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Commentary: Enhanced recovery after surgery: Does ketorolac get in the WAE of anastomotic healing following esophagectomy?

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CENTRAL MESSAGE

As part of a multimodal, opioid-limiting, Enhanced Recovery After Surgery protocol, ketorolac does not increase the risk of anastomotic leak following esophagectomy.

Following the success of Enhanced Recovery After Surgery (ERAS) protocols for lower gastrointestinal malignancies,¹ similar pathways have emerged for patients undergoing esophagectomy.^{2,3} By standardizing perioperative patient care, ERAS pathways have the potential to improve the quality and efficiency of perioperative patient care, thereby reducing hospital length of stay, health care costs, perioperative morbidity, and potentially enhancing patient-centered outcomes.⁴ Central to ERAS pathways is multimodal perioperative analgesia, which often include selective or nonselective non-steroidal anti-inflammatory drugs (NSAIDs).⁵

During wound (anastomotic) healing, cyclooxygenase converts arachidonic acid into prostaglandins, which play a central role in orchestrating a number of essential events, such as the activation of wound-associated epithelial (WAE) cells and fibroblasts.⁶ These actions are critical for promoting epithelialization of and providing tensile strength to the anastomosis. Therefore, cyclooxygenase inhibitors carry a theoretical risk of increasing the risk of

anastomotic leaks. Indeed, there is (albeit not strong) evidence that NSAIDs may increase the risk of a leak following colectomy or proctectomy.⁷ Therefore, the possible benefits of NSAIDs in ERAS pathways must be balanced against their potential negative effects, including the risk of poor anastomotic healing.

In this issue of the *Journal*, Corsini and colleagues⁸ performed a retrospective review of 1016 patients who underwent esophagectomy for esophageal cancer at a single high-volume institution over a 12-year period (2006-2018) to assess the association between ketorolac use and clinically significant anastomotic leaks, defined as those leaks requiring endoscopic, surgical, or percutaneous intervention. Importantly, over the course of the study, the authors evolved to a practice of selective use of imaging when a leak was suspected, which limits the generalizability of their findings to clinically insignificant leaks detected on routine postoperative screening.

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Interestingly, following the integration of ERAS protocols into routine practice (in 2012), their rate of clinically significant anastomotic leaks decreased (from 13% to 4%; $P < .001$), which may be confounded by other beneficial components of the ERAS care pathway, improvements in perioperative care, and by surgeon experience. After adjusting for potential confounding variables in a multivariable analysis, ketorolac use, classified either as a categorical variable (odds ratio, 0.89; 95% confidence interval, 0.49-1.59) or continuous variable (odds ratio, 1.00; 95% confidence interval, 1.00-1.00) to account for a potential dose-dependent effect, was not associated with increased odds of anastomotic leak. Prospective trials are needed to further assess the risks and benefits of NSAID use, as well as other elements in ERAS protocols.

Until then, given our growing appreciation of the importance of physician stewardship toward the current opioid epidemic, Corsini and colleagues provide additional evidence supporting the safe use of NSAIDs as a component of multimodal opioid-limiting postoperative analgesia protocols for patients undergoing esophagectomy.

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