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Nonsteroidal anti-inflammatory drugs and the risk of anastomotic leakage after anterior resection for rectal cancer☆

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used in colorectal surgery due to their opioid-sparing effect. However, several studies have indicated an increased risk of anastomotic leakage following NSAID treatment, although conflicting results exist. The primary goal of this study was to further examine whether postoperative NSAIDs are independently associated with anastomotic leakage after anterior resection for rectal cancer.

Methods: Patients who underwent anterior resection for rectal cancer during 2007–2013 in 15 different hospitals in three healthcare regions in Sweden were included in the study. Registry data and information from patient records were retrieved. The association between NSAID treatment (for at least two days in the first postoperative week) and symptomatic anastomotic leakage (within 90 days) was evaluated with multiple logistic regression, with adjustment for pertinent confounding factors.

Results: Some 1495 patients were included in the study. Of these, 27% received postoperative NSAIDs for at least two days in the first postoperative week. Symptomatic anastomotic leakage occurred in 11% and 14% in the NSAID and non-NSAID group, respectively. With adjustment for confounders, the odds ratio for leakage among patients who received NSAIDs compared with those who did not was 0.88 (95% CI 0.65–1.20). No differences were seen between non-selective and COX-2-selective NSAIDs.

Conclusion: Postoperative NSAID treatment does not seem to increase the risk of symptomatic anastomotic leakage after anterior resection for rectal cancer. NSAID use appears to be safe, but a well-powered randomized clinical trial is warranted.

Keywords: NSAID; COX-2 selective; Non-selective; Anastomotic dehiscence; Postoperative complications

Introduction

When treating tumours in the upper and mid rectum, anterior resection is usually performed. Following this procedure, 10–19% of patients suffer an anastomotic leakage[1–3] which leads to increased risk of mortality,[3] impaired anorectal function,[4] permanent stoma[1,5] and possibly an increased risk of local and systemic recurrence.[6]

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Along with the implementation of accelerated postoperative care programmes, such as enhanced recovery after surgery,[7] nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used in order to decrease opioid usage, in attempts to reduce negative effects on return of bowel function and length of hospital stay.[8,9] NSAIDs exert their analgesic effect by inhibiting the enzymes cyclooxygenase (COX) 1 and 2, involved in prostaglandin synthesis. However, several experimental and retrospective studies indicate an association between postoperative use of NSAIDs and anastomotic leakage,[10–14] a suggested explanation of which has been reduced collagen production and impaired angiogenesis after NSAID treatment.[15,16] Although this association is not confirmed, several surgical centres have, following these reports, ceased to use NSAIDs as analgesics after colorectal surgery where an anastomosis has been constructed.[17] Furthermore, previous research has evaluated colorectal resections in general, although there might be differences between colonic and colo-rectal anastomoses regarding anastomotic healing.

The primary goal of this study was to further investigate the association between postoperative treatment with NSAIDs and the risk of anastomotic leakage after anterior resection for rectal cancer. As a secondary goal, we wanted to evaluate whether this association differs between the two main subtypes of NSAIDs: non-selective and COX-2 selective agents.

Methods

Study design

This is a retrospective multi-centre cohort study. Eligible for inclusion were all patients operated with anterior resection for rectal cancer during 2007–2013 in 15 different hospitals in the Northern, Southern and Western healthcare regions in Sweden. These patients were identified through the Swedish Colorectal Cancer Registry,[18] which contains a comprehensive amount of information regarding patient demographics, the surgical procedure, postoperative course, oncological treatment and pathological assessment. Registrations in the registry were reported for the period 1995–2003 and were found to represent almost complete coverage of patients with rectal cancer in Sweden.[18] The completeness of the registry is maintained by regularly checking it against the national cancer registry, which receives notification of new cancer cases from both clinicians and pathologists. The regional ethical review boards at Umeå University and the University of Gothenburg approved the study.

Data collection and definition of study exposure and outcome

The following clinical and demographic data were collected from the registry: age, sex, American Society of Anaesthesiologists (ASA) class, body mass index, neoadjuvant therapy, TNM tumour stage, open or laparoscopic surgery, intraoperative blood loss and 90-day mortality. Medical records were studied for information on smoking status (current smoker [≤2 weeks of preoperative cessation] or non-smoker), comorbidities (kidney disease requiring medication, diabetes mellitus requiring medication, ischaemic heart disease, severe pulmonary disease, rheumatic disease, and systemic steroid treatment), type of mesorectal excision, and presence of diverting stoma.

Medical records were also studied for information on the study exposure and outcome. The main study exposure was defined as treatment with any NSAID for at least two days within the first week after surgery. Type of NSAID (active agent), duration of use until hospital discharge, first postoperative day of treatment and total dosage were recorded. A dose of postoperative NSAID was only registered if it was recorded as taken by the patient, as indicated in the digital or analogous charts maintained by the nursing staff.

The primary outcome was symptomatic anastomotic leakage within 90 days of surgery. Patients who had a leakage diagnosed before the third postoperative day were excluded from the study, as these leaks were considered to be caused by a probable technical error, rather than NSAID treatment. This is supported by the notion that anastomotic strength is minimal during the first two days after surgery, before new collagen can be produced,[19] and is thus dependent on the sutures or staples during that time. Leakage was defined as leakage from any staple or suture line, pelvic abscess (without radiologically proven leakage) or rectovaginal fistula, in accordance with previous research.[1] The leaks were categorized according to the grading system proposed by the International Study Group of Rectal Cancer (ISREC); type A leaks result in no change in patients' management, type B leaks require treatment other than laparotomy, and type C leaks require laparotomy.[20] The diagnosis was made by the treating clinicians using radiological (rectal contrast study, computerized tomography, magnetic resonance imaging), endoscopic (rigid or flexible sigmoidoscopy), or clinical (digital palpation, inspection of drain contents, or verified at laparotomy) investigations.

Statistical analyses

Distributional differences of the baseline characteristics between the tie levels were analyzed using Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Multiple logistic regression was performed to evaluate postoperative treatment with NSAID as an independent predictor for anastomotic leakage, striving to determine the total effect of the exposure on the outcome. The covariates included in the adjustment set were determined from a

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