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# The effects of iloprost on colonic anastomotic healing in rats under obstructive ileus conditions

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## ABSTRACT

**Background:** The aim of this study was to investigate the effects of iloprost, on colonic anastomotic healing in rats, under obstructive ileus conditions.

**Materials and methods:** Eighty male Albino rats were randomized into four groups of 20 animals each. They underwent colonic resection followed by an inverted anastomosis. The rats of group 1 (control) and group 2 (ileus) received 3 mL of saline 0.9% intraperitoneally and those of group 3 (iloprost), and group 4 (ileus + iloprost) iloprost (2 µg/kg of body weight), immediately postoperatively and daily until the day of sacrifice. Each group was further divided into two equal subgroups, depending on the day of sacrifice. The animals of subgroup "a" were sacrificed on the fourth postoperative day, whereas those of "b" on the eighth day. Macroscopic and histologic assessment was performed, whereas anastomotic bursting pressures and the tissue concentrations in hydroxyproline and collagenase I were evaluated. **Results:** Means of bursting pressure, neoangiogenesis, fibroblast activity, and hydroxyproline concentration were significantly increased in group 4 compared with group 2. In addition, on the fourth postoperative day, the inflammatory cell infiltration and the collagenase I concentration were significantly decreased in group 4 compared with group 2. Moreover, on the eighth postoperative day, collagen deposition was significantly increased in group 4 compared with group 2.

**Conclusions:** Iloprost after intraperitoneal administration reverses the negative effect of obstructive ileus. It promotes not only the angiogenic activity but also collagen formation, resulting in increased bursting pressures on the fourth and eighth postoperative days.

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## 1. Introduction

Anastomotic leakage is a serious complication in colorectal surgery that increases postoperative morbidity and mortality

rates [1,2], especially after urgent procedures, for example, after colonic obstruction by colorectal cancer. Numerous local and systemic factors can impair the healing mechanism, leading to anastomotic dehiscence [3,4].

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Obstructive ileus is a major local and systemic factor, which impairs the anastomotic healing process. Because of the obstruction, the collagen at the proximal anastomotic edge is degraded, leading to increased rates of anastomotic dehiscence, especially at the antimesenteric site [5]. Iloprost, a stable analog of prostacyclin, is a potent vasodilator and inhibitor of platelet aggregation, which also shows cytoprotective action as it improves colonic mucosa microcirculation and inhibits leukocyte adhesion on the vessel endothelium in case of endotoxemia [6–8].

In a previous experimental study, we have demonstrated that iloprost after intraperitoneal administration promotes the healing of colonic anastomosis [9]. The main field of interest in urgent colorectal surgery still remains the enhancement of anastomotic integrity, in patients undergoing one-step approach, mainly after colonic obstruction. To our knowledge there is no up-to-date study evaluating the impact of this further used vasodilator on the colonic anastomotic healing under obstructive conditions.

The aim of this present experimental study was to investigate the effects of intraperitoneal administration of iloprost, on colonic anastomotic healing in rats, under artificial obstructive conditions.

## 2. Materials and methods

The experimental study was designed under the supervision and permission of the Department of Veterinary Services of the Prefecture of Thessaloniki (S.N.: 13/12, 355/26-09-08). All animals received humane care in accordance with the “Principles of Laboratory Animal Care,” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals,” prepared by the Institute of Laboratory Animals Resources and published by the National Institute of Health (NIH Publication No. 96-01, revised 1996).

Eighty male Albino–Wistar rats, weighing between 20 and 300 g were used. The animals were housed individually under stable conditions and had unrestricted access to standard food and tap water. All rats were weighed on the day of operation and before sacrifice. They were acclimatized to our laboratory for a week preoperatively and did not receive any course of chemoprophylaxis.

### 2.1. Anesthesia and operative technique

The animals were anaesthetized by an intraperitoneal injection of thiopental (30 mg/kg of body weight). Surgery was performed under standard aseptic conditions through a 3-cm midline incision. A 1-cm colonic segment, 5 cm proximal to the rectum, was resected. An end-to-end anastomosis was performed using eight interrupted sutures (6/0 polypropylene) in one-layer way, and the abdominal wall was closed with three interrupted 3-0 silk sutures. Obstructive conditions were achieved, in specific study groups (groups 2 and 4), by ligating the large bowel with a 3-0 silk suture 5 cm above the rectum, 24 h before primary anastomosis was performed. The use of ligation (silicon ring or suture) of the bowel is a well known and widely used method to represent experimentally the effects of bowel obstruction. The absence of peristalsis in

paralytic ileus could not represent accurately the dynamic changes affecting the anastomosis integrity [10–12].

### 2.2. Groups

The animals were randomized to groups and subgroups through the use of computer-generated random numbers, and there was allocation concealment after randomization.

#### 2.2.1. Group 1 (control), n = 20

Subgroup 1a, (n = 10): primary anastomosis and intraperitoneal injection of 3 mL of NaCl 0.9% solution, immediately postoperatively and daily from the first to the third postoperative day. Subgroup 1b, (n = 10): primary anastomosis and intraperitoneal injection of 3 mL of NaCl 0.9% solution, immediately postoperatively and daily from the first to the seventh postoperative day.

#### 2.2.2. Group 2 (ileus), n = 20

Subgroup 2a, (n = 10): obstructive conditions for 24 h, primary anastomosis and intraperitoneal injection of 3 mL of NaCl 0.9% solution, immediately postoperatively and daily from the first to the third postoperative day.

Subgroup 2b, (n = 10): obstructive conditions for 24 h, primary anastomosis and intraperitoneal injection of 3 mL of NaCl 0.9% solution, immediately postoperatively and daily from the first to the seventh postoperative day.

#### 2.2.3. Group 3 (iloprost) n = 20

Subgroup 3a, (n = 10): primary anastomosis and intraperitoneal injection of iloprost (2 µg/kg body weight), immediately postoperatively and daily from the first to the third postoperative day.

Subgroup 3b (n = 10): primary anastomosis and intraperitoneal injection of iloprost (2 µg/kg body weight), immediately postoperatively and daily from the first to the seventh postoperative day.

#### 2.2.4. Group 4 (ileus + iloprost) n = 20

Subgroup 4a (n = 10): obstructive conditions for 24 h, primary anastomosis and intraperitoneal injection of iloprost (2 µg/kg body weight), immediately postoperatively and daily from the first to the third postoperative day.

Subgroup 4b (n = 10): obstructive conditions for 24 h, primary anastomosis and intraperitoneal injection of iloprost (2 µg/kg body weight), immediately postoperatively and daily from the first to the seventh postoperative day.

### 2.3. Macroscopic examination

All animals of the subgroup “a” were sacrificed on the fourth postoperative day, whereas those of subgroup “b” on the eighth postoperative day. During postmortem examination, the anastomotic integrity, the adhesion formation, the existence of perianastomotic abscess, or any sign of peritonitis was recorded. The results were evaluated in a blind fashion according to the scale of van der Hamm *et al.* [13], as follows: 0 = no adhesions, 1 = minimal adhesions, mainly between anastomosis and the omentum, 2 = moderate adhesions, between the omentum and the anastomotic site and/or between

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