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Reinforcement of the colon anastomosis with cyanoacrylate glue: a porcine model

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ABSTRACT

Background: Previous experimental studies on cyanoacrylate (CA) glue for the prevention of colorectal anastomotic leakage (AL) have shown promising results. The aim of this study was to investigate the effect of CA in prevention of leakage in a porcine model of ischemic colorectal AL. **Methods:** Twenty-four animals were divided into four groups of six: (1) ischemic anastomosis with sufficient suture (ISCH), (2) ischemic anastomosis with sufficient suture and CA reinforcement (CA-ISCH), (3) ischemic anastomosis with insufficient suture (ISCH-AI), and (4) ischemic anastomosis with insufficient suture and CA reinforcement (CA-ISCH-AI). In CA groups, N-butyl-2-cyanoacrylate was applied between the colon ends. Anastomotic bursting pressure, abscess formation, and adhesion formation were evaluated on postoperative day 7. Tissue samples were obtained for histologic evaluation of foreign body reaction.

Results: The AL rate was 4 of 6 (67%) in the ISCH-AI group compared with none in the other three groups. The ISCH and ISCH-AI groups had significantly higher AL scores compared with the CA groups. The mean anastomotic bursting pressure was 167 ± 54 mm Hg in the ISCH-group versus 213 ± 43 mm Hg in the CA-ISCH-group ($P =$ nonsignificant) and 145 ± 102 mm Hg in the ISCH-AI group versus 187 ± 19 mm Hg in the CA-ISCH-AI group ($P =$ nonsignificant). The average adhesion score was significantly higher in the ISCH group than in the CA-ISCH group (4.2 ± 1.3 versus 1.7 ± 0.82 ; $P = 0.019$). Stricture of the anastomosis occurred only in the non-CA groups (3/12, 25%).

Conclusions: Anastomotic reinforcement with CA is effective and safe to prevent leakage in a high-risk colorectal anastomosis in a porcine model.

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Introduction

Anastomotic leakage (AL), with an incidence between 3% and 19%, is a severe complication after colorectal surgery and is associated with high morbidity and mortality rates.^{1,2} Despite proper patient selection and operative technique, AL cannot be completely avoided.

Staple line or anastomotic reinforcement techniques have been developed in attempts to decrease leakage in the first week postoperatively. A recent review published by Betzold *et al.* described three main categories of products that reinforce the anastomosis including permanent, semi-absorbable, and bioabsorbable materials.³ Of the bioabsorbable materials, only fibrin glue and the polyglycolic acid–trimethylene carbonate reinforcement of staple lines (Gore-Tex Bioabsorbable Seamguard; W.L Gore and Associates, Flagstaff, AZ) have been investigated in clinical trials on colorectal surgery.⁴⁻⁷ The fibrin glue study included 223 patients undergoing laparoscopic rectal surgery but could not show a significantly reduction in AL.⁷ Also, in the largest, randomized, controlled trial including 258 patients with application of Gore Seamguard could not show a reduction.⁶

The use of a synthetic, bioabsorbable reinforcement material for the anastomosis has considerable advantages over nonabsorbable or semi-absorbable staple line reinforcement and may help to reduce anastomotic dehiscence while avoiding the risk of strictures.^{1,4} N-butyl-2-cyanoacrylate (CA) is one of these biodegradable tissue adhesives. In our previous *ex vivo* porcine study and *in vivo* rat studies, CA had the highest mechanical strength in normal anastomoses, incomplete “insufficient” anastomoses, and anastomoses in a bacterially contaminated field, compared with other tissue adhesives.⁸ Besides the good adhesiveness of CA to the colonic surface, CA also enhanced the anastomotic healing by mediation of anti-inflammatory macrophages, and no adverse foreign body reaction could be observed.^{9,10}

The promising results from these previous experimental studies suggest that CA may be used safely to reinforce colorectal anastomoses. The objective of the present study was to investigate if the application of CA could prevent anastomotic leakage (AL) defined as either fecal peritonitis or macroscopic dehiscence of the anastomosis in a translational porcine model of a partially ischemic colo-colonic anastomosis.

Materials and methods

Study design

This study was a prospective, randomized, controlled animal experiment evaluating the effectiveness of N-butyl-2-cyanoacrylate, to prevent colo-colonic AL in pigs with a partially ischemic colo-colonic anastomosis using AL (dehiscence of the anastomosis or fecal peritonitis) as the primary outcome parameter. All experiments were performed with approval of the Erasmus University Medical Center Animal Care Committee in accordance with national law regarding the protection of animals, approval number DEC-3167; 105-13-07. The

article was written according to the Animal Research: Reporting In Vivo Experiments guidelines.

Experimental animals

Twenty-four female domestic pigs (Yorkshire × Landrace), with an average weight of 40.7 ± 3.0 kg, were purchased from a licensed breeder in the Netherlands. The sex of the pigs was chosen based on previous literature.^{11,12} The pigs were randomly divided into four groups of six animals per group; the randomization occurred based on the breeder assigned ear number of the pigs. The pigs were operated in pairs, and the animal with the lowest ear number was assigned to a glue group. In the next session, the opposite order was used the animal with the lowest ear number was assigned to a nonglue group. All animals were housed in pairs and had an acclimatization period of 1 wk before operation. Pigs were fed 2 kg of pig feed daily and had free access to water.

Anesthesia and operative procedure

The animals were fasted 1 d before surgery but with free access to fluid. Preoperatively, the animals were sedated with tiletamine/zolazepam (5 mg/kg), xylazine (2.25 mg/kg), and atropine (0.03 mg/kg) intramuscularly. Colon preparation was achieved by administration of sodium phosphate enema (Colestymin; Tramedico BV, the Netherlands) directly after induction of anesthesia to allow easier transrectal introduction of the empty circular stapler. An ear vein was used for intravenous fluid administration of 500 mL of 5% glucose throughout the procedure. General anesthesia was maintained by intubation and ventilation with O₂/N₂ (1/3 vol/vol) enriched with 1%-3% isoflurane. Animals received a single intramuscular dose of procainebenzylpenicilline/dihydrostreptomycin (per mL. 200.000 i.E./200 mg; 0.05 mL/kg) as antibiotic prophylaxis, and buprenorphine (0.015 mg/kg) for analgesia. Depth of anesthesia was monitored by regular checking absences of pain reflexes and cardiac monitoring.

A midline laparotomy was conducted after standard aseptic preparation of the surgical field, and the distal colon was exposed. Subsequently, the mesenteric branches were ligated over a length of 10 cm and the mesentery was cleared from the serosa of the colon in the same area to achieve an ischemic 10 cm segment. Before and after ligation of the mesenteric vessels, the Local Hemodynamic Index (LHI) was measured with a miniaturized, Dynamic Light Scattering device (Elfor; Elfi-Tech Ltd, Israel) to evaluate the degree of ischemia.¹³

In all groups, the distal colon was transected at approximately 40 cm from the anal verge. The colo-colonic anastomosis was constructed hand-sewn end-to-end using an empty (staplers were removed) circular 28 mm stapler (Chex CS surgical staplers; Arseus Medical, distributor of Frankenman International Limited, Hong Kong).¹² The empty circular stapler was used to facilitate the application of the CA glue between both ends and to standardize the formation of the inverted hand-sewn anastomosis. The proximal colon cutting edge was secured around the anvil with a purse-string suture (4.0 PDS; Johnson & Johnson, Medical BV, the Netherlands). The shaft of the stapler was inserted transanally, and the lower cutting edge

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