Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery


Abstract

Background: With the implementation of multimodal analgesia regimens in fast-track surgery programmes, non-steroidal anti-inflammatory drugs (NSAIDs) are being prescribed routinely. However, doubts have been raised concerning the safety of NSAIDs in terms of anastomotic healing.

Methods: Data on patients who had undergone primary colorectal anastomosis at two teaching hospitals between January 2008 and December 2010 were analysed retrospectively. Exact use of NSAIDs was recorded. Rates of anastomotic leakage were compared between groups and corrected for known risk factors in both univariable and multivariable analyses.

Results: A total of 795 patients were divided into four groups according to NSAID use: no NSAIDs (471 patients), use of non-selective NSAIDs (201), use of selective cyclo-oxygenase (COX) 2 inhibitors (79), and use of both selective and non-selective NSAIDs (44). The overall leak rate was 9.9 per cent (10.0 per cent for right colonic, 8.7 per cent for left colonic and 12.4 per cent for rectal anastomoses). Known risk factors such as smoking and use of steroids were not significantly associated with anastomotic leakage. Stapled anastomosis was identified as an independent predictor of leakage in multivariable analysis (odds ratio (OR) 2.22, 95 per cent confidence interval 1.30 to 3.80; P = 0.003). Patients on NSAIDs had higher anastomotic leakage rates than those not on NSAIDs (13.2 versus 7.6 per cent; OR 1.84, 1.13 to 2.98; P = 0.010). This effect was mainly due to non-selective NSAIDs (14.5 per cent; OR 2.13, 1.24 to 3.65; P = 0.006), not selective COX-2 inhibitors (9 per cent; OR 1.16, 0.49 to 2.75; P = 0.741). The overall mortality rate was 4.2 per cent, with no significant difference between groups (P = 0.438).

Conclusion: Non-selective NSAIDs may be associated with anastomotic leakage.

Critical appraisal

Value of the article

The article provides a retrospective data analysis addressing an important research question related to the risk of anastomotic leakage with the use of non-steroidal anti-inflammatory drugs (NSAID) after colorectal surgery within
the enhanced recovery protocol. The majority of cases were carried out by open surgery and the study showed a significant increase in anastomotic leakage in patients using any NSAID: the most profound effect was found in the group that used non-selective NSAIDs compared to selective COX2 inhibitors. A significant relationship was also found between the duration of NSAID use within the first 5 days after surgery and anastomotic leakage. Use of any NSAID for 3 days or more was associated with a higher rate of anastomotic leak than use for only 1 or 2 days (16.6 vs. 10 %, respectively). In addition, the study showed that stapled anastomosis was identified as an independent predictor of leakage in multivariable analysis with an odds ratio 2·22. However, as the authors acknowledged that study was not designed to investigate this as an endpoint, this result must be interpreted with caution. There was no influence of NSAIDs on leakage from stapled versus handsewn anastomoses.

**Strengths of the article**

A large series of 792 patients undergoing colorectal surgery included in the analysis and divided into 4 groups according to the utilization of NSAIDs. The groups were well-matched in perioperative characteristics relevant variables for anastomotic leakage despite the lack of randomization. Sound statistical analysis was carried out using multivariable logistic regression models and Odd ratios were calculated and provided with 95 per cent confidence intervals.

**Weaknesses of the article**

As recognized by the authors, the main limitation of this paper was the non-randomized and observational nature. Possible confounding factors may have introduced when patients received more NSAIDs because of higher pain levels caused by greater surgical trauma, or indeed by the anastomotic leakage itself. Also the groups were disproportionate as the non-NSAID group had 471 patients while the combined NSAIDs group had only 44 patients. In addition, the overall anastomotic leak was 11.7% which seems to be higher than what is usually reported in large RCTs although the authors acknowledged that their anastomotic leak rate is in accordance with the Dutch Surgical Colorectal Audit register of 2010.

**Comments**

The article raises a concern that is concordant with the prospective data published by Klein in BMJ 2002; Kehlet’s seminal paper in BJS 2009 and many animal studies (Ronan Cahill’s letter in Ann Surg 2006). However, the level of evidence so far is not robust enough. The findings of this article must be taken with caution prior to changing practice of routine use of NSAIDs at the post-operative recovery after colorectal surgery. Further larger studies are required in this field.
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