EVIDENCE-BASED REVIEWS IN SURGERY

# A systematic review and meta-analysis of postoperative use of NSAIDs and risk of anastomotic leak

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## Selected article

Smith SA, Roberts DJ, Lipson ME, et al. Postoperative nonsteroidal anti-inflammatory drug use and intestinal anastomotic dehiscence: a systematic review and meta-analysis. *Dis Colon Rectum* 2016;59:1087–97.

## Key points about the article

**Background:** Enhanced recovery after surgery (ERAS) including use of nonsteroidal anti-inflammatory drugs (NSAIDs) is considered the standard of care for most abdominal operations. However, there is controversy around the association between these drugs and anastomotic dehiscence. **Study objective:** To determine whether postoperative NSAID use was associated with intestinal anastomotic dehiscence. **Methods:** The meta-analysis included published randomized controlled trials (RCTs) and observational studies that compared postoperative NSAID use with nonuse and reported on intestinal anastomotic dehiscence. Key databases searched were PubMed, EMBASE and CENTRAL, without date or language restriction. **Results:** The study included 6 RCTs that included anastomotic dehiscence as a secondary outcome ($n$ = 473) and 11 observational studies ($n$ = 20 184). Among RCTs, pooled analyses revealed that NSAID use was clinically but not statistically associated with anastomotic dehiscence (relative risk [RR] 1.96, 95% confidence interval [CI] 0.74–5.16, $I^2$ = 0%). Among observational studies, pooled analyses revealed that NSAID use was significantly associated with anastomotic dehiscence (odds ratio [OR] 1.46, 95% CI 1.14–1.86, $I^2$ = 54%). **Conclusion:** The RCTs included in the meta-analysis were of high methodologic quality, although none included a prespecified definition of anastomotic dehiscence. Five of the 11 observational studies did not include a clear definition of criteria for anastomotic dehiscence. None accounted for preoperative NSAID use. The authors concluded that postoperative nonselective NSAID use compared with nonuse was associated with significantly higher odds of intestinal anastomotic dehiscence. We surmise that this meta-analysis represents the best available evidence to date. However, the small negative impact of NSAID use on anastomotic leak must be weighed against the potential benefits in postoperative pain and recovery.

## Commentary

The era of enhanced recovery after surgery (ERAS) has fuelled a massive increase in the use of NSAIDs.[1] They function as inhibitors of the cyclo-oxygenase inflammatory pathway and have become a useful alternative to narcotic pain medication given the latter's physiologically depressive and potentially addictive adverse effects. Clinical studies of intestinal surgery have shown a plausible causal association between ERAS protocols and decreased postoperative ileus, reduced length of stay, reduced readmission rates and greater patient satisfaction.[2,3] Consequently, ERAS, including NSAID use, is now considered the standard of care for most abdominal operations.[4]

Several clinical and experimental studies have noted, however, that NSAIDs may impair wound healing through inhibition of collagen deposition among other mechanisms.[5–7] Such concerns are particularly relevant to intestinal surgery because of the potentially devastating effects of anastomotic dehiscence, which has been linked to high rates of urgent reoperation, prolonged hospitalization, an up to 4-fold increase in short-term mortality and a 2-fold increase in long-term mortality.[8] Thus far, no previously published RCTs studying the effect of NSAIDs on outcomes of intestinal surgery have been adequately powered to examine the risk of anastomotic dehiscence because of its uncommon occurrence.

To address this study question, Smith and colleagues[9] conducted a meta-analyses of 6 published RCTs that included anastomotic dehiscence as a secondary outcome ($n$ = 473) and of 11 observational studies ($n$ = 20 184). For such a question, combining results from RCTs is useful because randomization ideally would eliminate the effect of unrecognized confounders as long as between-study heterogeneity is minimal. After the initial screening search, the investigators achieved outstanding agreement on article selection ($\kappa$ = 0.92, 95% CI 0.82–1.00) and found no statistical evidence of between-study heterogeneity ($I^2$ = 0%, Cochrane Q test $p$ = 0.84). While the RCTs were of high methodological quality, none prespecified a definition for anastomotic dehiscence.

Inclusion of observational studies enhanced the validity of the meta-analysis because it permitted pooling of a very large number of cases — but it also introduced bias. In observational studies, accounting for potential confounders is paramount, and only 1 study accounted for the most important confounders. The studies were moderately heterogeneous ($I^2$ = 54.4%, Cochrane Q test $p$ = 0.02) and none accounted for preoperative NSAID use. In addition, although anastomotic dehiscence was the outcome of interest, only 6 of 11 studies prespecified a definition for it. Smith and colleagues[9] attempted to minimize bias with numerous stratification and sensitivity analyses to substantiate their other findings.

### *What were the results?*

Among RCTs, pooled analyses revealed that NSAID use was clinically but not statistically associated with anastomotic dehiscence (RR 1.96, 95% CI 0.74–5.16, $I^2$ = 0%). The wider CI in this case reflects a small sample size — only 5 studies involving 249 participants in total were analyzed — and larger standard deviation. Among

observational studies, pooled analyses revealed that NSAID use was significantly associated with anastomotic dehiscence (OR 1.46, 95% CI 1.14–1.86, $I^2$ = 54%), and in this case the effect size was quite precise. The results were robust to a sensitivity analysis that showed a larger rather than the expected smaller effect size among studies that accounted for more than 4 potential confounding variables (OR 1.60, 95% CI 1.25–2.05, $I^2$ = 46%). Based on these findings, the authors concluded that postoperative nonselective NSAID use compared with nonuse was associated with significantly greater odds of intestinal anastomotic dehiscence.

### *Can the results be applied to my patients?*

The conclusions from these paired meta-analyses should compel surgeons to carefully weigh the increased use of NSAIDs in clinical practice. It is unlikely that substantively higher-quality data pertaining specifically to anastomotic dehiscence will become available given the prohibitively high enrolment required, especially if nonpelvic anastomoses are included. In the broader context of postoperative recovery, where NSAID use is only part of a multifaceted approach to optimizing recovery, the small difference in anastomotic healing may be negligible or negated if the overall benefits of NSAID use result in less pain and quicker discharge from hospital for the vast majority of patients. A composite outcome measure that incorporates multiple outcomes relevant to NSAIDs would be useful. Additional studies could help to elucidate an algorithm for tailoring the "best" ERAS regimen, including choice of NSAID, duration and dose, to individuals based on appropriate selection.

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