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2-Octylcyanoacrylate for the prevention of anastomotic leak

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ABSTRACT

Background: Anastomotic leak after colorectal surgery is a significant cause of morbidity and mortality. The aim of this study was to evaluate the impact of a reinforced colo-colonic anastomosis with tissue adhesive, 2-octylcyanoacrylate (2-OCA), on the integrity of anastomotic healing as measured by anastomotic bursting pressure.

Methods: Sixty-eight female Sprague–Dawley rats underwent a rectosigmoid colon transection and a sutured end-to-end anastomosis followed by randomization to receive no further intervention or reinforcement with the tissue adhesive, 2-OCA. After seven postoperative days, a macroscopic assessment of the anastomosis, mechanical assessment to determine anastomotic bursting pressure, and a detailed semi-quantitative histopathologic healing assessment were performed.

Results: Thirty-four animals were randomized to each group. Study characteristics did not differ between the groups. There was also no difference in the degree of adhesions present postoperatively. Although there was no difference between the net proximal and distal luminal areas in the two groups (0.37 cm^2 *versus* 0.55 cm^2, $P = 0.26$), the 2-OCA group exhibited evidence of stricture in 15% of anastomoses as compared with 3% in the suture-only group ($P < 0.0001$). Histologically, the presence of only fibroblasts density was statistically more evident in the 2-OCA group compared with the sutured-only anastomosis ($P = 0.0183$). There was not a significant increase in mechanical strength in the 2-OCA group (238.9 mm Hg) *versus* in the suture-only group (231.8 mm Hg). There was no difference in the rate of anastomotic leak in the 2-OCA as compared with the suture-only group (9.1 *versus* 8.8%).

Conclusions: Application of 2-OCA to reinforce a colo-colonic anastomosis clinically provides no benefit to its mechanical strength and detrimentally increases the rate of obstruction and/or stricture in this *in vivo* model.

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Introduction

Disseminated intraperitoneal cancers, such as ovarian cancer, frequently involve the bowel and upper abdomen. Anastomotic leak after colorectal surgery is a significant cause of morbidity and mortality with the incidence in the gynecologic literature ranging from 0.8% to 6.8%.[1] In the colorectal literature, mortality rates associated with anastomotic leak range from 6% to 22%.[2-6]

Many factors impact anastomotic healing including the surgical technique employed, prolonged operative times, tension on the anastomosis, nutritional status of the patient, comorbidities, type of material used for the anastomosis, distance from the anal verge, previous pelvic irradiation, and experience of the surgeon.[2] Many techniques have been attempted to provide "prophylaxis" against anastomotic leaks, including intraperitoneal drains, a protective stoma, and fibrin glue.[7-11] Only a protective stoma has been shown to consistently and significantly reduce the overall risk of a clinical leak, as well as the need for reoperation.[12-14] However, not only are there inherent complications with ostomy surgery but also a patient's quality of life is negatively impacted by this procedure.[15]

Cyanoacrylate was first manufactured in 1949, and tissue adhesives have been in use for more than 20 y. Their composition has been constantly improved over the years, and most recently 2-octylcyanoacrylate (2-OCA) has been shown to have less toxicity and three times the strength as its predecessor, N-butyl-2-cyanoacrylate.[16] The US Food and Drug Administration, along with its indication for closure of incised skin, approved 2-OCA for use against common bacterial microbes, including certain staphylococci, pseudomonads, and *Escherichia coli*.[17] Experimentally, 2-OCA and similar products have been used in urologic, vascular, and gastrointestinal surgery in animals ranging from rats and rabbits to dogs and monkeys.[18,19] Tissue adhesives before 2-OCA have been used for ureteroureteral anastomoses, vascular anastomoses, and bronchial anastomoses.[20-22] In gastrointestinal surgery specifically, 2-OCA has been used intraperitoneally for reinforcement of pancreaticojejunostomies to reduce the risk of pancreatic fistula formation in human patients.[23]

Recently, tissue adhesives have been used to attempt a sutureless colonic anastomosis and using the tissue adhesive as a sealant in high-risk anastomoses.[24-33] Although a sutureless anastomosis could decrease operative times and decrease the risk of intraoperative needle sticks, it has not been shown to provide equivalent strength to a conventional sutured anastomosis.[25,30] In addition, many surgeons would be skeptical about a sutureless anastomosis given that patients undergoing gastrointestinal surgery suffer from many of the previously described preoperative risk factors of impaired nutrition and multiple comorbidities.

Anastomotic leaks not only have a significantly negative impact on the patient but also increase the total clinical and economic burden on the physician, care team, and hospital.[34] In an *ex vivo* animal model, 2-OCA showed promise by significantly increasing the anastomotic bursting pressure (ABP) of a colonic anastomosis.[31] This study attempts to develop a unique technique to improve colonic anastomoses, with respect to anastomotic leaks, utilizing an *in vivo* animal model to determine the change in anastomotic strength between a standard hand-sewn colo-colonic anastomosis with and without reinforcement with 2-OCA.

Methods

This study included 74 female Sprague–Dawley rats weighing approximately 250-400 g. The procedures and study were conducted in accordance with the Institutional Animal Care and Use Committee of Cleveland Clinic guidelines as well as complied with the requirements of the Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals. The animals were initially acclimatized for 72 h before performance of any procedure and were housed individually. Six animals served as controls to perfect the model, initial bursting measurements, and standardization of the histopathologic assessment.

The rats were given a liquid diet consisting of a nutritional supplement 10-12 h before surgery without bowel preparation. Anesthesia was in the form of vaporized isoflurane. The abdomen was shaved followed by aseptic application of chlorhexidine gluconate and isopropyl alcohol. Ceftriaxone (75 mg/kg IM) was administered, and a single incisional infiltration of 0.25% bupivacaine was given preoperatively. Surgical instruments and surgical technique were performed in an aseptic manner under an operating microscope.

Randomization and blinding

The rats were randomized to a standard hand-sewn anastomosis or reinforcement with 2-OCA in equal numbers. The randomization procedure utilized a blocked scheme to minimize any impact of improvement in the surgical technique over time. The macroscopic and histopathologic assessment was performed by a blinded surgeon and pathologist, respectively. The bursting pressure measurement was performed by the nonblinded surgeon; however, this measurement was standardized across both groups given that an infusion pump with a predetermined rate was used.

Surgical procedure in control group

A median laparotomy was performed, and the sigmoid colon was mobilized. There was complete transection of the lumen and an interrupted inverting, single-layer, Lembert technique was implored to complete an end-to-end colo-colonic anastomosis, using a monofilament absorbable suture (Maxon; Medtronic, Minneapolis, MN) (Fig. 1). If stool was present at the anastomotic line, this was removed before reanastomosis. Each suture was spaced approximately 2-3 mm apart with an overall length across the anastomotic line of 3-4 mm. The colon was returned to the abdomen, and the abdomen was closed in layers with suture.