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ORIGINAL ARTICLE

# Role of diclofenac sodium and paracetamol on colonic anastomosis: An experimental rodent model

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analgesia;
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**Summary** *Background:* Despite many advances in surgery and technology, colonic anastomosis remains a challenge after colonic resection. The purpose of this study is to compare the safety of using diclofenac sodium and paracetamol for analgesia in colonic anastomosis on rats.
*Methods:* Wistar–Hannover rats were randomly allocated to four groups: Group 1, sham-operated group; Group 2, control group; Group 3, diclofenac sodium group; Group 4, paracetamol group. After laparotomy, the left colon was transected and a single-layer anastomosis was made with 5/0 vicryl in Groups 2, 3, and 4. Only laparotomy was performed in Group 1. After anastomosis, we administered saline to Group 2, diclofenac sodium to Group 3, and paracetamol to Group 4 for 7 days. Then, all animals were decapitated. The anastomotic region was resected, and bursting pressure was measured. Then, the specimen was sent to the laboratory for histological examination and hydroxyproline analysis.
*Results:* Bursting pressure and hydroxyproline level were significantly higher in the paracetamol group ($p < 0.05$). When we looked at the fibrosis levels of these groups, it was also higher in paracetamol group.

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*Conclusion:* Bursting pressure, hydroxyproline levels, and fibrosis levels indicate that the perioperative use of paracetamol for analgesia when undergoing colonic anastomosis is safer than diclofenac sodium.


## 1. Introduction

The incidence of anastomotic leakage is 3—6% after colonic resection and 10—12% after rectal resection.[1]

The main factors affecting these complications are anastomotic tension, deterioration of blood supply, local trauma, obstruction, infection, and comorbid diseases of the patient.[2] Overall, 1% of patients who have anastomosis are rehospitalized because of anastomotic leakage and dehiscence or the duration of their hospital stay becomes longer and they may have to undergo reoperation.[3] Secondary interventions performed in such patients are very difficult.[3]

Paracetamol and diclofenac sodium, because of their analgesic, antipyretic, and anti-inflammatory effects, are widely used drugs in gastrointestinal surgery clinics.[4] Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). It is safe and effective when used in therapeutic doses.[5] It is used for the treatment of acute and chronic pain due to many different types of diseases.[6] The mechanism of action is via the inhibition of cyclooxygenase (COX).[7] It inhibits uptake and release of arachidonic acid.[7] The anti-inflammatory effect of diclofenac sodium depends on inhibition of COX, which arises from modulation of chemical mediators.[8]

Paracetamol is used for the treatment of postoperative pain alone or combined with other analgesics.[9] The mode of action of paracetamol is not clear.[9] Some studies showed that it exerts its effects centrally rather than peripherally.[10] It accomplishes its central effects by inhibiting the serotonergic pathway.[10]

Recent findings indicate that paracetamol is highly selective for COX-2 and is probably selective for COX-3.[11] Other mechanisms proposed for central effects are inhibition of L-arginine-nitric oxide, *N*-methyl-D-aspartate, and substance P pathways or active metabolite *p*-aminophenol that has effects on cannabinoid receptors.[12—14] The peripheral effect may be explained by the reduction of prostacyclin synthesis.[15]

The effects of paracetamol and diclofenac sodium, which are prescribed for analgesia after colorectal surgery, are controversial on the safety of anastomosis.

In this study, we aimed to demonstrate and compare the safety of using diclofenac sodium and paracetamol for the analgesia in colonic anastomosis.

## 2. Methods

### 2.1. Study design

Wistar—Hannover rats (300—500 g), supplied by the Bagcilar Training and Research Hospital Animal Center (BADABEM), Istanbul, Turkey, were maintained under laboratory conditions, housed in a controlled room with 12-hour light—dark cycles, and fed standard pellet chow and water *ad libitum*. Rats were divided into four groups of eight animals each, a sham group, a control group, and two experimental groups. On Day 0, laparotomy and manipulation of the left colon were performed in the sham group. The left colon was transected horizontally, and end-to-end anastomoses were constructed, in the control and experimental groups. The first experimental group received diclofenac sodium (4 mg/kg/d, intramuscularly; Diclomec; A. Ibrahim, Istanbul, Turkey), twice a day for 7 days; the second experimental group received paracetamol (50 mg/kg/d, intraperitoneally; Perfalgan; Bristol Myers Squibb, New York, NY, USA) once a day for 7 days. Rats were observed closely and had free access to water and standard rodent chow (MBD Animal Feed, Kocaeli, Turkey) throughout the entire experimental period. All groups were sacrificed by cardiac puncture under high-dose ketamine anesthesia on postoperative Day 7. The Bagcilar Training and Research Hospital Animal Care and Use Committee approved all experimental procedures.

### 2.2. Operative procedure

Abdomens of rats were shaved under ketamine hydrochloride (50 mg/kg; Ketalar; Parke-Davis, Istanbul, Turkey) and xylazine (10 mg/kg; Rompun; Bayer, Istanbul, Turkey) anesthesia. After cleaning the abdominal part with 10% povidone—iodine solution (Betadine, Bagcilar Training and Research Hospital, Istanbul, Turkey) a 3-cm midline laparotomy was performed. The left colon was transected horizontally by using a standard scalpel in control and experimental groups. End-to-end anastomosis was done with eight single-layer, inverting, interrupted sutures (Vicryl 5/0; Sutures Limited UK, Wrexham, UK). The abdominal incision was closed in two layers with a 3.0-silk suture (Dogsan, Trabzon, Turkey). All surgical procedures were performed by the same surgeon. During the operations, body temperature was maintained at 38°C by using a heated operating table. Intestines were covered with gauze pads soaked with 0.9% NaCl to minimize desiccation. To prevent dehydration, 10 mL of 0.9% NaCl was administered subcutaneously after the operation. Feeding was started immediately after the operation. The first experimental group received diclofenac sodium (4 mg/kg/d, intramuscularly; Diclomec; A. Ibrahim) for 7 days. The second experimental group received paracetamol (50 mg/kg/d, intraperitoneally; Perfalgan; Bristol Myers Squibb) for 7 days. The daily dose of diclofenac sodium was divided into two parts, which were given at least 8 hours apart during the experimental period, whereas paracetamol was given once a day and was initiated just after the surgery.

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