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Parecoxib's effects on anastomotic and abdominal wound healing: a randomized control trial

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ABSTRACT

Background: Current evidence regarding the effects of selective cyclooxygenase inhibitors on gastrointestinal anastomoses is controversial. An experimental randomized control study was conducted in our institution to histopathologically evaluate the consequences of parecoxib, on intestinal and abdominal wound healing.

Methods: Twenty-four adult Wistar rats underwent laparotomy, ascending colon transection, and hand-sewn anastomosis. They were randomized to receive either parecoxib (0.5 mg/kg twice daily) or 0.9% normal saline by intraperitoneal injection postoperatively. Animals were euthanized either on the third or the seventh postoperative day. Semi-quantitative methods were used to evaluate both intestinal and abdominal wounds for inflammatory cell composition, angiogenesis, fibroblasts, granular tissue, collagen deposition, epithelization, and presence of necrosis, exudate, and abscess formation. Results are presented as (parecoxib: median [IQR] *versus* control: median [IQR], *P*-value).

Results: No macroscopic anastomotic leakage or wound dehiscence was observed. Intestinal anastomoses in the parecoxib group, showed significantly decreased epithelization (2 [1] *versus* 3 [1], [$P = 0.004$]) and collagen deposition (2 [0] *versus* 3 [1], [$P = 0.041$]). No difference was observed in angiogenesis (3 [1] *versus* 2.5 [1], [$P = 0.158$]). Abdominal wall specimens appeared to demonstrate decreased epithelization (2 [2] *versus* 4 [0.5], [$P = 0.0004$]) in the treatment group. No difference between the two groups was identified regarding collagen deposition (2.5 [1] *versus* 2 [0.5], [$P = 0.280$]) and angiogenesis (2.5 [1] *versus* 2 [1], [$P = 0.633$]). Necrosis was significantly more present in the parecoxib group in both specimen types, (3.5 [1] *versus* 2.5 [1], [$P = 0.017$]) and (3 [1] *versus* 1 [0.5], [$P < 0.0001$]).

Conclusions: The present study shows that despite the absence of clinical adverse effects, parecoxib can impair anastomotic and abdominal wound healing on a histopathological level.

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Introduction

"Fast-track" rehabilitation protocols after colorectal surgery have encouraged the use of opioid-sparing analgesia, with nonsteroidal antiinflammatory drugs (NSAIDs) being increasingly administered in the postoperative period. Inhibition of the 2-cyclooxygenase isoenzymes (COX-1, COX-2) is the primary mechanism of action by which NSAIDs produce their analgesic effects.[1,2] Selective drugs have been developed that preferentially inhibit either COX-1 or COX-2. The former display considerable side effects, presumably resulting from the inhibition of COX-1, with gastric ulceration and bleeding disorders being the most troublesome. Therefore, selective COX-2 inhibitors are preferred as postoperative analgesics since they are considered safer than non-selective NSAIDs.[3]

Anastomotic leak following colorectal surgery is a potentially serious complication resulting in an increased postoperative morbidity and mortality. Inhibition of cyclooxygenases has been suggested as a possible risk factor for the development of anastomotic leakage and impairment of cutaneous wound healing.[4-7] Experimental studies have shown inferior anastomotic healing following the use of either non-selective or selective NSAIDs.[8-10] Besides, clinical observational studies have reported increased frequency of anastomotic leakage with the administration of both types of NSAIDs following colorectal surgery.[11-14] On the other hand, a recent multicentre clinical study showed that early use of NSAIDs is associated with a reduction in postoperative adverse events following major gastrointestinal surgery.[15]

The investigation of the possible adverse effects of a selective COX-1 or COX-2 inhibitor on intestinal or abdominal wound healing in humans, in terms of a randomized control trial, may encounter ethical limitations. Thus, current research studies are being conducted in an experimental model using animals either rabbits or rats.[8-10] The purpose of the present experimental study was to microscopically evaluate the effects of a widely used in clinical practice, selective COX-2 inhibitor: parecoxib, on colonic anastomotic and abdominal wound healing in a rat model.

Methods

Animal model

The study protocol was approved by the Athens Prefecture Directorate of Veterinary Services (EL 25 BIO 024, 1582/19.03.2012) and the Ethical Committee of the second Department of Surgery "Aretaieio" Hospital, National and Kapodistrian University of Athens School of Medicine, Athens, Greece, (M-108/23-02-2012). Twenty-eight male Wistar rats with a median weight of 290 g (260–320 g) were obtained from Hellenic Pasteur Institute. All animals were housed two per cage under standard conditions, controlled light cycle (12-h light and 12-h darkness), temperature (22°C ± 2°C), and humidity (45%-65%). Animals were allowed a minimum acclimatization of 7 d before the commencement of the experimental phase. All rats were given ad libitum access to food (standard laboratory rat chow, 4RF25 – Mucedola, Milano, Italy) and water. All procedures were performed in accordance with the European Directive of November 24, 1986 (86/609/EEC), regarding the protection of animals used for experimental and other scientific purposes.

Experimental design—operative technique

Using an online randomization software (www.randomizer.org), each rat was assigned a unique number from 1 to 24. The randomization process generated two numerically equal groups. Group 1 was decided to be the treatment group, whereas group 2 was the control one. All procedures were performed by a consultant surgeon (GPF) blindly assigned to group allocation, on a specific day and time each week and under veterinary supervision. After a general anesthesia with intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg), the rats were placed in supine position, shaved and prepared with povidone-iodine. A 4-cm midline laparotomy was performed followed by an ascending colon transection (2–3 cm distally of the ileocaecal junction; Fig. 1). An end-to-end anastomosis was constructed in a single-layer interrupted technique with 6/0 monofilament polydioxanone sutures (PDS). The abdominal wound was closed in a two-layer fashion with 3/0 MonoPlus sutures. Postoperatively, rats were given ad libitum access to food and water. Group 1 received parecoxib at a clinically relevant dose of 0.5 mg/kg intraperitoneally twice a day,[16] whereas group 2 received 0.9% normal saline (placebo). All animals were observed thrice a day for overall activity which was characterized either as impaired or unimpaired in comparison with an equivalent group of rats that have not undergone yet the

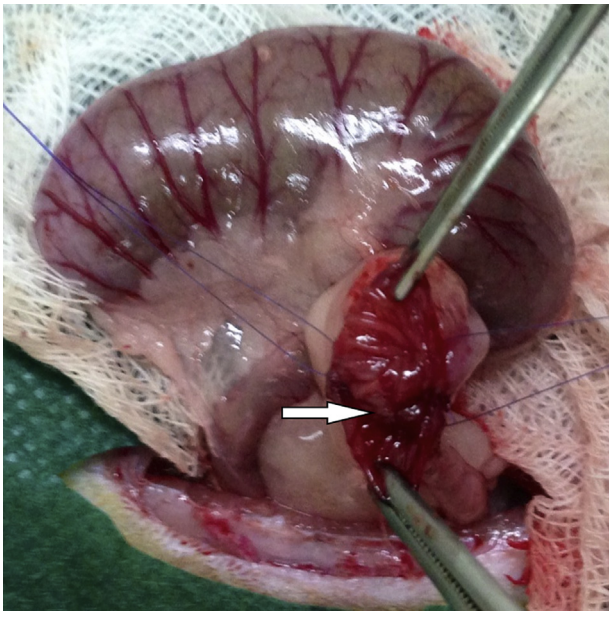

Fig. 1 – Intraoperative photo depicting the colo-colic end-to-end hand-sewn anastomosis at the ascending colon. (Arrow shows the posterior wall of the anastomosis). (Color version of figure is available online.)