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Research

Diclofenac causes anastomotic leakage in the proximal colon but not in the distal colon of the rat

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Abstract

BACKGROUND: Nonsteroidal anti-inflammatory drugs have been associated with anastomotic leakage. It was studied if diclofenac affects anastomoses differently depending on the location in the gut.

METHODS: Ninety-five rats were randomized to 6 groups with an anastomosis in either ileum (IL), proximal colon (PC), or distal colon (DC). Groups IL+ (n = 10), PC+ (n = 30), and DC+ (n = 10) received diclofenac (3 mg/kg/day) from day 0 until sacrifice on day 3. Group PC− (n = 15) did not receive diclofenac. Groups PC1+ and PC2+ (n = 15 each) were given diclofenac from day 1 to 4 and from day 2 to 5.

RESULTS: Leak rates were 10/10 in group IL+, 22/30 in PC+, 1/10 in DC+, and 1/15 in PC−. Delayed administration of diclofenac by 1 or 2 days (6/15, $P = .05$) resulted in reduced leakage rates. Mechanical strength results corresponded with leak rates.

CONCLUSIONS: Diclofenac causes leakage of anastomoses in rat IL and PC, but not in the DC. This suggests a role for the ileal and proximal colonic content in diclofenac-induced leakage.

Leakage is the most serious complication of surgeries that include the construction of intestinal anastomoses and is associated with a mortality between 6% and 15%.[1] Leakage occurs in 3% to 14% of all intestinal anastomoses, a percentage that has not significantly changed in the past 2 decades.[1–3] Although the highest rates have been reported for the most distal rectal anastomoses, ileocolonic anastomoses also may leak in up to 10% of the cases.[4] The persistence of high leakage rates is indicative of insufficient understanding of leakage etiology and urges for improving knowledge of factors influencing anastomotic healing.

In 3 retrospective studies and a recent review of randomized clinical trials, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with increased rates of anastomotic leakage.[4–7] In rat studies, NSAIDs with selectivity for COX-2 (carprofen, diclofenac, and celecoxib) have repeatedly shown to cause leakage of ileal, but not of distal colonic anastomoses.[8–10] Despite these data, NSAIDs are listed as perioperative analgesia for gastrointestinal surgery in present international guidelines and are recommended in fast track surgery.[11]

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More evidence is necessary to better understand the pathological mechanisms involved and, possibly, to adjust postoperative pain treatment recommendations.[12,13]

Two hypotheses for a detrimental effect of NSAIDs have been raised. First is the general suppressive effect of COX-2 inhibition on the principal inflammatory and proliferative activity in the early phase of wound healing.[4,8] Second is the formation of microthrombi by COX-2 inhibition inducing ischemia.[5] So far, evidence supporting either hypothesis and at the same time explaining the difference between ileum (IL) and distal colon (DC) is lacking. In fact, other mechanisms than a direct effect of COX-2 inhibition on wound healing may play a role.

Previous studies have shown that COX-2 inhibitors cause leakage of ileal but not distal colonic anastomosis in rats.[9,10] A possible explanation is that the rat DC is thicker and stronger than the IL and thus more resistant to leakage. However, IL and DC also differ in fecal content with respect to liquidity, microflora, and bile acids. A good way to study the relevance of the gut content is to investigate the effect of NSAID on anastomotic healing of the proximal colon (PC), where gut morphology is more similar to DC, but intraluminal content corresponds to the distal IL. This study investigates the effects of diclofenac on early anastomotic healing in the PC of the rat.

Patients and Methods

Ethics

This experiment was conducted according to the Dutch "Experiments on Animals Act" and European Federation of Laboratory Animal Science Associations guidelines and was approved by the institutional Animal Ethics Committee of the Radboud University. After the start of the experiment, the animals were inspected twice daily for signs of reduced well-being, including dirty nose, dirty eyes, piloerection, aberrant behavior, distended abdomen, or diarrhea. Animals were weighed daily. Humane endpoints were defined to avoid unnecessary suffering of animals during the study period.

Animals

Adult male Wistar rats (Harlan, Horst, The Netherlands) were accustomed to laboratory conditions for 1 week and weighed 309 (standard deviation ±24) g at the start of the experiment. The rats were housed 2 per cage at 22 to 23°C with a 12 hour day cycle and had free access to standard rodent chow (Ssniff R/M-H, Bio Services BV, Uden, Netherlands) and acidified tap water. The cages were enriched with a shelter and nesting material and were randomly placed on the shelves.

Groups

Ninety-five rats were randomly assigned to one of the 6 groups (Fig. 1). Rats in group PC− (n = 15) served as control group and were subjected to a PC anastomosis without receiving diclofenac. An anastomosis was made in the IL in group IL+ (positive control; n = 10), in the DC in group DC+ (negative control; n = 10), and in the PC in group PC+ (n = 30), all receiving diclofenac for 3 days with the first dose given 15 minutes before operation. Rats in groups PC1+ (n = 15) and PC2+ (n = 15) had a PC anastomosis and also received diclofenac for 3 days but with the first dose delayed 1 or 2 days after operation, respectively.

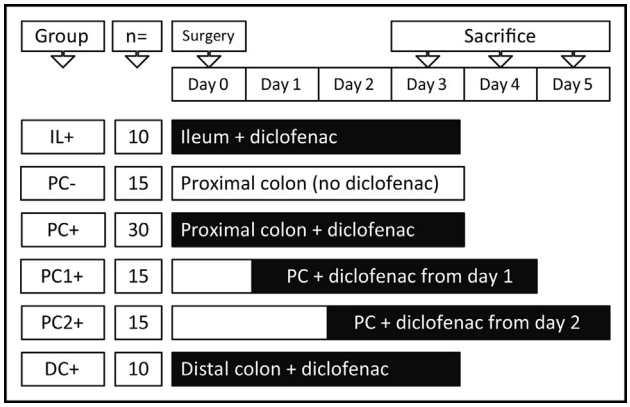

Figure 1 Experimental setup.

Intervention and surgical technique

The rats were anesthetized by inhalation of 3% isoflurane (Abbott, Hoofddorp, The Netherlands) mixed with pressurized air and oxygen. They were shaved and operated under sterile conditions with the aid of an operation microscope at 10× magnification.

Through a 3 cm midline laparotomy, a 1 cm resection was performed of either the IL (15 cm proximal to the cecum), the PC (2 cm from the ileocecal transition), or the DC (3 cm proximal to the peritoneal reflection), and continuity was restored with an inverted single layer anastomosis made by 8 interrupted 8-0 Ethilon (Ethicon, Norderstedt, Germany) sutures. Precautions were taken preventing leakage of intestinal content into the abdominal cavity. During the operation, the intestine was covered with gauzes soaked in .9% NaCl to minimize desiccation. Body temperature was kept at 38°C with a heating pad and lamp. The abdominal wall was closed with a running suture (Vircryl 3-0; Ethicon) and the skin with staples. Immediately postoperatively, 10 ml of .9% NaCl was administered subcutaneously for rehydration. For analgesia, buprenorphine (Schering Plough, Houten, The Netherlands) .02 mg/kg was given subcutaneously every 12 hours, starting 15 minutes before the operation and ending 48 hours later. Diclofenac sodium (Cayman Chemical Company Ann Arbor, MI) was dissolved in .1% polysorbate in saline and was given in a dose of 3 mg/kg/day (in 2 equal doses) by oral gavage for 3 days.

Outcome assessment

On postoperative day 3, animals from groups PC+, PC−, IL+, and DC+ were euthanized by CO_2 asphyxiation. For