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Review Article

Non-steroidal anti-inflammatory drugs in the oncological surgical population: beneficial or harmful? A systematic review of the literature

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Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesic drugs. Recent studies have indicated a potential beneficial effect on long-term survival outcomes after cancer surgery but a negative impact on anastomotic leaks. The objective of this study was to objectively assess the implications of the perioperative NSAIDs use on anastomotic leaks and cancer recurrence.

Methods: We searched PubMed, MEDLINE, Embase and Cochrane Library for publications up to mid-January 2017. Randomized controlled trials (RCTs) and observational studies in adults undergoing cancer surgery were included for quality assessment. We excluded animal studies, *in vitro* experiments and case reports. The selected sudies were graded using the Jadad score or Newcastle–Ottawa scale for RCTs and observational retrospective studies, respectively.

Results: The systematic review identified 25 trials that explored the impact of NSAIDs on anastomotic leaks and 16 trials that assessed the association between perioperative NSAIDs and cancer recurrence. Meta-analyses were not performed because of high heterogeneity and low quality of the included studies.

Conclusions: The literature is not conclusive on whether the use of NSAIDs is associated with anastomotic leaks after gastrointestinal cancer surgery. Also, the current evidence is equivocal regarding the effects of short-term NSAIDs on cancer recurrence after major cancer surgery. Three RCTs are being conducted to assess the impact of NSAIDs on cancer recurrence. There are no registered RCTs that are testing the hypothesis of whether the perioperative use of NSAIDs increases the rate of anastomotic leaks.

Key words: analgesics; general surgery; neoplasms; recurrence

The current evidence suggests that the perioperative period plays a significant role in patients with potentially curable solid tumours.[1–3] It has been suggested that the analgesics used during and after surgery might not only have a major impact on short-term outcomes but also on long-term outcomes such as cancer recurrence.[4 5] Analgesic strategies for cancer surgery are evolving from the systemic administration of i.v. opioids *via* patient-controlled analgesia (IV-PCA) to the combination of regional analgesia techniques and systemic non-opioid analgesics (i.e. multimodal analgesia).[6–8] Non-steroidal anti-inflammatory drugs (NSAIDs), which include both traditional NSAIDs and cyclooxygenase (COX)-2-specific inhibitors (coxibs), have been demonstrated to play an important role in multimodal analgesia for oncological surgery.

A meta-analysis of randomized controlled trials (RCTs) demonstrates that NSAIDs reduce opioid consumption, vomiting and sedation by 30%, 32% and 29%, respectively.[9] Furthermore, the administration of NSAIDs is associated with improvement in the quality of recovery and satisfaction.[10] Hence, they are currently recommended for enhanced recovery after surgery protocols for gastrointestinal cancer surgery; however, several clinical studies have suggested an association between the use of NSAIDs and anastomotic leaks after gastrointestinal surgery.[11–16]

In the present systematic review, we assessed the evidence regarding the use of NSAIDs during oncological surgery and their impact on anastomotic leaks and cancer recurrence.

Methods

Literature search

Two independent series of database searches were performed covering each of the topics of the review: (1) NSAIDs and anastomotic leaks, and (2) NSAIDs and postsurgical cancer recurrence. The databases searched for each topic were Medline (Ovid), Embase (Ovid), Cochrane Library (Wiley) and the non-Medline portion of PubMed (NLM). These databases were searched from inception through to mid-January 2017. A medical librarian with more than 25 years of database-searching experience conducted all the literature searches.

The search strategies for both series of literature searches consisted of a combination of controlled vocabulary (e.g. MeSH) and keyword terms. NSAID-related terms were searched at both the drug class and individual drug name level and included common acronyms. Variations of anastomotic leak terms that were searched included anastomotic failure, dehiscence, complications, perforations and healing. The postsurgical cancer recurrence search strategy incorporated common surgical procedures in cancer patients, such as craniotomy, lobectomy, lumpectomy and prostatectomy. To help ensure no cancer recurrence records were missed, survival (cancer surgery or recurrence or survival or relapse or disease-free or progression free) and metastasis-related (metastasis or micrometastasis) search terms were added to the search strategies. Additional articles were retrieved by manually searching the reference lists in included studies as well as other review articles.

Inclusion and exclusion of trials

Inclusion criteria for studies that assessed anastomotic leaks included: (1) RCTs and observational cohort studies published in English language, (2) studies including adult patients, (3) reports including patients undergoing oncological surgery, (4) publications including treatment with a single dose or multiple doses of NSAIDs before (within 24 h from surgery), during or after surgery (within 30 days), and (5) investigations that reported anastomotic leak, cancer recurrence or survival endpoints as primary or secondary outcomes. Exclusion criteria: (1) animal studies, (2) *in vitro* studies, and (3) case reports. Also, studies that recruited both cancer and non-cancer patients and did not provide data on primary or secondary outcomes were not included. Outcome measures assessed for studies on anastomotic leaks included postoperative upper or lower gastrointestinal anastomotic leaks as assesed by radiological techniques or need for surgical re-intervention. Studies that did not report anastomotic leaks using these definitions were excluded.

Studies assessing the effects of NSAIDs on postoperative cancer outcomes such as cancer recurrence rate, recurrence-free survival, disease-free survival, cancer-specific survival and/or overall survival were included.

Selection of studies and quality assessment

Two authors (J.P.C. and V.G.) independently screened titles and abstracts for inclusion. A third author resolved any disagreements between the two reviewers. Included studies were assessed for quality using the Jadad score and Newcastle–Ottawa scale for RCTs and observational retrospective studies, respectively. The analysis included studies only graded as high quality (i.e. Jadad score $\geq$3 or Newcastle–Ottawa score $\geq$8). The information from each included study was extracted according to the list of outcome measures discussed above.

Results

Perioperative NSAIDs and anastomostic leaks

Two hundred and seventeen titles were retrieved from the literature search. Figure 1 illustrates the PRISMA flow diagram to detail the literature search and selection process. Of the 45 studies that were thoroughly reviewed, 25 studies were considered for quality assessment, which included nine RCTs or meta-analysis of RCTs and 16 observational trials. Seven studies were excluded because of low quality. The remaining studies were not included in a quantitative analysis because of the following issues: (1) mixed population of risk of anastomotic leaks (high risk *vs* low risk) and/or cancers (colorectal *vs* hypopharyngeal tumours), (2) anastomotic leak was not the primary outcome in any of the RCTs, and (3) inconsistent NSAIDs type, dose and duration of administration. While several observational studies did have anastomotic leaks as the primary outcome, only six reported the outcome of interest in cancer patients. The remaining studies included a mixed population of cancer and non-cancer patients. Tables 1 and 2 contain the data extracted from each of the included studies.

Perioperative NSAIDs and cancer recurrence

A total of 550 titles were retrieved from the literature search. The PRISMA flow diagram to detail the literature search and selection process is included in Figure 2. Of the 30 studies that were fully reviewed, 14 were excluded because they were narrative review articles, case reports or laboratory studies. Sixteen studies underwent quality assessment. Five studies were scored as low quality. Despite being high quality, the remaining studies did not enter into a quantitative analysis because they: (1) included different cancer histologies or tumour stages, and (2) did not consistently report on NSAIDs type, dose, time and