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REVIEW

Colonic anastomoses and non-steroidal anti-inflammatory drugs



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KEYWORDS

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NSAID;
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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

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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 cyclooxygenases (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],

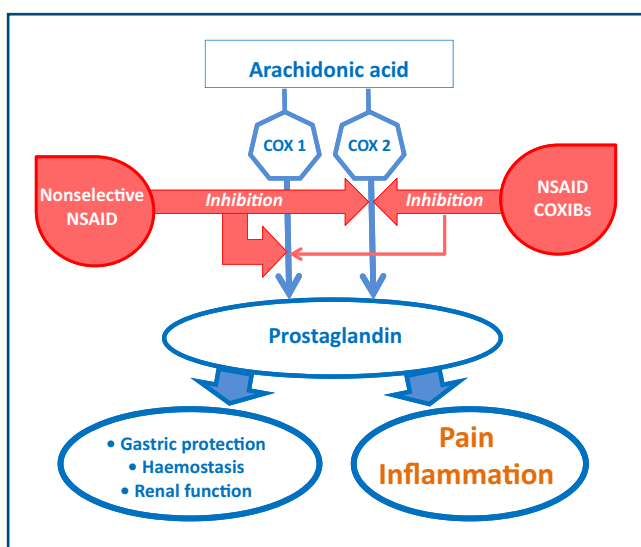


Figure 1. Mechanism of action of selective and non-selective NSAID used peri-operatively.

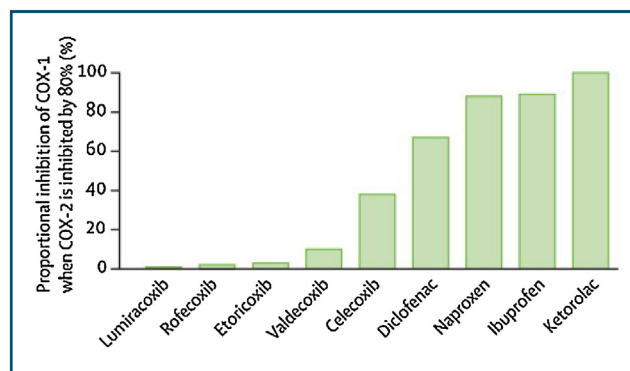


Figure 2. The degree of selectivity for COX-1 of non-selective NSAID and of COXIB (selective NSAID) when COX-2 is 80% inhibited. From Warner et Mitchell [6] with the permission of Lancet.

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	

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