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REVIEW

Colonic anastomoses and non-steroidal anti-inflammatory drugs

K. Slim^{a,*}, J. Joris^b, H. Beloeil^c, le Groupe Francophone de Réhabilitation Améliorée après Chirurgie (GRACE)^d

^a Service de chirurgie digestive, CHU Estaing, place Lucie-Aubrac, 63003 Clermont-Ferrand, France

^b Département d'anesthésie, CHU de Liège, Liège, Belgium

^c UMR 991, CIC 1414, service anesthésie-réanimation 2, université Rennes 1, 35000 Rennes, France

^d 9, allée du Riboulet, 63110 Beaumont, France

KEYWORDS

Colonic anastomosis;
Anastomotic leak;
NSAID;
Enhanced recovery

Summary Nonsteroidal anti-inflammatory drugs (NSAID) play an important role in the treatment of post-operative pain, particularly in the context of enhanced recovery after colorectal surgery. Several recent articles have suggested that NSAID may have a deleterious effect on colo-colic or colo-rectal anastomoses. The aim of this review is to analyze the evidence based on meta-analyses and cohort studies in the literature. A systematic review of clinical studies identified twelve studies including two meta-analyses and ten comparative cohort studies that included a large number of patients. The data in these studies are heterogeneous, often biased, and do not permit a formal recommendation based on a high level of evidence. The main conclusion of this review is that the balance of benefit vs. risk (analgesic effect/risk of anastomotic disruption) is acceptable; it appears (with a low level of evidence) that a prescription of NSAID for 48 h after surgery may be recommended for elective colon surgery. Nevertheless, it is important to respect the specific contra-indications of NSAID and avoid post-operative NSAID use if there are risk factors for anastomotic leakage: advanced age, malnutrition, severe co-morbidities, intra-operative difficulties.

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Introduction

Post-operative pain management has an essential place among the various elements of peri-operative care recommended in the context of enhanced recovery program after surgery (ERP) [1–3]. Pain management is based on a multimodal approach including local analgesia techniques that are started intra-operatively and often extended post-operatively (epidural, transversus abdominis plane [TAP] block, intravenous lidocaine, wound irrigation with

* Corresponding author.

E-mail address: kSlim@chu-clermontferrand.fr (K. Slim).

local anesthetic) along with systemically administered non-opioid analgesics (including NSAID). This strategy reduces the need for opioid analgesics with their gastrointestinal side effects of ileus, post-operative nausea and vomiting, and facilitates early mobilization and intensive ambulation with many benefits contributing to the success of ERP. Most of the recommendations by scientific societies insist on this multimodal approach [1–3]. However, some of the experimental data and recent clinical publications (detailed below) have suggested the possibility that post-operative NSAID use after colo-rectal surgery may result in an increased risk of anastomotic leak (AL). The aim of this review is to review the literature to better assess the risk of NSAID in colorectal surgery. We excluded from this analysis situations where NSAID are classically contra-indicated such as colorectal surgery performed in the emergency setting or for inflammatory bowel disease. This review addresses different aspects of this problem: the role of NSAID in the management of post-operative pain, the incidence of AL in elective colorectal surgery, evidence-based data from the literature on the relationship between NSAID use and AL, and possible mechanisms for this relationship.

Peri-operative NSAID use

Nonsteroidal Anti-inflammatory drugs inhibit cyclo-oxygenases (COX), thus preventing the formation of prostaglandins (Fig. 1), which contribute to post-surgical inflammation, sensitize and activate peripheral nociceptive nerve endings, and also sensitize the nerves of the dorsal horn of the spinal cord responsible for post-operative hyperalgesia. Prostaglandin synthesis primarily involves so-called inducible COX Type 2, because it is activated by surgical trauma. Inhibition of prostaglandin release explains both the analgesic and anti-hyperalgesic properties of NSAID.

Prostaglandins participate in various homeostatic processes such as gastric mucosal protection, renal physiology (vasodilation of pre-glomerular arterioles), and hemostasis. Prostaglandins are also involved in the healing process. Prostaglandin inhibition explains the main side effects of non-specific NSAID that inhibit both COX types 1 and 2 [4],

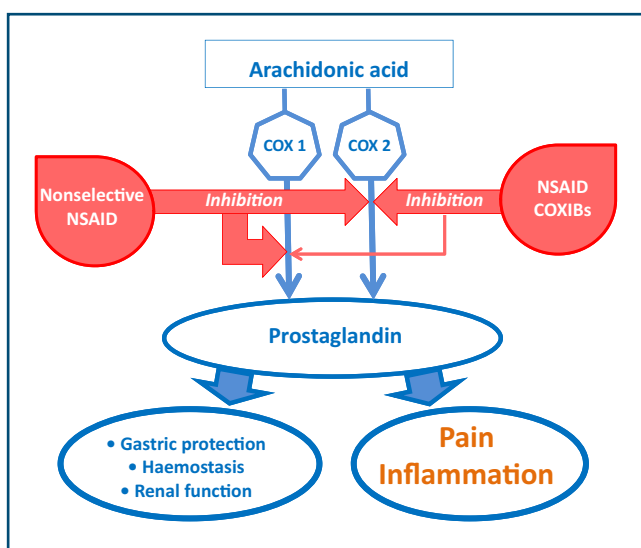


Figure 1. Mechanism of action of selective and non-selective NSAID used peri-operatively.

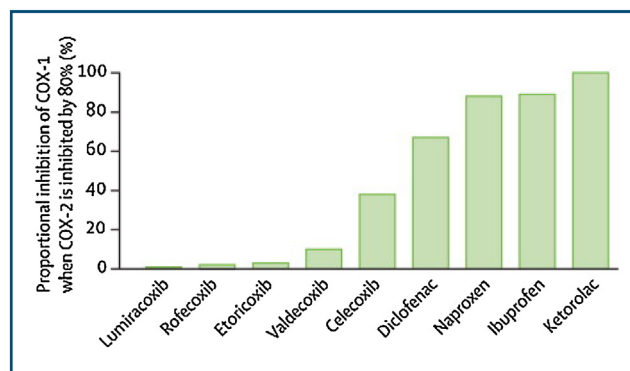


Figure 2. The degree of selectivity for COX-1 of non-selective NSAID and of COXIB (selective NSAID) when COX-2 is 80% inhibited. From Warner et Mitchell [6] with the permission of Lancet.

which will not be detailed in this article. It was long believed that the prostaglandin synthesis involved in the homeostatic process depended solely on the action of COX-1, also called constitutive. Therefore, the synthesis of specific COX-2 inhibitors (COXIB) nurtured the hope that NSAID would be able to exert their anti-inflammatory and analgesic properties without producing side effects. It is now known that constitutive COX-2's exist and also contribute to protective mechanisms. Also, while it is true that COXIB offer better gastro-intestinal tolerance, they share most of the other side effects of non-specific NSAID as shown in Fig. 2 [5,6].

Despite an abundant rheumatologic literature concerning the side effects of prolonged administration of NSAID, short-term administration is associated with a low incidence of adverse events [7] explaining why there is persistent interest in these painkillers for post-operative analgesia. Table 1 summarizes the most-commonly used NSAID in the post-operative period. Given that the concept of "selectivity" is altogether relative, the recent demonstration of NSAID-related cardiovascular risk, including COXIB, has obliged physicians to consider cardiovascular risk factors in their prescribing practices [8,9]. Finally, NSAID interference with the inflammatory response may be responsible for both beneficial and deleterious side effects. On the one hand, NSAID prevent the formation of peritoneal adhesions [10], are associated with a shorter duration of post-operative ileus [11], and reduce tumor recurrence [12], all of which may occur secondary to surgical inflammation. On the other hand, because NSAID reduce the inflammatory response necessary for wound healing, they could possibly increase the

Table 1 The most commonly used NSAIDs in the peri-operative period. The classification of NSAIDs as selective or non-selective is given for convenience but selectivity is entirely relative for all these drugs.

Non-selective NSAIDs	Selective NSAIDs-COXIBs or COX-2
Ibuprofen	Celecoxib
Ketoprofen	Etoricoxib
Ketorolac	Lumiracoxib
Aceclofenac	Parecoxib
Diclofenac	Rofecoxib
Naproxen	Valdecoxib
Piroxicam	
Tenoxicam	

Table 2 Summary of current recommendations by Learned Societies.

Society (year of publication)	Recommendation	Level of evidence	Grade of recommendation
ERAS (2013) [1,2]	There is not sufficient evidence to contra-indicate the use of NSAID as a component of multimodal post-operative analgesia	Medium	Strong
SFAR-SFCD (2014) [3]	NSAIDs are probably recommended for use after colorectal surgery although some doubts persist regarding the risk of anastomotic leak	Medium	Weak

incidence of AL after colorectal surgery. This is the subject of this review article.

Role of NSAID in the ERP programs for colorectal surgery

There is significant variability in the prescription of peri-operative NSAID for colorectal surgery [13]. Yet since the first description of the role of NSAID in multimodal or “balanced” analgesia by Dahl and Kehlet in 1991 [14], numerous publications have reported NSAID to be beneficial for post-operative analgesia, in all types of surgery including gastrointestinal surgery. The efficacy of NSAID, whether COX-2 selective or not, has been confirmed by several recent meta-analyses [15–17]. It is interesting to note that the decrease in morphine requirements seen with NSAID is greater than with other non-narcotic analgesics such as acetaminophen [16]. This “morphine-sparing” effect is accompanied by a corresponding decrease in opioid side effects such as nausea, vomiting and ileus. This finding, less notable with other analgesics, is obviously crucial to the success of ERP programs. In addition to the morphine-sparing effects of NSAID, pain scores were reduced, not only in patients at rest, but also during ambulatory mobilization and coughing (needs a reference). This property has a beneficial impact in ERP where early patient mobilization is a critical element. For all these reasons, NSAID analgesics are preferred for ERP, even after weighing their contra-indications [18].

Recommendations of Learned Societies

There are very few formal recommendations concerning ERP from learned societies (Table 2). In 2013, the ERAS® Society published a series of recommendations for different types of surgery including colorectal surgery [1,2]. The French Society of Anesthesia and Reanimation (SFAR) and the French Society of Gastrointestinal Surgery (SFCD) jointly issued recommendations for ERP after colorectal surgery [3]. Both of these sets of clinical practice guidelines, based on pre-2012 data, do not contra-indicate the use of NSAID for analgesia during the first 48 post-operative hours.

Anastomotic leaks in colorectal surgery

AL is the most commonly reported and most feared complication after colo-rectal surgery [19]. The incidence of AL ranges from 2 to 15% depending on the site of the anastomosis (ileo-colic, colo-colic, intraperitoneal or subperitoneal

colo-rectal, colo-anal) and various patient factors (age, comorbidity, malnutrition, alcohol and tobacco use), as well as surgical indications (cancer, diverticulitis, colitis), the stage of the disease in question, neo-adjuvant treatment, or factors related to the surgeon/anesthesiologist team and the surgical procedure (operative duration/operative difficulties, intra-operative blood loss, adequacy of blood supply to the anastomosis, peri-operative hypoxemia or volume deficits) [20,21].

Probable mechanism of the NSAID effect on colonic anastomosis healing

The actual mechanism by which NSAID increase the risk of AL has not been clearly demonstrated. Various mechanisms have been suggested to explain the possible deleterious effects of NSAID on the healing process of colonic anastomoses, such as a reduction in the production of cicatricial collagen or perhaps microthrombi. The results of experimental studies are sometimes contradictory [22–26]. By reducing prostaglandin production (Fig. 1), NSAID reduce the production of hyaluronic acid necessary for collagen formation in the healing of anastomoses.

Results of published studies

Several studies have evaluated the effect of NSAID on post-operative colorectal surgery [27–40]. Among the 12 articles we reviewed, two were meta-analyses [37,38], and ten were comparative clinical studies. We did not individually analyze the three comparative studies [27–29] that were also included in the meta-analyses. The cohort study by Klein et al. [30] is reviewed since it reported the most significant results of one of the two meta-analyses. The literature review of Rushfeldt et al. [39] was not included in this review because it is a qualitative review (neither systematic nor quantitative). Finally, STARS [40] is a cohort study that did not specifically analyze colorectal surgery.

The quality of original articles that were not included in the meta-analyses was assessed by the MINORS (Methodological Index for Non-Randomized Studies) score [41]. The quality of systematic reviews was assessed using PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) criteria [42].

Meta-analysis of experimental studies

The meta-analysis published by Bhangu et al. in 2014 [37] included 12 experimental studies that variously employed selective or non-selective NSAID. The rate of AL was

Table 3 Main characteristics and results of meta-analyses of clinical studies.

	Burton et al. [38]	Bhangu et al. [37]
Year of publication	2013	2014
PRISMA criteria [42]	24/27	23/27
Number of studies included	6	8
Ratio of RCS to NRS	6/0	5/3
Total number of patients	480	4668
Principal endpoint	Anastomotic disruption	Anastomotic disruption
Overall result (OR ^a)	2.16 (0.85–5.53)	2.14 (1.69–2.71)
Difference	5.1% vs. 2.4%	10.1% vs. 5.0%
Heterogeneity	No	No
Sub-group analysis	No	Yes (cf. text of article)
Authors' conclusions	No statistically significant difference was demonstrated. But the OR and the absence of heterogeneity suggest that lack of statistical significance is more likely due to the lack of power than to a negative finding	The results suggest a strong relationship between NSAID use and AL, even though the studies suffered from selection bias. The experimental and clinical data argue for caution in the use of NSAID in patients with risk factors for AL

RCS: randomized controlled study, NRS: non-randomised study; AL: anastomotic leak.
^a OR: odds ratio with CI^{95%}.

significantly increased with NSAID use, with an odds ratio (OR) of 9.5 (95% confidence interval [CI]: 4.6–19.5) for all NSAID, an OR of 8.3 (95% CI: 3.8–17.9) for non-selective NSAID, and an OR of 13.8 (95% CI: 2.6–72.1) for selective NSAID. It is important to note that the duration of post-operative NSAID use exceeded 48 h in most of the studies, the duration most widely recommended in clinical practice.

Meta-analysis of clinical studies

Two meta-analyses with good methodological quality (according to the PRISMA criteria) have been published [37,38]. The characteristics and results of these meta-analyses are summarized in Table 3. The meta-analysis by Burton et al. [38] showed that NSAID use doubled the relative risk of AL, but this increased risk did not reach statistical significance. It is likely that this lack of significance is related to small numbers and lack of statistical power, especially since this meta-analysis included only randomized controlled trials. The most interesting result was the finding that the increased risk of AL varied depending on the duration of NSAID administration and was low for a period of less than three days.

The meta-analysis by Bhangu et al. [37] included more cohort studies and more patients, allowing its authors to obtain results that were more statistically significant. The inclusion of the cohort study by Klein et al. [30] largely accounted for improved statistical power. Thus, the Bhangu meta-analysis offered statistically significant confirmation of the overall results of previous studies that had shown deleterious effects of NSAID (Table 3).

However, this meta-analysis has many flaws: the inclusion without distinction of randomized trials and cohort studies, the heterogeneity of the studies since only two studies considered confounding factors, and the absence of distinct factual data concerning results for the specific medications in question (diclofenac, ketorolac, celecoxib). Nevertheless, one can note that sub-group analysis showed no difference in the AL odds ratio depending on whether

selective or non-selective NSAID were used: non-selective NSAID (6 studies) OR=2.37 (95% CI: 1.7–3.3); selective NSAID (4 studies) OR=2.3 (95% CI: 0.7–7.6).

In this sense, subgroup analysis in the Klein cohort study [30] suggested that ibuprofen with an OR of 1.5 (95% CI: 0.8–2.90) had a lesser deleterious effect on colonic anastomoses than diclofenac with an OR of 7.2 (95% CI: 3.8–13.4).

Recent comparative studies (not included in the two meta-analyses)

None of the six studies that met our inclusion criteria were prospective. The results of these studies, summarized in Table 4, are sometimes divergent or even contradictory. Two studies had low numbers [31,32]. The study by Hakkarainen et al. [33] showed an increased risk of AL only when NSAID were used in the setting of emergency surgery (NSAID are not generally not indicated in this setting). The study by Paulasir et al. [34] showed no statistically significant difference. The study by Rutegård et al. [35] was specific to rectal surgery. The study by Kotagal et al. [36] concerned the use of ketorolac, a drug that is seldom prescribed in France, and was based on administrative data with a principal end-point of unscheduled re-operation for whatever cause. It is therefore difficult to draw factual conclusions concerning which class or type of NSAID may be deleterious, or the duration of treatment likely to promote post-operative complications. These studies also did not analyze the effect of NSAID as a function of other potential risks of AL such as the clinical setting, or the presence or absence of predisposing factors for AL after colorectal surgery (see above paragraph on AL in colorectal surgery). Because of the retrospective nature of the studies, confounding factors may not have been included in the published comparative studies.

The STARS study [40] is a prospective multicenter study that examined several types of surgeries. It was conducted over a two-week period in 2013 at 109 institutions in the UK and included 1503 patients, 242 of whom received NSAID.

Table 4 Comparative clinical studies evaluating the effect of NSAID on the risk of anastomotic disruption after colorectal surgery that were not included in the meta-analyses.

Authors Year of publication	Type of study	MINORS score [41] (maximum 24)	NSAID (class)	Duration of NSAID use (days)	Number of patients NSAID vs. controls	Anastomotic leaks (AL)	Severe morbidity	Conclusions Remarks
Zittel et al. [31] 2013	Retrospective	15	Etoricoxib (selective)	–	101 vs. 104		22.8% vs. 9.6% ($P=0.01$)	In multivariate analysis, etoricoxib was an independent risk factor for severe complications with a relative risk of 2.5 ($P=0.03$)
Saleh et al. [32] 2014	Prospective	12	Ketorolac	5	376 vs. 355	2.2% vs. 3.4%	–	No formal conclusion could be reached due to the retrospective nature of the study
Hakkarainen et al. [33] 2015	Retrospective	20	?	?	2194 vs. 6049	OR = 1.13 (CI ^{95%} 0.87–1.49)	–	NSAID was prescribed in 25% of operated patients during the period of the study (Registry). The risk of AL was especially increased in those patients treated with NSAID during emergency surgery
Paulasir et al. [34] 2015	Retrospective	18	?	1	1297 vs. 3063	OR = 1.33 (CI ^{95%} 0.86–2.05)	SSI: OR = 1.26 (CI ^{95%} 0.96–1.66)	The increased rate of SSI was at the limit of statistical significance and needs to be confirmed by other studies
Rutegård et al. [35] 2016	Retrospective	15	?	?	1458 vs. 1023	7% vs. 10.8% OR = 0.68 (CI ^{95%} 0.48–0.96)		The risk of AL, calculated after adjustment of other confounding factors, was reduced in the NSAID group. These results must be interpreted with caution in light of the retrospective nature of the study and because it was specifically limited to rectal surgery
Kotagal et al. [36] 2016	Retrospective ^a	16	Ketorolac	?	11,622 vs. 310,959	OR = 1.20 ^b (CI ^{95%} 1.06–1.36)	OR = 1.20 ^c (CI ^{95%} 1.08–1.32)	Ketorolac was significantly associated with an increase in readmissions, reinterventions and post-operative digestive surgery consultations

SSI: surgical site infection.
^a Analysis based on administrative data.
^b Global results (no colorectal surgery sub-group) and the endpoint was: readmission for anastomotic complication.
^c Global results (no colorectal surgery sub-group) and the endpoint was: unscheduled surgical reintervention.

After various adjustments, it showed that NSAID (various molecules) were associated with a significant reduction in the risk of post-operative complications (OR 0.72, 95% CI: 0.52–0.99; $P=0.04$) without a significant increase in AL (OR 1.30, 95% CI: 0.61–2.68; $P=0.48$). This “beneficial” effect was not significant with regard to major complications. However, these results should be interpreted with caution because of the small number of patients in the study who actually received NSAID. These favorable results are at odds with those of the two previously cited meta-analyses [37,38], but we have seen that both meta-analyses had major limitations due to heterogeneity while their methodological quality was not optimal, particularly because of the quality of the included studies (according to the concept: “garbage in – garbage out”). Furthermore, all the major cohort studies were retrospective. Either they did not offer factual evidence of a significantly increased risk of AL with NSAID [34], or they confirmed the deleterious effect of NSAID only in the context of emergency surgery [33], or they suggested (as did the STARS study [40]) a possible beneficial effect after adjustment for confounding factors [35].

Conclusion

This systematic review of the literature aimed to assess the potential deleterious effect of NSAID usage after colorectal surgery (as reflected by the incidence of AL); it has failed to provide a factual answer with a high level of evidence. It appears that the risk has been overestimated in two published meta-analyses. Moreover, even though the methodological quality of most of the recent comparative studies is not optimal (retrospective collection, failure to consider confounding factors, no specific analysis of specific NSAID), the large number of patients included suggests that the deleterious effect of NSAID has been overestimated and that a short 48 h course of NSAID may be recommended as long as there are no surgical conditions that threaten the quality of the anastomosis (see Key points). The standard contra-indications of NSAID, however, remain valid.

Key points:

- NSAID play a major role in the management of post-operative pain.
- The suggested relation between NSAID use and the risk of AL has recently been called into question.
- While some studies have included large numbers of patients, the patient samples are very heterogeneous.
- Meta-analyses suggest that a short course (48 hours) of post-operative NSAID administration is not deleterious in the setting of ERP.
- Few studies have analyzed the confounding factors for AL that may bias the interpretation of results with NSAID use.
- NSAIDs should not be used if there are risk factors for the development of AL: advanced age, malnutrition, severe co-morbidities, intra-operative difficulties, etc.
- Large randomized studies are needed to better evaluate the hypothetical relation between NSAID use and AL.
- Contra-indications to NSAID use should be respected throughout the peri-operative period.

Disclosure of interest

The authors declare that they have no competing interest.

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