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Effects of Ketorolac on Colorectal Anastomosis in Rats

Efectos del ketorolaco sobre la anastomosis colorrectal en ratas

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ABSTRACT

Despite being a significant cause of morbidity and mortality, colorectal anastomoses are an indisputable gastrointestinal system reconstruction surgery routine. Many patient- and disease-specific factors, including surgical technique, affect anastomotic healing. This study discusses the effects of ketorolac, used for analgesia after colorectal surgery, on the continuity of colorectal anastomoses and intraabdominal adhesions in a rat model. A prospective randomized study was performed at Laboratory of Experimental Animals and Research in the Institute. Thirty Wistar Albino rats were randomized into three equal groups, each consisting of 10 rats. Following rectal transection, end-to-end colorectal anastomosis was performed. During the postoperative period, animals received intramuscular injections of 10 mg/kg isotonic saline, 20 mg/kg meperidine, and 1 mg/kg ketorolac. On the post-operative day seven, the anastomotic segment was resected, and the Nair Score, anastomotic burst pressure, and OH-Proline levels were compared. The OH-Proline values were not statistically significant between the groups (P = 0.566). There was no statistically significant difference between the groups in terms of Nair Scores (P = 0.118). The anastomotic burst pressures of the groups were statistically significantly different (P = 0.017). The anastomotic burst pressures in the group receiving ketorolac were statistically significantly higher than the group receiving meperidine (P = 0.020). In conclusion, this study did not associate perioperative use of ketorolac with anastomotic leakage in the rat model.

Key words: Anastomotic Leakage; anastomotic burst pressure; colorectal anastomosis; ketorolac; non-steroidal anti-inflammatory drugs.

RESUMEN

Las anastomosis colorrectales son procedimientos rutinarios en la cirugía gastrointestinal, aunque representan una causa importante de morbilidad y mortalidad. Diversos factores del paciente, la enfermedad y la técnica quirúrgica influyen en su cicatrización. El objetivo del estudio fue evaluar los efectos del Ketorolaco, empleado para la analgesia posoperatoria, sobre la continuidad de las anastomosis colorrectales y las adherencias intra-abdominales en un modelo experimental con ratas. Para ello se utilizaron treinta ratas Wistar Albinas, las cuales fueron asignadas aleatoriamente en tres grupos de diez ratas cada uno. Tras una anastomosis colorrectal término-terminal, los grupos recibieron 10 mg/kg de solución salina isotónica, 20 mg/kg de Meperidina o 1 mg/kg de Ketorolaco por vía intramuscular. En el séptimo día se resecó la línea anastomótica y se compararon el puntaje de Nair, la presión de ruptura y los niveles de hidroxiprolina. Los resultados obtenidos nos indicaron que no hubo diferencias significativas en los valores de hidroxiprolina (P = 0,566) ni en los puntajes de Nair (P = 0,118). Mientras que, las presiones de ruptura si difirieron significativamente (P = 0,017), siendo mayores en el grupo con Ketorolaco en compracion al grupo con Meperidina (P = 0,020). El uso perioperatorio de Ketorolaco no se asoció con fugas anastomóticas en este modelo experimental.

Palabras clave: Fuga anastomótica; presión de ruptura anastomótica; anastomosis colorectal; ketorolaco; antiinflamatorios no esteroideos.

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INTRODUCTION

Colorectal surgical operations are performed frequently in many benign and malignant diseases of the gastrointestinal tract, especially in colorectal cancers [1]. Colo-colonic anastomoses are usually performed for reconstruction after large bowel resections to ensure continuity of passage. Individuals undergoing colorectal surgery for any reason carry a risk of perioperative complications and mortality [1].

These can be minor complications such as wound infection and intra-abdominal abscess, but serious complications such as anastomotic leakage and sepsis can also be encountered. Anastomotic leakage remains one of the most feared complications of colorectal surgery that can lead to significant morbidity and mortality in the postoperative period [2].

Despite innovations and developments in colorectal surgery in recent years, mortality rates related to anastomotic leakage are still quite high [2, 3, 4]. Management of anatomotic leakage ranges from a course of antibiotics to percutaneous drainage or reconstruction of the anastomosis. All these treatments mean significant morbidity, cost, and prolonged hospital stay [5].

Since narcotics slow intestinal healing, any treatment includes oral and/or intravenous Non-Steroidal Anti-Inflammatory Drugs (NSAID) to reduce the amount of narcotics taken. NSAID are an essential component of contemporary perioperative analgesia. Although this topic has different results, anastomotic leakage has been associated with nonsteroidal anti-inflammatory drugs in most experimental and observational clinical studies [6, 7, 8, 9].

Although anastomosis healing has increased over the past decade, leak rates have not decreased and remained between 2-24 % [1, 3]. Successful anastomotic healing and the final stability of the injured bowel after anastomosis depends not only on the surgical technique but also on many patient- and disease-specific factors [10].

Non-Steroidal Anti-Inflammatory Drugs, including ketorolac, often adversely affect the early inflammatory phase of wound healing. This detrimental effect is due to the COX inhibition-mediated effects on inflammatory and proliferative activity [6, 9, 11].

Recent studies have shown that effective analgesia increases movement and appetite, and shortens post-operative recovery time for humans, rodents, rabbits, and other species particularly susceptible to pain and inflammation [12]. However, these analgesic drugs used in the perioperative period may affect the outcome of anastomotic healing through the tissue inflammatory response [6, 7, 8, 9].

Given that many patients recieve NSAID in the early postoperative period, whether these drugs are a risk factor for anastomotic leakage has often been discussed in the literature, especially through well-structured animal experiments [6, 7, 8, 9].

The present study aimed to reveal the effects of ketorolac, which has been used frequently in analgesia after colorectal surgery in recent years, on the continuity of colorectal anastomoses and intra-abdominal adhesions in a rat model. We hypothised that perioperative ketorolac administration would not impaircolorectal anastomotic healing or compromise anastomotic integrity compared with meperidine or saline in a rat model.

MATERIALS AND METHODS

The experimental study was carried out between February and March 2019 at Experimental Animals and Research Laboratory. Approval of the animal protocols was granted by the Local Ethics Committee (Number of approbation: 2019-3-24).

The protocols were performed following the Guidelines for Experimentation with Vertebrate Animals (UN, Stroudsburg, February 20, 1985). This experimental protocol was performed in compliance with the ARRIVE guidelines [13]. In this study, Male Wistar Albino rats (Rattus norvegicus), 36 to 38 weeks old, weighing 200-250 grams (Sartorius Cubis II MSA225S, Germany), were used and randomized into three groups, with ten rats in each group, kept on a 12-h light and 12-h dark cycle, and fed ad libitum. Rats in all groups underwent end-to-end colorectal anastomosis after rectal transection. Following surgery, 10 mg/kg isotonic saline (Group A), 20 mg/kg Meperidine (Aldolan, GL Pharma GmbH, Austria) (Group B), and 1 mg/kg Ketorolac (Medrolgin, World Medicine, Türkiye) (Group C) were administered intramuscularly, respectively. Randomization of drugs was done with the research randomizer program (https://www.randomizer.org/), and administration of drugs was done by animal technicians who didn't know the ingredients and groups.

Operative procedure

After 12 h of fasting, subjects were given general anesthesia with a mixture of 80 mg/kg Ketamine Hydrochloride (Ketalar® 30 mg/kg, Pfizer Inc., UK) and 8 mg/kg Xylazine HCl (Rompun® 10 mg/kg, Bayer AG, Germany) intraperitoneally. The abdominal skin was shaved, and the skin and the area were cleaned with 10 % povidone iodine to ensure skin sanitation.

A standard incision of 5 cm was made on the skin. All procedures were performed under aseptic conditions. A standard 4 cm incision was made in the anterior abdominal wall (FIG.1).

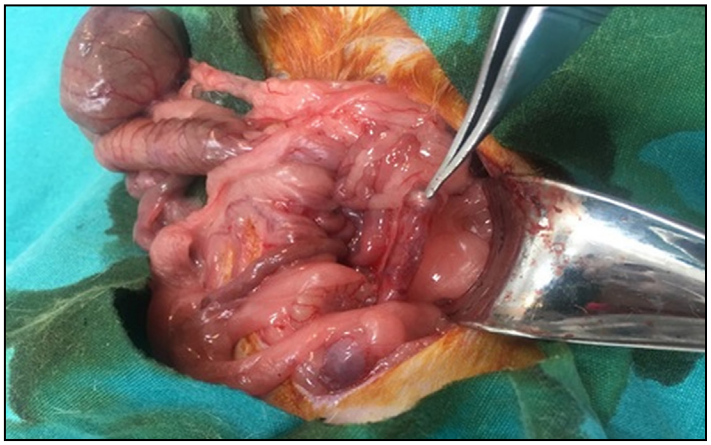

FIGURE 1. A 5 cm probe was advanced through the anus of the rats and the descending colon was cut to ensure compliance with the study.

The fascia and the skin were sutured with 3/0 polypropylene sutures (Prolene, Ethicon, New Jersey, USA). Rats received a randomized intramuscular injection of 1 mg/kg ketorolac (Medrolgin, World Medicine, Istanbul, Türkiye), 20 mg/kg meperidine (Aldolan, GL Pharma GmbH, Vienna, Austria) or 10 mg/kg isotonic saline twice a day. All procedures were performed

by a single surgeon to ensure standardization (FIG.2). Drugs were administered according to randomization by animal technicians, who also recorded any laboratory animal suffering or illness.

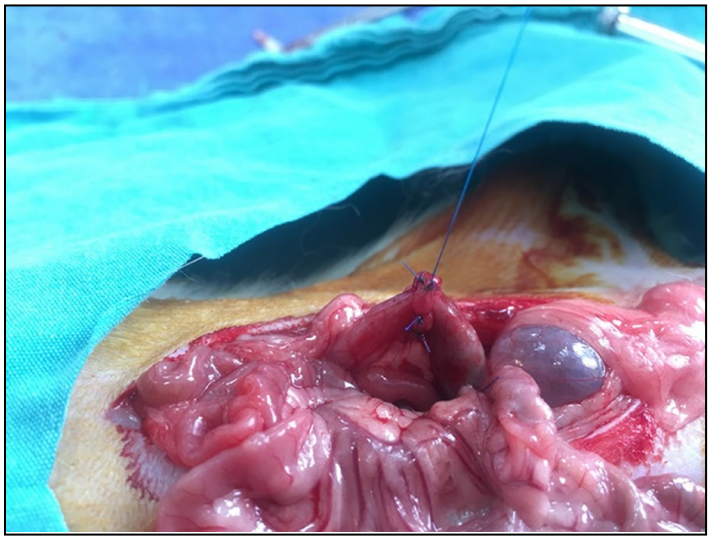

FIGURE 2. A single-row colorectal anastomosis was performed with 8 pieces of 3/0 polypropylene (Prolene, Ethicon, New Jersey, USA) sutures.

Macroscopic evaluation

Re-Laparotomy was performed on the seventh postoperative day. The abdomen was examined for signs of adhesions according to the modified Nair Score [14] (TABLE I). In accordance with the double-blind study principles, the evaluation was made by another researcher who did not know the groups.

TABLE I
Modified Nair Score

Grades	Features
Grade 0	No adhesion
Grade 1	Single band of adhesion between viscera to abdominal wall
Grade 2	Two adhesive bands either between viscera or viscera to abdominal wall
Grade 3	More than two bands between viscera or viscera to abdominal wall or intestines forming a mass without being adherent to the abdominal wall cohesive attachment
Grade 4	Dense and complex adhesive bands between viscera or viscera to abdominal wall, or visceral adhesion to abdominal wall directly

Intraperitoneal adhesions were evaluated using the modified Nair scoring system. This is a 5 point scoring system (0-4) classified adhesions into no adhesions to multiple dense adhesions [14].

Anastomotic bursting pressure measurement and data sampling

On post-operative day 7, the rats were re-anesthetized and the adherents were carefully separated, and the anastomosis line was excised as a whole. The intestine, encompassing the anastomosis line and 2 cm proximal and 2 cm distal to anastomosis, was resected.

The colon segment was inflated by administering 2 mL/min saline with the infusion pump. In the meantime, the highest pressure value was determined on the monitor and recorded as the anastomotic burst pressure. In accordance with the double-blind study principles, the evaluation was made by another researcher who did not know the groups (FIG.3). Following the anastomotic burst pressure measurements, the anastomosis line was transected 0.5 cm proximal and 0.5 cm distal and placed in polypropylene microcentrifuge tubes. These fractions were frozen at -80 C until the day of biochemical analysis (TSX series - TSX60086V, Thermo Fischer Scientific, USA).

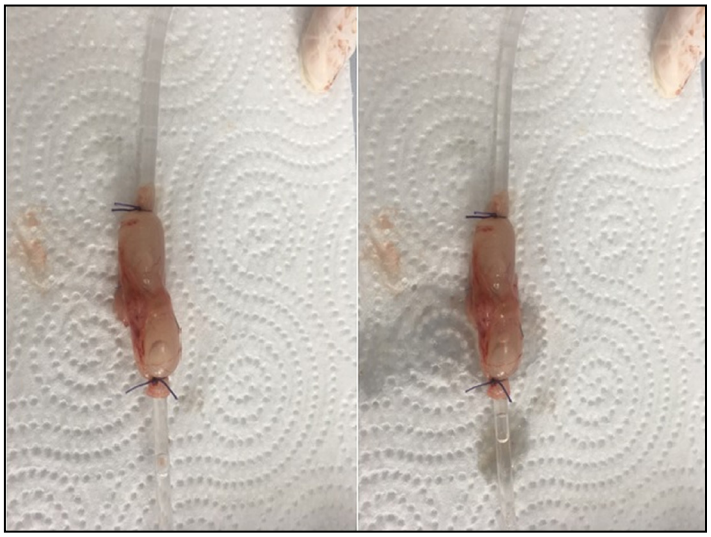

FIGURE 3. After the existing fecal content was removed by washing with saline, the colon was connected with 3/0 silk sutures (Sterisilk, SSM Sterile Health Products, Istanbul, Turkey), one end to the infusion pump (Infusomat® Space, Braun, Melsungen, Germany) and the other end to the arterial line of the monitor (Adecon DK-8000S, Shenzhen ADECON Technology Co.,Ltd, Shandong, China).

Biochemical analysis

A tissue fraction of 100 mg was weighed and lysed in 6 N HCl in a digestion oven (Buchi, K-446 Digestion Unit, Switzerland). Of these lysed tissues, 25 µL was placed into tubes and left to dry. Then, chloramine T solution was pipetted onto the samples. After 10 minutes (min), Erlich working solution was added, and the samples were incubated at 50 °C for 90 min (Memmert, IN110, Germany). At the end of the incubation, the samples were read at 560 nm wavelength. The amount of hydroxyproline in the samples was calculated as µg/mg tissue using the graph prepared based on the standards [15].

Statistical analyses

The normality of continuous variables was evaluated visually (histogram and probability graphs) and analytically (Smirnov test). One-way ANOVA test was used to compare more than two groups. The variances showed homogeneity and were evaluated by the Tukey test in paired group comparison (post-hoc test). Statistical significance was accepted as $P < 0.05$ and SPSS 15.0 statistical program (IBM Corp., New York, USA) was used.

RESULTS AND DISCUSSION

Prevention of anastomotic leaks is one of the crucial challenges in colorectal surgery. In order to reduce mortality and morbidity in the postoperative period, factors causing leakage are frequently investigated. Although the risk of anastomotic leakage is not statistically significant, there are concerns regarding

preoperative and post-operative NSAID use in colorectal surgery [6]. These concerns are also valid for ketorolac, which tends to leak out dose-dependently or independently [16, 17].

Non-Steroidal Anti-Inflammatory Drugs constitute an important component of contemporary perioperative analgesia. Injectable NSAID, such as ketorolac have an analgesic effect comparable to morphine in major abdominal surgery and reduce the use of opioid drugs [18, 19].

The success of anastomotic healing is described by injured bowel's ability to resist tensile forces. The integrity of the anastomosis is ensured by tension-free technique and intact perfusion, mainly; however, patient-specific factors may affect the healing process [10].

Collagen in the submucosal tissue forms the continuity and mechanical strength of the intestinal wall. Consequently, the most important biochemical parameter of anastomotic healing is the concentration of collagen. OH-proline level is an indirect marker of the amount of collagen in tissue and anastomotic healing (TABLE II) [20].

TABLE II
Levels of OH-Proline of Subjects (µg/mg)

	A	B	C
Subject-1	0,180	0,363	0,381
Subject-2	0,174	0,310	0,587
Subject-3	0,180	0,357	0,280
Subject-4	0,197	0,203	0,174
Subject-5	0,428	0,203	0,138
Subject-6	0,233	0,162	0,239
Subject-7	0,251	0,499	0,233
Subject-8	0,392	0,304	0,617
Subject-9	0,274	0,705	0,428
Subject-10	0,422	0,286	0,209

The OH-Proline values were not statistically different between the groups (P = 0.566). The median value in the group receiving isotonic saline (Group A) was 0.27 ± 0.1 (0.18-0.422) µg/mg. The median value in the group receiving meperidine (Group B) was 0.34 ± 0.16 (0.162-0.705) µg/mg. The median value in the group receiving ketorolac (Group C) was 0.33 ± 0.17 (0.138-0.617) µg/mg (TABLE III).

In this study, OH-proline levels of ketorolac and meperidine groups were found to be higher than the control group, although not statistically significant. This effect may be attributed to the fact that analgesia shortens the postoperative recovery time by increasing movement and appetite [12].

TABLE III
Modified Nair Score

Variables		N	Mean	Std. Deviation	P
OH-proline	A	10	0.27	0.10	
	B	10	0.34	0.16	0.566
	C	10	0.33	0.17	
	Total	30	0.31	0.15	
Anastomotic Burst Pressure	A	10	48.30	13.75	
	B	10	44.90	18.33	0.017
	C	10	65.70	16.03	
	Total	30	52.97	18.13	
Anastomotic Burst Pressure	A	10	2.40	1.08	
	B	10	2.80	1.03	0.118
	C	10	1.80	1.03	
	Total	30	2.33	1.09	

N: number, Std. Deviation: standard deviation, P: P-value

Recent studies linked NSAID and an increased incidence of anastomotic leakage in gastrointestinal surgery. However, some publications reporting that this increase does not reach statistically significance [6], there are also conflicting reports showing that NSAID consumption increases the AL rate in the post-operative period [9].

Anastomotic burst pressures in the group receiving ketorolac were significantly higher compared to the group receiving meperidine. However, the OH-Proline values were not statistically significantly different between the groups.

Wound healing and intestinal anastomosis may be adversely affected by the inhibitory effects of NSAID on inflammation [16]. In clinical and experimental models, NSAID were found to significantly reduce collagen deposition in colonic anastomoses in rats, but this did not transform into reduced breaking strength of the anastomosis [9]. The absence of differences in hydroxyproline levels despite higher bursting pressures suggests that collagen quantity alone may not fully reflect the biomechanical strength of the anastomosis.

On the other hand, the anastomotic burst pressures of the groups were statistically significantly different (P = 0.017) (TABLE IV). The anastomotic burst pressures in the group receiving ketorolac were statistically significantly higher than the group receiving meperidine (P = 0.020) (TABLE V). The higher bursting pressure observed in the ketorolac group may indicate better preservation of the mechanical integrity of the anastomosis despite similar collagen content. The biological response to ketorolac is likely multifactorial, involving modulation of inflammatory pathways that may influence tissue remodeling beyond collagen deposition alone.

TABLE IV
Anastomotic Burst Pressures (mmHg) of Subjects

	A	B	C
Subject-1	57	38	87
Subject-2	54	37	66
Subject-3	44	60	90
Subject-4	30	33	53
Subject-5	63	23	61
Subject-6	48	46	71
Subject-7	28	47	52
Subject-8	45	21	50
Subject-9	42	75	46
Subject-10	72	69	81

The median value was 48.3 ± 13.75 (28-72) mmHg in Group A, 44.9 ± 18.33 (21-69) mmHg in Group B, and 65.7 ± 16.03 (46-90) mmHg in Group C.

TABLE V
Comparison of Anastomotic Bursting Pressures between groups

	Group	Group	Mean Difference	Standard Error	95 % Confidence Interval		P
					Lower	Upper	
Anastomotic Burst Pressure	A	B	3.4	7.22	-14.5	21.3	0.885
	A	C	-17.4	7.22	-35.3	0.5	0.058
	B	C	-20.8	7.22	-38.7	-2.9	0.020

Tukey HSD test

The Modified Nair Scores of the subjects are given in TABLE VI. The median value was 2.4 ± 1.08 (1-4) in Group A, 2.8 ± 1.03 (1-4) in Group B, and 1.8 ± 1.03 (1-4) in Group C.

Although the Nair Scores were lower in the ketorolac group, there was no statistically significant difference between the groups (P = 0.118) (TABLE III).

TABLE VI
Modified Nair Scores of Subjects

	A	B	C
Subject-1	1	4	2
Subject-2	2	2	1
Subject-3	2	3	1
Subject-4	4	3	2
Subject-5	3	4	2
Subject-6	3	3	1
Subject-7	4	2	4
Subject-8	2	4	1
Subject-9	2	2	1
Subject-10	1	1	3

Another animal study found that proximal anastomoses are more susceptible to leakage than distal anastomoses and that some NSAID may be more harmful than others [21]. This detrimental effect is most likely due to an effect on collagen metabolism resulting in the weakening of the connective tissue surrounding the anastomosis [6, 11]. From a biological perspective, these findings suggest that perioperative ketorolac did not impair the healing process of colorectal anastomoses under the conditions of this experimental model.

The extent of COX enzyme inhibition varies widely among different non-selective NSAIDs. Although ketorolac is considered a non-selective NSAID, human whole blood tests have shown it to be COX-1 selective [18]. Although the evidence seems to point to NSAID as responsible for the increased leakage, the fact that no association was found in our study may be related to the selectivity of ketorolac against COX-1. As a matter of fact, studies in literature also support this finding [17, 22, 23].

Despite such adverse effects, a recent animal study has also shown that these NSAID minimize abdominal adhesions [24]. Peritoneal adhesions are a significant cause of morbidity in gastrointestinal surgery. Peritoneal adhesions result from peritoneal irritation due to infection or surgical trauma. Especially following any peritoneal injury secondary to abdominal surgery, it is part of the healing process.

Equilibrium between fibrin deposition and degradation is critical in peritoneal healing or adhesion formation. Although our study revealed lower Nair Scores in the group receiving Ketorolac, the difference between the groups was not statistically significant. The fact that ketorolac does not reduce adhesions as much as other NSAID may be due to its COX-1 selectivity.

Post-operative ketorolac use was not associated with anastomotic leakage. However, ketorolac has been linked to a higher likelihood of reintervention, emergency department visits and rehospitalization in both colorectal and non-colorectal GI surgery [16, 25, 26]. Although Saleh et al. did not detect ketorolac-related anastomotic leakage, they suggested in their subgroup analysis that there may be a dose-related increased leakage rate with ketorolac use [17].

In contrast, Subendran et al. showed that this relationship was not dose-dependent [16]. Nevertheless, once anastomotic leaks are ruled out, intravenous ketorolac is effective in improving pain control and reducing post-operative ileus [26].

Furthermore, the beneficial effects of ketorolac on postoperative pain control and recovery may have contributed to a more favorable healing environment. Although this hypothesis cannot be confirmed by the present data, improved postoperative recovery and reduced ileus may indirectly support anastomotic healing through better nutritional status, earlier restoration of bowel function, and more efficient tissue remodeling.

Rat studies have also reported that this detrimental effect of NSAID with selectivity for COX-2 is more pronounced in proximal anastomoses [21, 27]. Similarly, Ghiselli et al. reported that ketorolac and diclofenac had no adverse effect on colo-colonic anastomoses or wound healing in a rat peritonitis model [23].

Nevertheless, if there are risk factors for an anastomotic leak (advanced age, malnutrition, serious comorbidities, intraoperative difficulties), it is important to respect the specific contraindications of NSAID and be cautious in the use of NSAID after surgery.

Unfortunately, there are limtations in this study. The absence of histopathological evaluation, which could have provided compelemntary information refarding inflammatory cell infiltration, collagen organization and the tissue remodeling.

Future studiese with multicenter randomized designs and larger sample sizes are warranted to further clarify the effects of ketorolac on intestinal anastomotic healing while minimizing potential sources of bias. In addition, evaluating different ketorolac doses, comparting other non-selective NSAIDs, and investing bot proximal and distal intestinal anastomoses may provide a comprehensive understanding of the effects of NSAIDs on anastomotic healing.

Within the limitations of this experimental model, ketorolac administration was not associated with impaired colorectal anastomotic healing and was accompanied by higer anastomotic bursting pressuers without signigicant changes in hydroxyproline levels.

CONCLUSION

With the current literature, it is not possible to recommend definitive guidelines for perioperative NSAID use after colorectal surgery. Although no study has recommended perioperative discontinuation of ketorolac or other NSAID after colorectal surgery, both have relevant findings that should be considered. Ideally, a sufficiently robust, randomized, multicenter study is needed to clarify the issue definitively.

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Conflicts of interest

Authors declare that they do not have any conflict of interest.

Ethical Disclosures

This study adheres to the ARRIVE guidelines; the checklist has been submitted.

The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of footnotes and/or figure legends.

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