International Journal of Biomedicine 15(1) (2025) 200-204
http://dx.doi.org/10.21103/Article15(1)_OA26

ORIGINAL ARTICLE

Experimental Surgery

INTERNATIONAL JOURNAL OF BIOMEDICINE

Effect of Perioperative Ketorolac Tromethamine and Acetaminophen Analgesia on the Outcome of Intestinal Anastomosis in a Rat Model

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Abstract

Background: Despite advances in surgical techniques and perioperative care, intestinal anastomotic dehiscence remains a significant challenge in gastrointestinal surgery. This study aimed to clarify the morpho-functional effects of the postoperative administration of ketorolac tromethamine and acetaminophen during the healing of intestinal anastomoses in a rat model.

Methods and Results: Wistar–Hannover rats weighing between 200 g and 400 g were divided into 6 groups of 10 animals. All animals underwent resection of the cecum with ileo-colic anastomosis. The animals in Groups 1 and 2 received ketorolac tromethamine intraperitoneally (5 mg/kg/d), those in Groups 3 and 4 received acetaminophen intraperitoneally (50 mg/kg/d), and those in Groups 5 and 6 received tramadol subcutaneously (25 mg/kg in 2 mL saline solution). All groups were sacrificed by cardiac puncture under high-dose ketamine anesthesia on Day 7 after surgery, and 3–4 cm of the large intestine was resected at the anastomosis site, cleaned, placed in formalin, and sent for immunohistochemical examination. An immunohistochemical analysis was performed to evaluate inflammation, angiogenesis, and fibroblast proliferation. For this purpose, CD31, CD45, alpha smooth muscle actin [α-SMA]) and vimentin were detected. The histological and microscopic results showed no significant differences among the groups. In addition, no differences were observed in terms of mucosal epithelization.

Conclusion: The study results showed that neither ketorolac tromethamine nor acetaminophen affected the healing of colocolic anastomoses in a rat model.(**International Journal of Biomedicine. 2024;15(1):200-204.**)

Keywords: intestinal anastomosis • anastomotic dehiscence • ketorolac tromethamine • acetaminophen

For citation: Dafina M, Labinot S, Bedri B, Klodete K, Valon C, Oltion B. Effect of Perioperative Ketorolac Tromethamine and Acetaminophen Analgesia on the Outcome of Intestinal Anastomosis in a Rat Model. International Journal of Biomedicine. 2024;15(1):200-204. doi:10.21103/Article15(1)_OA26

Introduction

Intestinal anastomosis is a common surgical procedure performed to reconnect segments of the intestine after resection. However, it carries the risk of dehiscence, a serious complication with potentially devastating consequences. Dehiscence of intestinal anastomosis refers to the separation or opening of a surgical connection between 2 segments of the intestine. It can lead to intestinal contents leaking into the abdominal cavity, which can cause peritonitis and other life-threatening conditions. The incidence of anastomotic leakage after colorectal surgery varies from 2% to 19% across studies,[1-4] and the risk of morbidity and mortality is considerable when anastomotic leakage occurs after abdominal surgery.[5,6] Surgical repair is typically required to address this complication.[7]

Despite advances in surgical techniques and perioperative care, dehiscence remains a significant challenge in gastrointestinal surgery. In addition to increasing morbidity and mortality, it also increases healthcare costs. Understanding

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the risk factors, pathophysiology, and optimal management strategies for intestinal anastomotic dehiscence is crucial for surgeons and healthcare providers to mitigate its occurrence and improve patient outcomes. Hence, research is being conducted in this area to synthesize the available evidence and provide clinicians with valuable insights into how to prevent, recognize (at the earliest opportunity), and effectively manage this potentially life-threatening complication.[8-11]

Several key factors that contribute to intestinal anastomotic dehiscence have been identified. Preoperative risk factors include male sex,[12,13] alcohol and smoking,[14] and the presence of comorbidities.[15] Other important preoperative risk factors are obesity, hypoalbuminemia,[16] and preoperative chemoradiotherapy. Intraoperative risk factors include insufficient blood perfusion, vascular ligation level, poor technical construction and anastomotic tension, laparoscopic (vs. open) surgery, operative time, and emergency surgery in the case of obstruction. Perioperative factors associated with anastomotic leakage include infection, anemia, and blood transfusions.[17-19]

Many researchers have observed a significant association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and a higher risk of developing postoperative anastomotic leaks. It has been suggested that NSAIDs mediate their anti-inflammatory effect by inhibiting cyclooxygenase (COX)-1 and COX-2, intestinal epithelial cell migration, and mucosal restitution in animal models.[20-22] The effects of ketorolac tromethamine and acetaminophen on the outcomes of colonic anastomosis and the wound healing process are still unclear.

Therefore, this study aimed to clarify the morpho-functional effects of the postoperative administration of ketorolac tromethamine and acetaminophen during the healing of intestinal anastomoses in a rat model. To achieve this aim, we evaluated the effect of these drugs on the migration of leukocytes to the site of inflammation (by detecting CD31 and vimentin), the activation of the immune system (by detecting CD45), and the contractility of fibroblasts (by detecting alpha smooth muscle actin [α-SMA]).

Materials and Methods

Wistar–Hannover rats weighing between 200 g and 400 g were provided by the Institute of Pathophysiology and maintained under laboratory conditions. They were housed in a controlled room with 12-h light-dark cycles and fed standard pellet chow and water ad libitum.

The rats were divided into 6 groups of 10 animals: acetaminophen without peritonitis (Group 1), acetaminophen with peritonitis (Group 2), ketorolac tromethamine without peritonitis (Group 3), ketorolac tromethamine with peritonitis (Group 4), tramadol without peritonitis (Group 5; control), and tramadol with peritonitis (Group 6; control).

The animals in Groups 1 and 2 received ketorolac tromethamine intraperitoneally (5 mg/kg/d), those in Groups 3 and 4 received acetaminophen intraperitoneally (50 mg/kg/d), and those in Groups 5 and 6 received tramadol subcutaneously (25 mg/kg in 2 mL saline solution). All groups were sacrificed by cardiac puncture under high-dose ketamine anesthesia on Day 7 after surgery.

Operative Procedure

Peritonitis was induced in the animals in Groups 2, 4, and 6. For this, the cecum was ligated above the ileocecal valve 30% and stitched with a 19 G needle under the ligated section. In these animals, anastomosis was performed 24h later.

The anastomotic operations were performed under sterile conditions. Intraperitoneal anesthesia consisted of 50mg/kg ketamine (0.5 mL, 100 mg/mL), 5mg/kg xylazine (0.125 mL, 20 mg/mL), and 0.1 mL/100g body weight physiological solution (3mL). The abdominal wall was opened via a median laparotomy of about 3–4 cm. Resection of the cecum with ileocolic anastomosis was performed in all animals. Ethicon Vicryl 6.0 thread and separate and single-layer sutures were used. The abdominal wall was closed with simple interrupted sutures, and the animals were then resuscitated with 5mL of normal saline solution administered subcutaneously. All animals were administered imipenem (40 mg/kg, intraperitoneally) after anastomosis for 7 days. The rats were checked twice daily by doctors on the team assigned to the project and a biologist from the Institute of Pathophysiology.

All animals were sacrificed by cardiac puncture under high-dose ketamine anesthesia on Day 7 after surgery. The abdomen was reopened, and 3–4cm of the large intestine was resected at the anastomosis site, cleaned, placed in formalin, and sent for immunohistochemical examination.

Histological Analysis

The intestinal samples were fixed in 4% formaldehyde, embedded in paraffin, sectioned with a microtome to a 2–3 μm thickness, and stained with hematoxylin-eosin. The samples were histologically examined using a Canon microscope by a pathology specialist unfamiliar with the applied laparotomy wound closure technique.

The integrity of the muscle tissue of the large intestine and the mucosal anastomosis were evaluated. Granulation tissue was assessed by examining inflammatory cell infiltration in the anastomotic area.

A semi-quantitative method was used to assess the wound healing process. This involved evaluating several parameters: necrosis, inflammatory cells (polymorphonuclear and mononuclear cells), neovascularization, vascular congestion, edema, foreign body reaction, micro-abscesses, and collagenization. These parameters were quantified using numerical scales. The presence of necrosis was scored 0, and the absence was scored 1. A score of 0 was assigned when polymorphonuclear cells predominated, and a score of 1 was assigned when mononuclear cells predominated. Neovascularization was scored 0 (emphatic), 1 (mild), 2 (moderate), or 3 (high). Vascular congestion and edema were scored 0 (severe), 1 (moderate), 2 (mild), or 3 (absent). Foreign body reaction was scored 0 (absent), 1 (mild), 2 (medium), or 3 (pronounced). The presence of micro-abscesses was scored 0, and the absence of micro-abscesses was scored 1 (Figure 1).

Immunohistochemical Analysis

An immunohistochemical analysis was performed to evaluate inflammation, angiogenesis, and fibroblast

proliferation. For this purpose, CD31, CD45, α-SMA, and vimentin were detected (Figure 2).

Statistical analysis was performed using the statistical software package SPSS version 22.0 (SPSS Inc, Armonk, NY: IBM Corp).

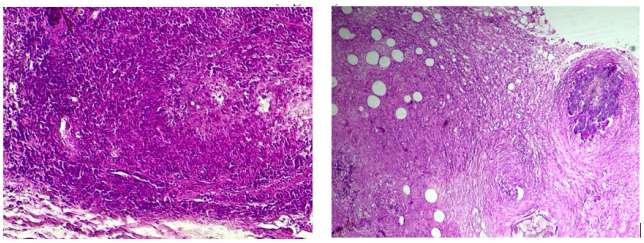

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***Figure 1**. Histological examination.*

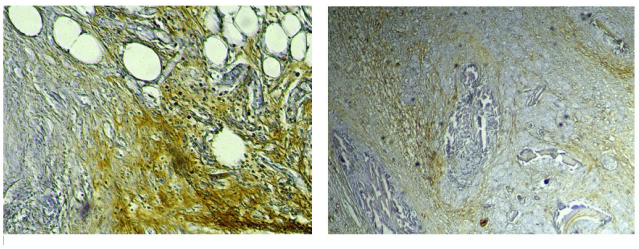

***Figure 2**. Immunohistochemical analysis (CD45 and α-SMA).*

Ethical Approval

The animals were housed in keeping with the rules for good laboratory practice (GLP). The experiments were performed in accordance with the norms for the humane treatment of animals, which are regulated by the International Guidelines of the Association for the Assessment and Accreditation of Laboratory Animal Care, followed the protocol approved by the Institutional Animal Care and Use Committee of the University Clinical Centre of Kosovo.

Results and Discussion

The histological and microscopic results showed no significant differences among the groups (Table 1). In addition, no differences were observed in terms of mucosal epithelization.

Table 1.

Quantification of necrosis (Nec), inflammation (Inf), neovascularization (NeoVas), congestion (Con), edema, foreign body reaction (FBR), and microabscesses (MA) present in the study groups.

Group	Nec	Inf	NeoVas	Con	Edema	FBR	MA
1	0.3	1.6	2.0	1.4	0.8	0.6	0.2
2	0.2	1.6	2.3	1.2	1.4	1.1	0.6
3	0.1	1.3	2.1	1.4	1.9	1.6	0.3
4	0.4	1.5	1.8	1.5	1.3	1.4	0.6
5	0.1	1.5	2.3	1.1	1.7	0.8	0.2

Despite advances in medicine, the surgical treatment of gastrointestinal disorders continues to present practitioners with several challenges. Re-intervention, stomal placement, deterioration of the patient's condition, extended hospital stays, and intrahospital mortality are some of the issues that have prompted research on the risk factors for gastrointestinal dehiscence to create conditions that would reduce the risk of developing this complication.

Some studies have shown that NSAIDs do not affect the occurrence of anastomotic leakage and wound healing;[23,24] however, other studies have shown the opposite.[25-28] Various parameters have been utilized in studies designed to evaluate the outcomes of anastomosis. For example, Ghiselli et al.[29] examined the level of MMP-9, among other parameters, and found that administration of diclofenac and ketorolac did not increase the risk of leakage after colocolic anastomosis. Others have reported that administering NSAIDs for peritonitis did not affect the healing of anastomotic wounds[29,30] or other important postoperative outcomes.[31,32] Regarding the use of acetaminophen, van der Vijver et al.[33] found that acetaminophen did not affect wound-breaking strength or hydroxyproline levels. In addition, Gulcicek et al.[34] reported that bursting pressure, fibrosis, and hydroxyproline levels were significantly higher in an acetaminophen group than in a diclofenac sodium group.

In conclusion, our results showed that neither ketorolac tromethamine nor acetaminophen affected the healing of colocolic anastomoses in a rat model.

Acknowledgments

The authors thank Dr. Kristen Sadler from Scribendi (www.scribendi.com) for editing a draft of this manuscript.

Competing Interests

The authors declare that they have no competing interests.

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