

## NSAID use and Colorectal Anastomotic Leaks. Caution and Further Investigation

Imran Hassan

Received: 21 May 2014 / Accepted: 29 May 2014 / Published online: 11 June 2014  
© 2014 The Society for Surgery of the Alimentary Tract

Non-steroidal anti-inflammatory drugs (NSAIDs) are an integral component of the postoperative analgesic regimen, particularly in enhanced recovery protocols for elective colorectal resections. They are administered to reduce opioid requirements and mitigate the side effects of narcotics on the gastrointestinal tract. Recently however, there have been reports in the literature that have raised the possibility of an association between the use of NSAIDs and an increased risk of colorectal anastomotic leaks (AL).<sup>1–4</sup>

The therapeutic effects of NSAIDs are due to their inhibition of the enzyme cyclooxygenase (COX) that occurs as two main isoforms, COX-1 and COX-2. This inhibition results in the decreased synthesis of prostanoids which are important mediators of inflammation and pain. NSAIDs are categorized based on the extent of inhibition of these isoforms as being either COX-2 selective or non-selective. However, the potency and selectivity of the different commercially available NSAIDs differ, as even non-selective inhibitors can preferentially inhibit COX-1. The exact mechanism by which NSAIDs result in an increased risk of AL remains unclear, but it is believed that the inhibition of COX interferes with the normal inflammatory processes necessary for wound repair including healing of intestinal anastomosis.<sup>5</sup>

Ketorolac is a commonly used NSAID that primarily inhibits COX-1, although it is classified as a non-selective inhibitor. In this issue of the *Journal of Gastrointestinal Surgery*, two reports have been published that have investigated the relationship between the postoperative use of ketorolac and the risk of AL. While both studies have asked the same research question, they have come up with conflicting findings.

In the first study by Saleh et al., using a retrospective cohort study design, 731 patients undergoing elective colorectal resections between 2004 and 2011 at the University Health Network, Toronto, were analyzed. Half of these patients ( $n=376$ , 51.4 %) received ketorolac as a part of their analgesic regimen. Using univariate analysis and multivariate logistic regression, the authors evaluated the association between ketorolac use in the first 5 days after surgery and AL. They reported an approximately 3 % ( $n=24$ ) incidence of AL, with 12 leaks in each group. After adjusting for smoking, steroid use, and age, there was no significant association between ketorolac use and AL. The second study by Govindarajan et al. was a nested case-control study that included elective colorectal resections performed between 2001 and 2012 at the Mount Sinai Hospital, Toronto. One hundred and thirty-one cases were identified based on the occurrence of a postoperative AL from a prospective database. Controls were selected using 1:1 case matching based on underlying diagnosis, type of surgery, age, gender, and year of surgery. In their adjusted analysis, the use of ketorolac was associated with a significantly higher risk of AL (OR 2.09, 95 % CI 1.12–3.89,  $P=0.021$ ).

While both studies looked at the same primary endpoint, there are distinct differences between the study populations that could account for the divergent findings. The study by Saleh et al. predominantly included patients in their 60s who were undergoing surgery for colorectal cancer (65 %) or other benign colorectal pathology (30 %), with only a minority having surgery for inflammatory bowel disease (IBD) (4 %). Conversely, the study population analyzed by Govindarajan et al. was younger, with the average age being in the 40s, and mainly included patients with IBD (65 %) with the remaining 35 % of patients undergoing surgery for cancer. Another difference was that the most common operation in one cohort was a right colectomy (42 %) and in the other, it was an ileal pouch anal anastomosis (IPAA) (46 %). Both these procedures

---

I. Hassan (✉)  
Department of Surgery, University of Iowa, Iowa City, IA, USA  
e-mail: imran-hassan@uiowa.edu

are almost at the opposite ends of the spectrum for the risk of AL, with ileocolic anastomosis having a much lower leak rate than an undiverted IPAA. Finally, one study reported a 79 % re-operative intervention rate for AL, while the other had a much lower rate of 31 %. This suggests that there may have been some variation in how AL were defined and diagnosed in both the reports.

Like all observational studies, both studies are susceptible to bias and confounding. The authors have attempted to control for this by using sophisticated study designs and analytical techniques, but the fact remains that they can only adjust for measured confounders. The underlying etiology of colorectal AL is multifactorial and is impacted by patient-, disease-, and treatment-related factors such as operative technique, intraoperative complications and conditions, patient age, comorbidity, nutrition, extent and nature of immunosuppression, and the underlying disease. While certain variables have been accounted for, some have not been, in both studies raising the possibility of residual confounding.

Despite limitations, these reports draw our attention to an important issue in the management of patients undergoing colorectal surgery. Adequate pain control is an important part of postoperative care however AL have significant and serious consequences. While most of the risk factors for AL are not

necessarily modifiable, those that can be changed should certainly be addressed. Whether NSAID use is indeed a clinically relevant risk factor for anastomotic complications still requires further investigation, but some caution is certainly warranted.

## References

1. Burton TP, Mittal A, Soop M. Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence in bowel surgery: systematic review and meta-analysis of randomized, controlled trials. *Dis Colon Rectum*. Jan 2013;56(1):126-134.
2. Gorissen KJ, Benning D, Berghmans T, et al. Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. *Br J Surg*. May 2012;99(5):721-727.
3. Holte K, Andersen J, Jakobsen DH, Kehlet H. Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery. *Br J Surg*. Jun 2009;96(6):650-654.
4. Klein M, Gogenur I, Rosenberg J. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. *BMJ*. 2012;345:e6166.
5. Klein M, Krarup PM, Burcharth J, et al. Effect of diclofenac on cyclooxygenase-2 levels and early breaking strength of experimental colonic anastomoses and skin incisions. *Eur Surg Res*. 2011;46(1):26-31.