IS THERE AN INCREASE OF ANASTOMOTIC LEAKS WITH NSAID USE IN COLORECTAL SURGERY?

CINDY GILMORE, DMSC, CCPA

PHYSICIAN ASSISTANT; EDMONTON, ALBERTA
MISERICORDIA COMMUNITY HOSPITAL
GENERAL SURGERY DEPARTMENT

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ABSTRACT

Purpose: The purpose of this article is to review the current guidelines for Enhanced Recovery After Surgery (ERAS) following colorectal surgery with nonsteroidal anti-inflammatory drugs (NSAID) use and its association with anastomotic leaks.

Method: A Medline literature search was conducted with search terms colorectal surgery, nonsteroidal anti-inflammatory drugs, and anastomotic leaks. Seventeen relevant articles served as the basis for this clinical review. This group was further refined to analyze selective vs non-selective NSAIDs to assess the overall risk of anastomotic leaks.

Results: The use of NSAIDs postoperatively was associated with an overall increased risk of anastomotic leaks. This risk varied with the type of NSAID taken for pain control: selective vs non-selective. Non-selective NSAIDs had an increased risk while selective NSAIDs appeared safe.

Conclusion: NSAIDs are an important aspect of the ERAS guidelines to improve patient outcomes after surgery. They provide an alternative option for pain control for opioid medications and their known side effects. Recent literature varies in the risk profiles and safety of different classes of NSAIDs. Postoperative use of NSAIDs, particularly diclofenac, is associated with increased risk for anastomotic leak following colorectal surgery.

Keywords: Colorectal surgery, nonsteroidal anti-inflammatory drugs, anastomotic leaks.

INTRODUCTION

Colorectal surgery is an area of medicine dealing with the colon, rectum, and anus. There has been extensive research into the prevention of complications of major abdominal surgery while enhancing the recovery process. One such complication is the current opioid crisis with patients being addicted to opioids for pain control. In Canada, there have been over 10,000 apparent opioid related deaths between 2016 and September 2018.[1] To decrease these incidents and assist patients during the operative period, new guidelines have been implemented. These guidelines are known as Enhanced Recovery After Surgery (ERAS) protocols. ERAS provides guidance to assist in patient recovery and prevent postoperative complications while curbing addictions to opioids. ERAS is involved in the preoperative, perioperative and postoperative phases of surgery.[2] The end result is a faster recovery process with better clinical outcomes.

One component in the ERAS process has been encouraged use of nonsteroidal anti-inflammatory drugs (NSAIDs) in place of habit-forming opioids. However, new evidence is suggesting complications in colorectal patients, particularly those with anastomosis of the bowel. It is believed that NSAIDs have the potential to interfere with the healing process of the anastomosis leading to leaks, which is a devastating complication of bowel surgery.

Whether NSAIDs cause anastomotic leaks has been a controversial topic in current literary articles. Many surgeons dispute which class of NSAIDs are at fault as NSAIDs are available as selective and non-selective cyclooxygenase (COX) inhibitors. This study aims to determine if specific NSAIDs used in ERAS guidelines are associated with anastomotic leak.

ERAS

Colorectal surgery is used to treat many ailments including bleeding, obstructions, hernias, cancers, diverticulitis, ulcerative colitis, polyps or Crohn's disease. In a procedure known as a colectomy, the surgeon removes the afflicted segment of the intestine and then re-joins the bowel together forming a surgical anastomosis.[3] The entire operation can produce many adverse side effects. These include but are not limited to pain, bleeding, infection, and anastomotic leaks. The treatment of postoperative pain has been the focus of recent protocols to improve patient care and satisfaction.

Enhanced Recovery After Surgery (ERAS) integrates a team approach to the best surgical practice. It has brought together ideas from surgeons, anesthesiologists, nursing staff, and patients, for a comprehensive program. ERAS incorporates a multimodal approach aimed at improving the patient's road to recovery.[4] This provides definitive protocols based on the best available evidence for patients to follow during the entire surgical process. These guidelines have improved patient outcomes, length of stay, and chance of readmissions.

One aspect of ERAS recommends the regular use of NSAIDs to decrease postoperative consumption of opioids. This increased use of NSAIDs has led to many debates between surgeons and anesthesiologists on the probable cause or link with anastomotic leaks. Re-operation for an anastomotic injury puts patients at increased risk for mortality, a need for a possible permanent ostomy, or the recurrence of the malignancy.[5] The growing interest in this field has led to the development of many cohort studies, meta-analysis, and focused systematic reviews. As more studies suggest an association with anastomotic dehiscence and the use of NSAIDs, many surgeons are now changing their current practice and are omitting NSAIDs. It is because of this potential harm that it is crucial to educate our patients on the risks and benefits of NSAIDs as the literature is very unclear and constantly evolving.

NSAIDS

Prostaglandins are chemicals produced by the body that promote inflammation for healing but can result in pain and fever.[6] They are formed by an enzyme called cyclooxygenase (COX). There are two different forms of this enzyme, COX-1 and COX-2. These enzymes produce prostaglandins that are responsible for inflammation, pain, and fever.

NSAIDs work by blocking the COX enzymes. The classes of NSAIDs differ depending on which form of the enzyme they affect and how strong their ability is to block the enzyme. Non-selective

NSAIDs interfere with both COX-1 and COX-2 enzymes. These include medications such as aspirin, ibuprofen, naproxen, diclofenac, and ketorolac. They are associated with an increased risk of gastric ulcers and bleeding because they block the COX-1 enzyme.

Selective NSAIDs blocks the COX-2 enzyme only allowing for the protection of the stomach lining. By narrowing the effect to COX-2 specifically, selective NSAIDs do not have the anti-platelet effects that impair clotting.[7] This is believed to cause less interference with the anastomotic site leading to less leakage. The only current selective NSAIDs marketed in North America is celecoxib in an oral form.

It is theorized that NSAIDs potentially cause poor wound healing as they impede inflammation, which is a component of wound regeneration. They may also disrupt collagen production, increase the risk of microvascular thrombosis, and increase intestinal mucosal damage causing ulcers and strictures.[8,9] As a result of these findings, there is increasing interest in the potential association of NSAIDs and anastomotic leaks in bowel surgery. It is imperative that healthcare providers understand the differences in classes of NSAIDs available, how strongly they inhibit COX-1 or COX-2 enzymes, and the potential complications attributed to both forms.

Having good pain control is essential to the recovery process for colorectal patients, yet any risks attributed to anastomotic leakages should be avoided. The following table provides a list of commonly prescribed NSAIDs utilized by healthcare providers.

ANASTOMOTIC LEAKS

An anastomosis is formed by the joining of two pieces of intestine together. When this connection fails, a leakage occurs. This deterioration in the bowel wall at the anastomotic site can lead to bowel contents escaping into the abdomen, causing considerable complications. Patient mortality can be increased to 19.2% in anastomotic leaks.[13]

The first problem encountered in reviewing this subject, was having a clear definition of an anastomotic leak. An anastomotic leak is defined as "a defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extraluminal compartments."[14] The International Study Group of Rectal Cancer (ISREC) proposed that a pelvic abscess in the proximity of the anastomosis should be included whether or not a specific defect location was found in the intestinal wall.[15] This interpretation changed further findings of leak rates. The incidence of anastomotic leaks also varied by location with most occurring at the more distal portion of the gastrointestinal tract. Leakage rates can be as high as 13-18% in rectal surgery and 3-7% after more proximal colonic surgery.[16] Patient risk factors can also increase the incidence for anastomotic leaks. Additional risk factors include male patients, increased age, distal location of the anastomosis, malignant disease, long operation times, emergency procedures, preoperative radiation treatment, and patients receiving blood transfusions.[17] Medscape also includes obesity, smoking, chronic immunosuppression, and low platelet count as risk factors.[18] Any risk factors for leaks should, therefore, be prevented, avoided, or corrected to improve patient outcomes and ensure patient safety.

Table 1 Commonly Prescribed NSAIDs and their pharmacology

Enzyme Inhibited	Name		Bio-availability (%)	Half-life (h)	Dose (mg)	Dose Interval (h)	Max Daily (mg)
	Chemical	Trade					
COX-1 and COX-2	Aspirin		50-75	0.33	Enteric coated: 325 500 650	4	4000
	Ibuprofen	Advil Motrin IB	80	2	200	4-6	1200
	Diclofenac potassium	Cambia Cataplase Zipsor	50-55	1-2	25 50	6-12	200
	Indomethacin	Tivorbex	100	7.6	20 40	8-12	200
	Naproxen	Aleve Naprosyn	95	12-17	375 500	6-8	1250
	Piroxicam	Feldene	N/A	50	10 20	24	20
	Etodolac	Lodine	80	Tablet: 6.4	Tablet: 400 500	6-8	1200
	*Ketorolac tromethamine	Toradol	100	5.2-5.6	10	4-6	Age 17-65: 120 Age 65+ 60 Max 5 days
COX-2 Selective	Celecoxib	Celebrex	N/A	11	50 100 200 400	12	800
	**Nimesulide		54-64	1.8-4.7	100	12	200 Max 15 days

The values listed are for per oral (PO) formulation unless otherwise indicated.

*Intravenous (IV) values shown; PO formula discontinued in the USA. **Not available in the USA. The majority of this table was compiled based on two online databases[10,11], except for nimesulide[12]. COX cyclooxygenase

Review of Current Literature

Since the development of a clear definition for anastomotic leaks by ISREC, recent research has found significant findings to suggest the requirement for a change in clinical practice. Iversen et al achieved a significant reduction in anastomotic leaks after colorectal surgery by altering their practice along with the exclusion of NSAID use.[19] Bhangu et al evaluated selective vs non-selective NSAIDs and found that only non-selective NSAID was associated with an increased anastomotic leak rate.[21] Peng et al reported similar findings of increased leak rates with non-selective NSAID use.[20] Then a recent meta-analysis performed by Modasi et al noted a significant association with NSAIDs and an increased anastomotic leak rate following colorectal surgery. The overall leak rate was significantly higher in the NSAID group [OR 1.58 (1.23, 2.03), P=0.0003].[21] Non-selective NSAIDs had a higher leak rate when compared to selective. On further appraisal of specific non-selective NSAIDs, inconsistent findings were noted with conflicting risk profiles. Diclofenac was identified as a risk factor for anastomotic leaks while ketorolac was not. However, in a similar field of study, Fjederholt et al found a strong association between ketorolac and anastomotic leakage after surgery for gastro-esophageal-junction cancers.[22] This finding was similar to the van der Vijver et al study that found COX-2 inhibitors negatively affected the small bowel anastomosis.[23] Yet, Hawkins et al concluded ketorolac exposure in elective colorectal surgery was not associated with anastomotic leaks when administered in a standardized approach. Clearly the effects of NSAIDs vary by location and the specific NSAID utilized. Further randomized controlled studies are needed to evaluate the safety of selective vs non-selective NSAIDs particularly ketorolac in colorectal surgery and their association with anastomotic leaks.

CONCLUSION

In general, NSAID use in the postoperative colorectal patient was associated with a significant increased risk of anastomotic leak. The effects of NSAIDs varied depending on the class of NSAID used and the location of the anastomotic site. Small bowel anastomosis had the highest incidences of leaks compared to distal colonic anastomosis.[23,24] In colorectal surgery, the distal rectal anastomosis had the highest leakage rates.[16] Non-selective NSAIDs had a higher risk of anastomotic leaks compared to selective.[25] However, Modasi et al found inconsistent findings when directly comparing diclofenac and ketorolac. In this study, diclofenac had the greatest incidence of anastomotic leaks when compared to ketorolac.[21] The outcome of this report is a finding of an increased risk associated with NSAID use, particularly diclofenac, in our colorectal patients following surgery. Healthcare providers need a clear understanding of the various classes of NSAIDs, how strongly they inhibit COX-1 and COX-2 enzymes and the potential complications attributed to both forms.

ERAS is a collaborative effort from practice experts on the operative management of colorectal patients. The protocol suggests minimizing opioid use and maintaining pain control with regular NSAIDs. ERAS is associated with an earlier return of bowel function and shortened hospital length of stay. However, care should be taken when using NSAIDs in our colorectal patients with an anastomosis. Postoperative use of NSAIDs, particularly diclofenac, has been associated with an increased risk of anastomotic leaks. Other ERAS modalities should be utilized in the postoperative colorectal patients

with an anastomosis. These include the use of regularly scheduled acetaminophen and/ or gabapentin medications. Additionally, spinal/ epidural analgesic, a transversus abdominus plane (TAP) block, lidocaine infusion or a patient controlled analgesic (PCA) can be employed for pain control.[26] Although controversy remains on the dangers associated with ketorolac and colorectal patients, surgeons should be aware of the issues regarding the risks and benefits of this medication until specific studies can be concluded.

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