Meta-analysis of Clinical and Experimental Studies

Aneel Bhangu · Prashant Singh · J. Edward F. Fitzgerald · Alistair Slesser · Paris Tekkis

Published online: 31 March 2014

Abstract

Background Enhanced recovery programs following colorectal resection recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia. The present study aimed to assess whether postoperative NSAID use increased the risk of anastomotic leak.

Methods A systematic review of published literature was performed for studies comparing anastomotic leak following NSAID administration versus control. Meta-analysis was conducted for studies in human patients and experimental animal models. The primary endpoint was anastomotic leak.

Results The final analysis included 8 studies in humans and 12 experimental animal studies. Use of NSAIDs was significantly associated with anastomotic leak in humans (8 studies, 4,464 patients, odds ratio [OR] 2.14; $p < 0.001$). This effect was seen with nonselective NSAIDs (6 studies, 3,074 patients, OR 2.37; $p < 0.001$), but not with selective NSAIDs (4 studies, 1,223 patients, OR 2.32; $p = 0.170$). There was strong evidence of selection bias from all clinical studies, with additional inconsistent definitions and outcomes assessment. From experimental animal models, anastomotic leak was more likely with NSAID use (ten studies, 575 animals, OR 9.51; $p < 0.001$). Bursting pressures at day 7 were significantly lower in NSAID versus controls (7 studies, 168 animals, weighted mean difference −35.7 mmHg; $p < 0.001$).

Conclusions Emerging data strongly suggest that postoperative NSAIDs are linked to anastomotic leak, although most studies are flawed and may be describing pre-existing selection bias. However, when combined with experimental data, these increasing concerns suggest caution is needed when prescribing NSAIDs to patients with pre-existing risk factors for leak, until more definitive evidence emerges.

This report was presented to the Association of Surgeons of Great Britain and Ireland, Glasgow, April 2013.

Electronic supplementary material The online version of this article (doi:10.1007/s00268-014-2531-1) contains supplementary material, which is available to authorized users.

A. Bhangu (✉) · P. Singh · J. E. F. Fitzgerald · A. Slesser · P. Tekkis
Department of Colorectal Surgery, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK
e-mail: aneelbhangu@doctors.org.uk

P. Tekkis
e-mail: p.tekkis@imperial.ac.uk

A. Bhangu · P. Singh · J. E. F. Fitzgerald · A. Slesser · P. Tekkis
Division of Surgery, Imperial College, Chelsea and Westminster Campus, London, UK

Introduction

The last decade has seen developments in laparoscopic surgery and other measures of perioperative care cumulate in enhanced recovery after surgery (ERAS) programs [17, 26]. Randomized controlled trials across multi-institution, multi-country settings have provided evidence of their efficacy [40, 43]. They allow for a reduction in morbidity, rapid recovery, and reduced hospital stay. Early bowel function recovery is enhanced through avoidance of opioids for pain control, with a preference for epidural analgesia and augmentation with nonsteroidal anti-inflammatory drugs (NSAIDs).

Anastomotic leak following resectional colorectal surgery affects up to 10 % of patients and is associated with increased risk of mortality and local recurrence of cancer

[24, 30, 32, 36]. The predisposing factors and causes of leaks are multifactorial and often multiple [32, 36]. Reducing their risk is a priority for gastrointestinal surgeons. Following identification of increased cardiovascular [20] and gastrointestinal [25] risk with NSAIDs in non-surgical patients, there has been an interest in possible association between NSAIDs and anastomotic leak [16, 22].

The use of NSAIDs is recommended in the ERAS Society evidence-based multimodal care protocol [15]. Published in 2013, the guidelines for perioperative ERAS care after elective rectal and colonic surgery identify a possible link between NSAID use and anastomotic leak. The study found insufficient evidence to stop using NSAIDs as a component of multimodal analgesia until more thorough studies addressing this question have been carried out [17]. The aim of the present study was to assess the current evidence in a systematic way for an association between NSAID use and anastomotic leak. In order to increase the power of this analysis, evidence was sought form both human clinical studies and animal experimental models. By including laboratory data, proxy markers of the clinical effects of NSAIDs in patients can be assessed. Although these are imperfect, they can be used to assess what would otherwise be immeasurable.

Methods

Data sources and search strategy

This study was performed according to a prespecified protocol devised by the authors. A systematic search of the OVID SP version of Medline, the PubMed version of Medline, the Cochrane Library, and Clinicaltrials.gov was performed for published studies comparing anastomotic leak rates stratified for postoperative NSAID administration following colonic or small bowel resection in either humans or animals. No language or date restrictions were applied. MeSH terms were used to search Medline, with the search strategies presented in Supplemental Table 1. The search was performed independently by two researchers. The last search was performed in February 2013. A manual search of reference lists in relevant systematic reviews, meta-analyses, and published papers was undertaken to further identify studies of potential interest. Abstracts and conference proceedings were excluded because of the high probability of incomplete data.

Inclusion and exclusion criteria

The following a priori inclusion criteria were applied: (1) studies reporting the rate of anastomotic leak from colonic or small bowel anastomoses in either human patients or experimental animal models; (2) studies comparing cohorts receiving NSAIDs to a control group without; (3) study type was randomized controlled trial (RCT), prospective observational study, or retrospective cohort study. Studies were excluded according to the following criteria: (1) case reports and letters, due to the high probability of incomplete data; (2) studies with <10 patients or animals.

Data extraction

Data were extracted by one author with complete, independent verification by a second author. Discrepancies in outcome extraction were resolved by re-examination of the relevant study until consensus was achieved. Data extracted on study design of human patient trials included design, use of protocolized surgical pathways (including definitions of enhanced recovery pathways, standardized surgical practice, or other standardized perioperative care), definition of anastomotic leak, name and class of NSAID, colonic or small bowel resection, other analgesic use. Data extracted on study design from animal experimental models included type of animal model used, type of anastomosis, name and class of NSAID, randomization of NSAID delivery, definition of anastomotic leak, method of assessment of bursting pressure, and method of assessment of breaking strength.

Outcomes and definitions

The primary outcome assessed for meta-analysis was the rate of anastomotic leak from human patient studies. The secondary outcomes were taken from the experimental animal studies, and were the comparative rates of anastomotic leak, bursting pressure, and breaking strength.

Data were extracted to match pre-set criteria wherever possible. The best available data were recorded if either no definition was provided or if an alternative was given. Determination of anastomotic leak was allowed by radiological, clinical, or reoperative detection; the specific definition from each study was reported. Bursting pressure was the pressure (in millimetres of mercury [mmHg]) at which leakage was detected, preferentially from the anastomotic line. Breaking strength was defined as the rupturing pressure (Newton [N]) at the anastomotic line.

Assessment of bias

Due to the likely mix of RCTs and cohort studies, risk of bias was assessed using the Newcastle Ottawa Scale (NOS), with modification to take into account study characteristics of randomized trials [42]. Seven points or above was taken as indicating high quality.

Statistical analysis

Meta-analysis was conducted according to guidelines from the preferred reporting items for systematic reviews and meta-analysis group (PRISMA) [28]. The odds ratio (OR) was used as the statistical measure for dichotomous outcomes and the weighted mean difference (WMD) for continuous variables. Odds ratios were calculated from the original data and meta-analyzed with the Mantel–Haenszel method. An OR of >1.0 indicated greater risk of an adverse event occurring in the experimental group. Where adjusted odds ratios were provided, the generic inverse method was used for meta-analysis. A p value of <0.05 was considered significant for all analyses. Statistical algorithms were used to calculate the standard deviation if unavailable.

Between-study heterogeneity was assessed using the I^2 and χ^2 statistic and funnel plots. Higher values of I^2 and the χ^2 statistic signified increasing levels of heterogeneity, with a p value <0.05 or an $I^2 > 50$ % indicating significant heterogeneity [27]. In these cases, a random-effects model was used; otherwise a fixed-effects meta-analysis was performed [13]. Statistical analysis was performed with Review Manager 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Subgroup analysis

Analysis was planned to include mixed classes of NSAIDs to maximize the number of patients included, and then subgroup analysis of selective and nonselective NSAIDs was performed. Because of controversy over its definition as a selective NSAID, diclofenac was considered a nonselective NSAID [16]. For the mixed class analysis, if outcome from more than one NSAID was presented, data related to diclofenac were used. Further pre-planned analyses were conducted for the following subgroups when two or more studies were available: (1) studies scoring seven points or above on the NOS; (2) studies with adequate data for analysis on individual NSAID type.

Results

Demographics of clinical studies

The final analysis included eight studies on human patients [17], of which five were RCTs and three were retrospective database reviews (Table 1). Seven studies scored seven points or above on the Newcastle-Ottawa Scale (supplemental Table 2). Four RCTs used return of gastrointestinal function as the primary outcome, and one used length of hospital stay; none were powered to detect differences in rate of anastomotic leak.

Table 1 Basic demographic details of clinical studies

Study	Time period	Setting	Design	Data source	Surgery type	Total number of patients in study	Protocol surgery?
Chen et al. [8]	January 2003–December 2003	Taiwan	RCT	Trial data	Colon, rectum	79	Yes, single surgeon
Chen et al. [9]	June 2006–June 2007	Taiwan	RCT	Trial data	Colon, rectum	102	Yes, hospital/surgeon protocol
Gorissen et al. [16]	2008–2010	Netherlands	R	Database	Colon, rectum	795	Yes, fast-track surgery protocol
Holte et al. [18]	April 1997–May 2006	Denmark	R	Database	Colon	503	Fast track colonic surgery
Klein et al. [22]	01/01/2006–31/12/2009	Denmark	R	Database	Colon, rectum	2,756	Unclear
Schlachta et al. [34]	October 2002–March 2005	Canada	RCT	Trial data	Colon	44	Consistent between surgeons
Sim et al. [35]	December 2002–June 2004	Singapore	RCT	Trial data	Colon, rectum	79	Unclear
Wattchow et al. [41]	Unclear	Australia	RCT	Trial data	Colon, rectum, small bowel (<1 %)	210	Early recovery program

RCT randomized controlled trial; *R* retrospective

Of 4,568 patients undergoing bowel resection, 98.1 % received a primary anastomosis (4,482/4,568). A protocolized approach to surgery was identified in five studies (Table 1). Details regarding NSAID use are shown in Table 2. Three nonselective NSAIDs (diclofenac, ibuprofen, ketorolac) and two selective NSAIDs (celecoxob, valdecoxib) were assessed within these studies.

Anastomotic leak in clinical studies

The included studies comprised anastomoses of the colon or rectum, with <1 % of a single study including anastomoses of small bowel [41]. A definition of anastomotic leak was provided by three studies; two of these stipulated radiological or clinical findings and one a clinical finding only. The overall anastomotic leak rate was 6.8 % (305/4,482), which ranged between 1.0 and 11.4 % between studies.

Overall use of NSAIDs was significantly associated with anastomotic leak (OR 2.14; $p < 0.001$; Table 3; Fig. 1). Two studies provided adjusted odds ratios for mixed NSAID use, which when pooled showed an increased likelihood of anastomotic leak (OR 3.86, 95 % CI 1.18–12.67; $p = 0.030$). One of these studies adjusted risk for intraoperative transfusion, rectal versus colonic resection, gender, and hospital stay [22]; the other adjusted risk for pulmonary disease and stapled anastomosis [16].

An adverse effect was seen with nonselective NSAIDs (OR 2.37; $p < 0.001$), but not with selective NSAIDs (OR 2.32; $p = 0.170$; Fig. 1). However, heterogeneity with selective NSAIDs was high, and there was evidence of publication bias in funnel plots. Taking only patients receiving diclofenac, the significant effect with NSAIDs remained (three studies, 2,869 patients, OR 2.32, 95 % CI 1.66–3.25; $p < 0.001$). Considering only patients receiving ketorolac, the effect was no longer significant (OR 3.10, 95 % CI 0.81–11.82; $p = 0.100$), although patient numbers were low (three studies, 205 patients). The effect with celecoxib remained nonsignificant (two studies, OR 3.24, 95 % CI 0.53–19.77; $p = 0.200$).

Significance was unchanged for mixed and nonselective NSAIDs when only high-quality studies (i.e., NOS seven or above) were included. However, in the selective group, heterogeneity was reduced (three studies, 673 patients, I^2 35 %) and the adverse effect with NSAIDs achieved significance (OR 3.67, 95 % CI 1.06–12.64; $p = 0.040$). To test the influence of predominating studies, exclusion of the study with the highest number of patients in each analysis did not affect significance.

Demographics of experimental studies

Twelve studies including experimental animal models were included (Fig. 2). The studies reported on a total of 711 animals (animal types are shown in Table 4). Seven studies included colonic anastomoses only, four mixed colon/intestinal, and one intestinal only. Ten studies were randomized, with allocation being unclear in two. Eight nonselective (aspirin, carprofen, diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, piroxicam) and four selective NSAIDs (celexob, etodolac, rofecoxib, valdecoxib) were assessed.

Details of outcome assessment are shown in Supplemental Table 3. Five studies provided four different definitions of anastomotic leak, with the remainder stating either an unclear definition or no definition at all. Nine studies assessed bursting pressure and six assessed breaking strength (technical details shown in Supplemental Table 3).

Anastomotic leak from experimental studies

Anastomotic leak was significantly associated with NSAID use (OR 9.51; $p < 0.001$; Table 3, Fig. 3). The effect remained significant with both nonselective (OR 8.29; $p < 0.001$) and selective NSAIDs (OR 13.78; $p = 0.002$; Table 3). In six studies with data for nonselective NSAIDs and four with data for selective NSAIDs, the effects remained significant (Table 3).

Bursting pressure from experimental studies

Bursting pressures overall and for subgroups at each time point are shown in Table 5. At day 3–5, overall bursting pressures in the NSAID group were not significantly different from controls, but the selective NSAID group had a significantly lower bursting pressure (WMD—26.10 mmHg; $p = 0.001$). At day 7, overall bursting pressures in the NSAID group were significantly lower than in controls (WMD—33.10 mmHg; $p < 0.001$); this effect was also seen in nonselective NSAIDs (−32.32; $p < 0.001$) but not in selective NSAIDs (−30.09; $p = 0.260$).

Breaking strength from experimental studies

Breaking strength in colonic anastomoses on days 3 and 7, and ileal anastomoses on day 3, were not significantly different between the NSAID and control groups.

Discussion

Although emerging clinical findings presented in this study suggest that postoperative NSAIDs are linked to anastomotic leak, the data are currently flawed and may well be describing pre-existing bias. Nevertheless, when combined with experimental data, these increasing concerns suggest that caution should be exerted when prescribing NSAIDs to

Table 2 Demographics of nonsteroidal anti-inflammatory drugs (NSAIDs) treatment in clinical studies

Study	Indication for NSAID	NSAID given	Class of NSAID	Additional postoperative analgesic regimen	Definition of anastomotic leak	Rate of leak
Chen et al. [8]	Allocation arm	Ketorolac	Nonselective	PCA with morphine	Unstated	4.8 % (3/62)
Chen et al. [9]	Allocation arm	Ketorolac	Nonselective	PCA with morphine	Unstated	3.9 % (4/102)
Gorissen et al. [16]	Physician preference, only those within first 5 days of surgery included	Diclofenac, meloxicam, Celecoxib	Selective and nonselective	Epidural, Paracetamol	Clinical or radiological signs of anastomotic leak confirmed by reoperation or occurrence of an enterocutaneous fistula	1.0 % (79/795)
Holte et al. [18]	Change in protocol over time	Celecoxib	Selective	Epidural	Radiologically (contrast enema or abdominal computed tomography) or during surgery	5.6 % (28/502)
Klein et al. [22]	At least 2 days treatment within the first 7 days	At least 50 mg diclofenac or 800 mg ibuprofen per day	Nonselective	Unstated	Clinical leakages requiring acute surgical intervention, such as re-laparoscopy or re-laparotomy	6.5 % (179/2,756)
Schlachta et al. [34]	Allocation arm	Ketorolac	Nonselective	PCA with morphine	Unstated	11.4 % (5/44)
Sim et al. [35]	Allocation arm	Valdecoxib (first dose 1–3 h preoperatively)	Selective	PCA with morphine	Unstated	1.4 % (1/71)
Wattchow et al. [41]	Allocation arm	Celecoxib or diclofenac	Selective and nonselective	PCA or epidural	Unstated	4 % (6/150)

PCA patient-controlled analgesia

Table 3 Meta-analysis of effect of NSAIDs on anastomotic leak

NSAID group	Number of studies	Patients	Odds ratio (95 % confidence interval)	*p* value	Heterogeneity		
					I^2 (%)	χ^2	*p* value
Human							
Mixed	8	4,464	2.14 (1.69, 2.71)	<0.001	28	9.12	0.330
Nonselective	6	3,074	2.37 (1.71, 3.28)	<0.001	0	1.89	0.860
Selective	4	1,223	2.32 (0.71, 7.63)	0.170	68	9.50	0.020
Animal							
Mixed	10	575	9.51 (4.63, 19.53)	<0.001	12	7.81	0.350
Nonselective	7	350	8.29 (3.83, 17.94)	<0.001	20	7.50	0.280
Selective	4	245	13.78 (2.64, 72.06)	0.002	2	2.05	0.360

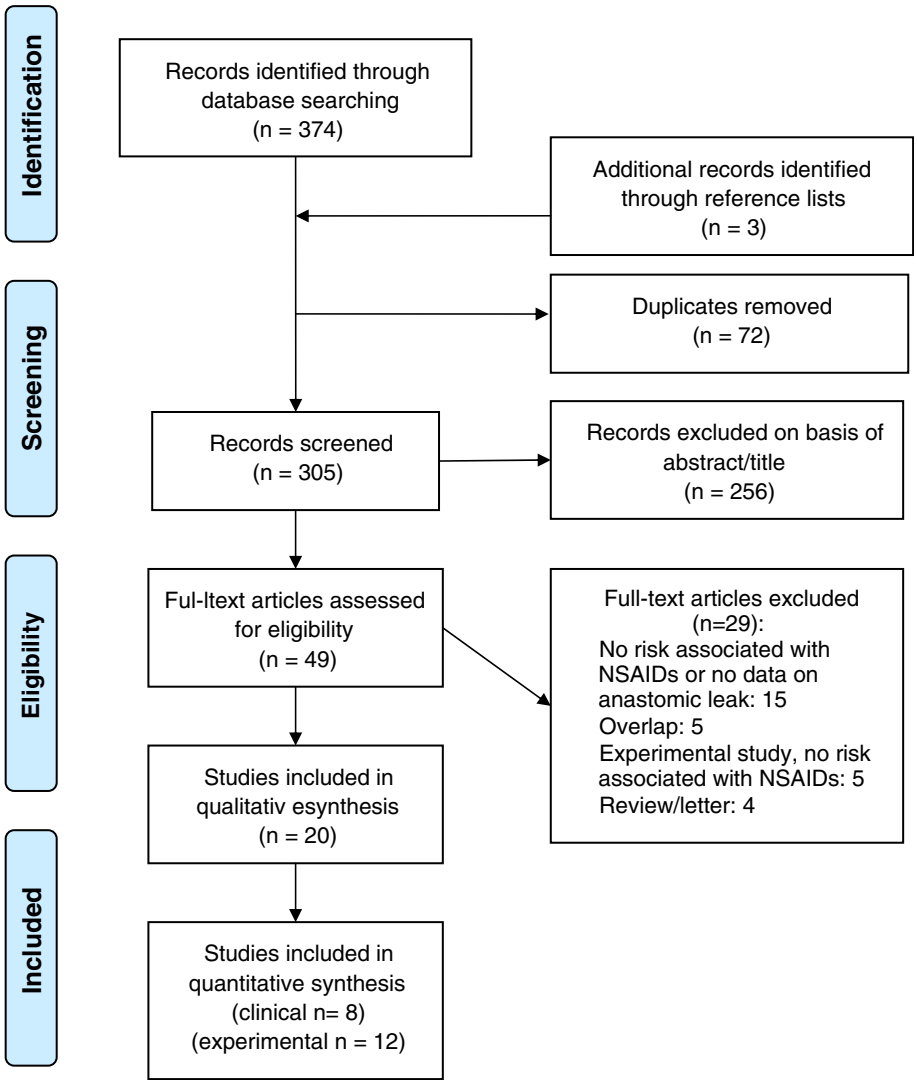

Fig. 1 PRISMA flowchart of included studies

patients with pre-existing risk factors for anastomotic leak. At present, ERAS protocols contain advice to administer NSAIDs to aid opioid sparing, without restriction [17]. Although a change in guidelines may be required to recommend caution in patients with risk factors, the limitations of the included studies and careful extrapolation of findings from experimental studies must be considered prior to a widespread change in practice affecting all patients.

The five included human RCTs were not powered to identify anastomotic leak as a primary endpoint, and the

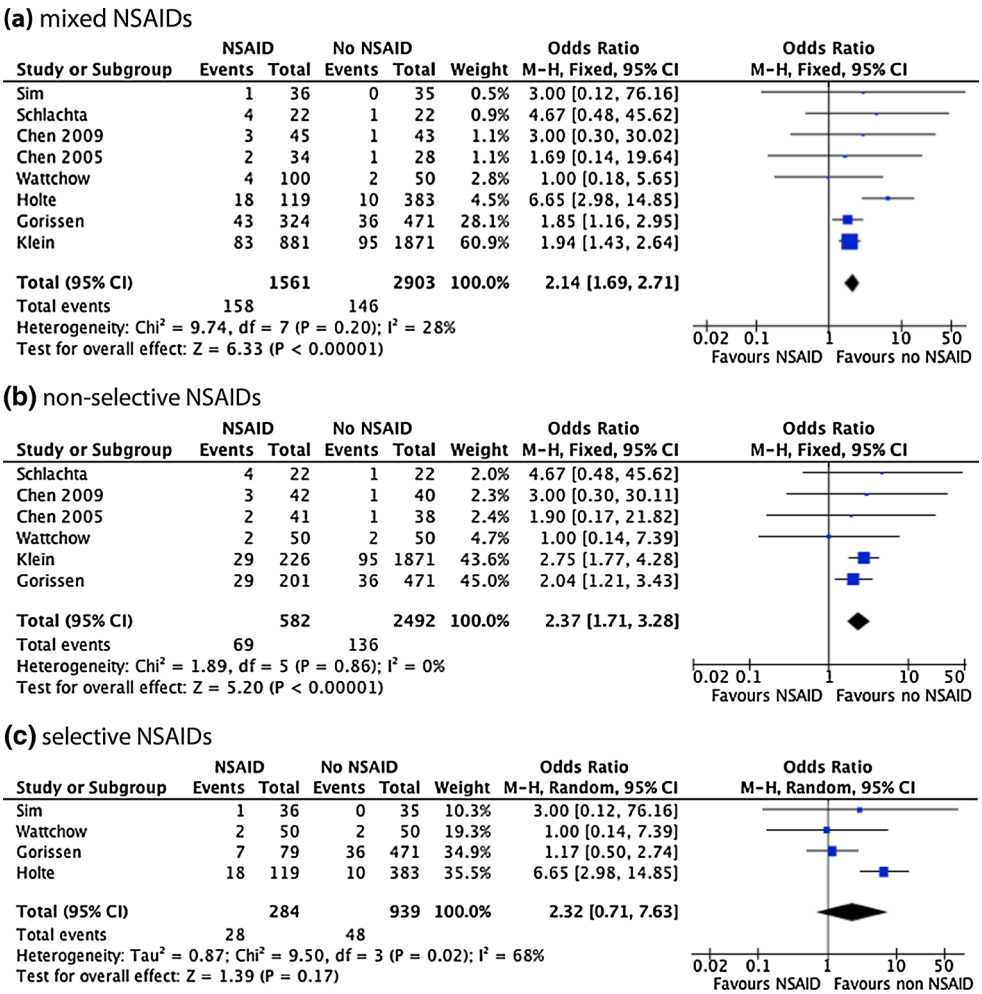

Fig. 2 Meta-analysis of effects of NSAIDs on anastomotic leak inclinical studies

nature of the information they provided meant that even spread of confounding factors could not be ensured. Combined with the nonrandomized nature of the cohort studies, confounding must be considered as a potential source of bias in the present analysis. The indications for NSAIDs cannot reliably be determined or examined from these database studies. In their study, Klein et al., showed only 32 % of patients received NSAIDs, which is unlikely to represent preoperative guidelines alone, and indicates that selection must have influenced the treatment group. Identifying the causes and mechanisms of this selection is important as it may correlate with other confounding factors, where prescription may have been for symptoms of a developing anastomotic leak or may represent additional morbidity (e.g., more extensive dissection, loop ileostomy formation). Therefore this meta-analysis, as for the studies it includes, cannot prove reverse causality between NSAID use and anastomotic leak.

Both the randomized and nonrandomized studies inadequately controlled for the other factors that contribute to anastomotic leak, and include (but are not limited to): colon versus rectal location; height within the rectum; bowel preparation; loop ileostomy; epidural anesthesia; comorbidity; corticosteroid use; neoadjuvant chemoradiotherapy; blood transfusion; uptake of ERAS; and laparoscopic learning curves [4, 32, 36]. The two studies included in the present meta-analysis which provided adjusted ORs maintained a higher risk of anastomotic leak with NSAIDs, although they were individually adjusted for different confounding factors [16, 22]. As identified by Klein et al. [22], however, an adequately powered RCT showing a 30 % reduction in the rate of anastomotic leak would require 2,100 patients. Setting up such a large RCT may prove impossible or, at best, challenging.

Some 99 % of the patients included in the present study had a colorectal anastomosis, and most of the experimental studies included colonic models, meaning that the results of this study are most relevant to colorectal surgery. While the mixture of operation types and indications increases heterogeneity, it also allows for a pragmatic and real-world assessment of the effects of NSAIDs. A consistent definition of anastomotic leak was lacking from all of the included studies and is likely to affect the true rates; this is also a consistent problem in colorectal studies beyond this

Table 4 Demographics of animal testing studies

Study	Model	Starting number	Anastomosis	Randomized	Class	NSAID used	Control
Benjamin et al. [3]	F344 rats	48	Colon	Yes	Selective	Etodolac	Placebo
Cahill et al. [7]	Sprague–Dawley rats	40	Colon	Yes	Selective	Rofecoxib	Placebo
de Hingh et al. [11]	Wistar rats	95	Colon, intestine	Yes	Selective	Celecoxib	Placebo
de Sousa et al. [12]	Hybrid rabbits	48	Intestine	Yes	Nonselective	Diclofenac	Placebo
Esen et al. [14]	Sprague–Dawley rats	48[a]	Colon	Unclear	Selective and nonselective	Diclofenac, metamizole, tenoxicam	Placebo
Inan et al. [19]	Sprague–Dawley rats	36	Colon	Yes	Nonselective	Diclofenac	Placebo
Klein et al. [21]	Wistar rats	32	Colon	Yes	Nonselective	Diclofenac	Placebo
Klein et al. [23]	Wistar rats	60	Colon	Yes	Nonselective	Diclofenac	Placebo
Mastboomet al [29]	Wistar rats	100	Colon, intestine	Unclear	Selective and nonselective	Celecoxib, piroxicam, aspirin, indomethacin	None
Neuss et al. [31]	New Zealand white rabbits	80	Colon	Yes	Selective and nonselective	Resveratrol, metamizole, valdecoxib	Placebo
Van der Vijver et al. [37]	Wistar rats	20	Colon, intestine	Yes	Selective	Caprofen	Buprenorphine
Van der Vijver et al. [38]	Wistar rats	104	Colon, intestine	Yes	Nonselective	Diclofenac, naproxen	Placebo

[a] Excludes six replacement rats for early deaths from anastomotic leak

meta-analysis [5]. Although the animal experimental models provide important data to support the notion that NSAIDs may be harmful, direct extrapolation from these carefully controlled experiments to human patients must be done with caution.

The subgroup findings of this study should also be interpreted with caution. Although the adverse effect seen from selective NSAIDs in clinical studies was not significant, numbers of patients were low and the results from experimental models were conflicting; it may be that the power was too low to adequately detect a difference. As high-quality pelvic surgery evolves into its own specialty, a large numbered analysis on the influence of NSAIDs in anterior resection, when adjusted for height of anastomosis, is warranted.

None of the breaking strength experiments showed significant differences but all contained low numbers. A subgroup analysis of colonic versus rectal anastomoses was not possible because of the lack of published studies.

The mechanism by which NSAIDs affect anastomotic healing remains unclear. Significant evidence is available from experimental studies showing the relationship between NSAIDs, reduced collagen, and anastomotic leak, with suggested downregulation of prostaglandin expression (through cyclo-oxygenase [COX] inhibition in healing tissues) as a proposed mechanism for reduction of measured hydroxyproline levels [19, 29]. However, conflicting data also exist [7, 11, 12, 31, 37]. The previous evidence of increased cardiovascular thrombotic risk from studies on adenoma prevention suggest that microthrombosis or microemboli restricting anastomotic blood supply may be causative [20]; further evidence from gastrointestinal anastomotic models is needed to support this theory.

Although disruption of the delicate blood supply to the anastomosis may predispose to anastomotic leak [1], evidence of the relationship of anastomotic leak with NSAIDs is lacking. Neuss et al. [31], analyzed vessel density in the anastomotic region in 80 animal models after colonic anastomosis, and although they noted a wide variation in microvessel density, they were unable to show a statistical pattern to this distribution.

A previous meta-analysis on this topic included five RCTs, and showed no increased risk of anastomotic leak with NSAID use [6]. The same subgroup analysis was not performed in the present study, because of the inherent high risk of bias from including only these RCTs, which were not designed or optimized to assess anastomotic leak. Further differences exist between inclusion criteria (one fewer study was included in the present meta-analysis) and data extraction (e.g., determination of denominators).

In fact, NSAIDs have been proved to have an important role in cancer prevention and reduction of cancer progression. Their use has been shown to reduce the incidence of

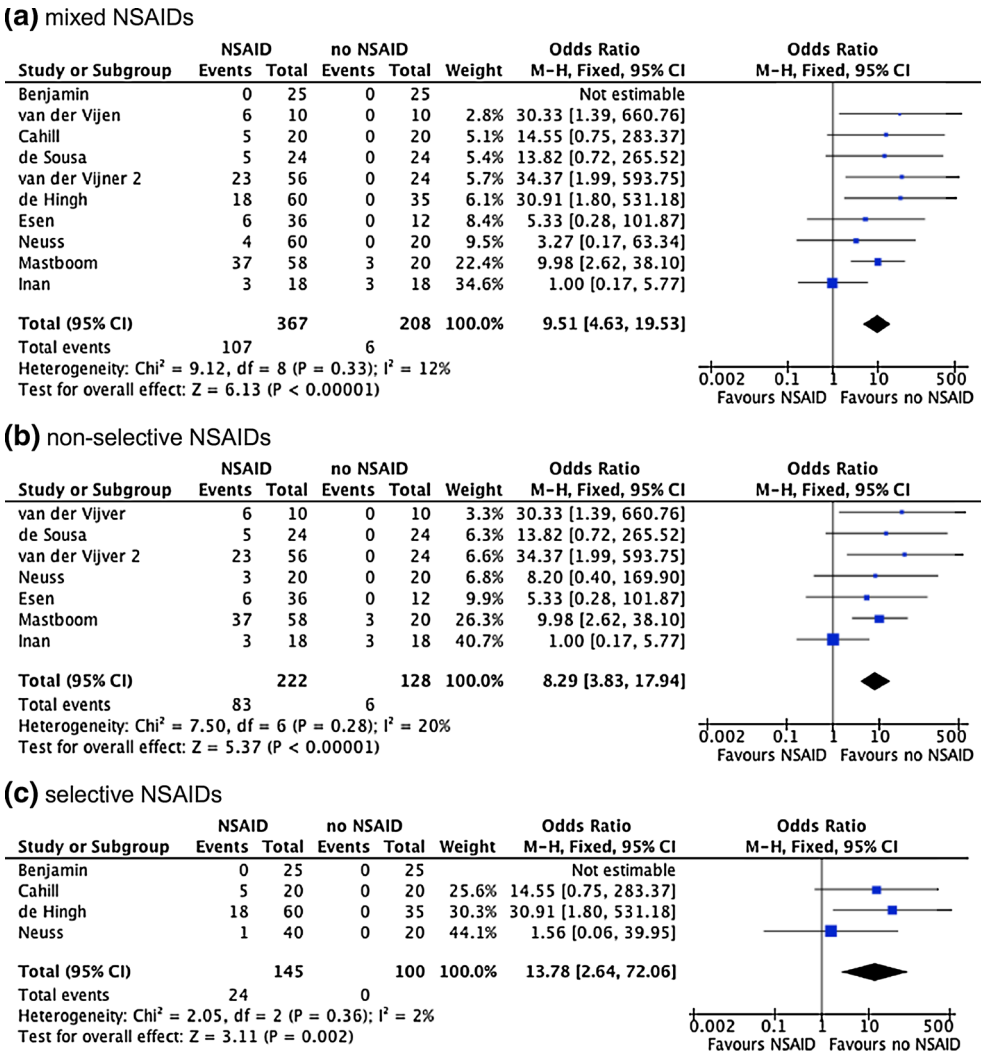

Fig. 3 Meta-analysis of effects of NSAIDs on anastomotic leak in experimental studies

Table 5 Meta-analysis of effect of NSAIDs on bursting pressure in animal models of colonic and ileal anastomosis

Group	Number of studies	Patients	Weighted mean difference	*p* value	Heterogeneity		
					I^2 (%)	χ^2	*P* value
Bursting pressure (mmHg)							
Day 3–5							
Mixed	7	187	−6.70 (–16.43, 3.04)	0.180	72	21.80	0.001
Nonselective	5	83	–1.80 (–11.40, 7.80)	0.710	70	13.27	0.010
Selective	2	104	–26.10 (–41.93, –10.27)	0.001	0	0.81	0.370
Day 7							
Mixed	7	168	–35.74 (–50.97, –20.51)	<0.001	63	16.17	0.010
Nonselective	4	71	–38.21 (–48.25, –28.18)	<0.001	0	1.65	0.650
Selective	3	97	–40.51 (–88.09, 7.08)	0.100	84	12.29	0.002
Breaking strength (N)							
Colonic, day 3	5	178	–0.02 (–0.12, 0.07)	0.620	43	6.99	0.140
Colonic, day 7	3	92	0.24 (–0.13, 0.62)	0.200	67	5.98	0.050
Ileal, day 3	3	80	0.00 (–0.04, 0.04)	0.920	40	3.31	0.190

colorectal cancer [33], improve long-term survival following colorectal cancer [10, 33], and reduce recurrence of adenoma following first treatment [2]. These desirable effects have been accompanied by severe cardiovascular and gastrointestinal toxicity [20, 25], which has prevented their routine use at population level. This means that their role in cancer prevention remains undefined. Because these beneficial effects are seen after prolonged treatment, any recommendation to avoid NSAIDs in the postoperative period should not affect future cancer-prevention strategies.

As avoidance of opioid analgesia during ERAS pathways is likely to reduce the rate of complications [39], it should be considered that the optimum analgesic strategy has not yet been determined. Use of NSAIDs remains an extremely useful analgesic adjunct, and further research is needed to define their precise role following colorectal anastomosis in terms of the optimum NSAID for the optimum patient. In their adjusted population level analysis, Klein et al. [22], showed no increased risk of anastomotic leak in 655 patients when considering ibuprofen (adjusted OR 1.54, 95 % CI 0.82–2.86). Subgroup analysis of ibuprofen was not undertaken in the present meta-analysis, because there were not enough studies. Further evidence is needed to prove the safety of selective NSAIDs, as their use may come at the risk of increased cardiovascular and/or gastrointestinal toxicity. There was inadequate information regarding the timing and duration of NSAID administration, which may also affect the risk of anastomotic leak. The animal experimental model reported by van der Vijver et al. [38], showed that a short postoperative delay in administration of NSAIDs reduced the risk of associated anastomotic leak. However, their experimental delay period was for 7 days post-anastomosis, by which time the maximum need for adjunctive analgesia may have passed.

Acknowledgments This work was funded by the Imperial College Cancer Research UK Center.

References

1. Allison AS, Bloor C, Faux W et al (2010) The angiographic anatomy of the small arteries and their collaterals in colorectal resections: some insights into anastomotic perfusion. Ann Surg 251:1092–1097
2. Baron JA, Sandler RS, Bresalier RS et al (2006) A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 131:1674–1682
3. Benjamin B, Hazut O, Shaashua L et al (2010) Effect of beta blocker combined with COX-2 inhibitor on colonic anastomosis in rats. Int J Colorectal Dis 25:1459–1464
4. Boccola MA, Buettner PG, Rozen WM et al (2011) Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg 35:186–195. doi:10.1007/s00268-010-0831-7
5. Bruce J, Krukowski ZH, Al-Khairy G et al (2001) Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg 88:1157–1168
6. Burton TP, Mittal A, Soop M (2013) Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence in bowel surgery: systematic review and meta-analysis of randomized, controlled trials. Dis Colon Rectum 56:126–134
7. Cahill RA, Sheehan KM, Scanlon RW et al (2004) Effects of a selective cyclo-oxygenase 2 inhibitor on colonic anastomotic and skin wound integrity. Br J Surg 91:1613–1618
8. Chen JY, Wu GJ, Mok MS et al (2005) Effect of adding ketorolac to intravenous morphine patient-controlled analgesia on bowel function in colorectal surgery patients—a prospective, randomized, double-blind study. Acta Anaesthesiol Scand 49:546–551
9. Chen JY, Ko TL, Wen YR et al (2009) Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel function in colorectal surgery patients: a prospective randomized double-blinded study. Clin J Pain 25:485–489
10. Coghill AE, Newcomb PA, Campbell PT et al (2011) Prediagnostic non-steroidal anti-inflammatory drug use and survival after diagnosis of colorectal cancer. Gut 60:491–498
11. de Hingh IH, van Goor H, de Man BM et al (2006) Selective cyclooxygenase 2 inhibition affects ileal but not colonic anastomotic healing in the early postoperative period. Br J Surg 93:489–497
12. de Sousa JB, Soares EG, Aprilli F (1991) Effects of diclofenac sodium on intestinal anastomotic healing. Experimental study on the small intestine of rabbits. Dis Colon Rectum 34:613–617
13. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
14. Esen E, Sucullu I, Sinan H et al (2008) The effects of non-steroid anti-inflammatory drugs on healing of colonic anastomosis in rats. Eastern J Med 13:13–18
15. Final Report on Carcinogens Background Document for Formaldehyde (2010) Rep Carcinog Backgr Doc (10-5981):i–512
16. Gorissen KJ, Benning D, Berghmans T et al (2012) Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. Br J Surg 99:721–727
17. Gustafsson UO, Scott MJ, Schwenk W et al (2013) Guidelines for perioperative care in elective colonic surgery: enhanced recovery after surgery (ERAS) society recommendations. World J Surg 37:259–284. doi:10.1007/s00268-012-1772-0
18. Holte K, Andersen J, Jakobsen DH et al (2009) Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery. Br J Surg 96:650–654
19. Inan A, Koca C, Sen M (2006) Effects of diclofenac sodium on bursting pressures of anastomoses and hydroxyproline contents of perianastomotic tissues in a laboratory study. Int J Surg 4:222–227
20. Kearney PM, Baigent C, Godwin J et al (2006) Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 332(7553):1302–1308
21. Klein M, Krarup PM, Burcharth J et al (2011) Effect of diclofenac on cyclooxygenase-2 levels and early breaking strength of experimental colonic anastomoses and skin incisions. Eur Surg Res 46:26–31
22. Klein M, Gogenur I, Rosenberg J (2012) Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. BMJ 345:e6166
23. Klein M, Krarup PM, Kongsbak MB et al (2012) Effect of postoperative diclofenac on anastomotic healing, skin wounds and subcutaneous collagen accumulation: a randomized, blinded, placebo-controlled, experimental study. Eur Surg Res 48:73–78

24. Kube R, Mroczkowski P, Granowski D et al (2010) Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. Eur J Surg Oncol 36:120–124
25. Lanas A, Baron JA, Sandler RS et al (2007) Peptic ulcer and bleeding events associated with rofecoxib in a 3-year colorectal adenoma chemoprevention trial. Gastroenterology 132:490–497
26. Lassen K, Soop M, Nygren J et al (2009) Consensus review of optimal perioperative care in colorectal surgery: enhanced recovery after surgery (ERAS) group recommendations. Arch Surg 144:961–969
27. Lau J, Ioannidis JP, Schmid CH (1997) Quantitative synthesis in systematic reviews. Ann Intern Med 127:820–826
28. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700
29. Mastboom WJ, Hendriks T, van Elteren P et al (1991) The influence of NSAIDs on experimental intestinal anastomoses. Dis Colon Rectum 34:236–243
30. Mirnezami A, Mirnezami R, Chandrakumaran K et al (2011) Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 253:890–899
31. Neuss H, Raue W, Muller V et al (2009) Effects of cyclooxygenase inhibition on anastomotic healing following large bowel resection in a rabbit model—a randomized, blinded, placebo-controlled trial. Int J Colorectal Dis 24:551–557
32. Peeters KC, Tollenaar RA, Marijnen CA et al (2005) Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 92:211–216
33. Rothwell PM, Wilson M, Elwin CE et al (2010) Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 376(9754):1741–1750
34. Schlachta CM, Burpee SE, Fernandez C et al (2007) Optimizing recovery after laparoscopic colon surgery (ORAL-CS): effect of intravenous ketorolac on length of hospital stay. Surg Endosc 21:2212–2219
35. Sim R, Cheong DM, Wong KS et al (2007) Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific inhibitor as opioid-sparing analgesia in major colorectal surgery. Colorectal Dis 9:52–60
36. Trencheva K, Morrissey KP, Wells M et al (2013) Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. Ann Surg 257:108–113
37. van der Vijver RJ, van Laarhoven CJ, de Man BM et al (2012) Perioperative pain relief by a COX-2 inhibitor affects ileal repair and provides a model for anastomotic leakage in the intestine. Surg Innov 20:113–118
38. van der Vijver RJ, van Laarhoven CJ, Lomme RM et al (2013) Diclofenac causes more leakage than naproxen in anastomoses in the small intestine of the rat. Int J Colorectal Dis 28:1209–1216
39. Varadhan KK, Neal KR, Dejong CH et al (2010) The enhanced recovery after Surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr 29:434–440
40. Vlug MS, Wind J, Hollmann MW et al (2011) Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg 254:868–875
41. Wattchow DA, De Fontgalland D, Bampton PA et al (2009) Clinical trial: the impact of cyclooxygenase inhibitors on gastrointestinal recovery after major surgery—a randomized double blind controlled trial of celecoxib or diclofenac vs. placebo. Aliment Pharmacol Ther 30:987–998
42. Wells GA, O'Connell D, Peterson J, et al (2000) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. In: 3rd symposium on systematic reviews: beyond the basics, Oxford, 2000
43. Wind J, Polle SW, Fung Kon Jin PH et al (2006) Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg 93:800–809