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ORIGINAL ARTICLE

Suture-Free Anastomosis of the Colon Experimental Comparison of Two Cyanoacrylate Adhesives

Jiri Paral · Zdenek Subrt · Petr Lochman · Leo Klein · Dimitar Hadzi-Nikolov · Zdenek Turek · Martin Vejbera

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Abstract
Background We explored the potential of two cyanoacrylate tissue adhesives for constructing colonic anastomoses.
Method The study involved 12 female domestic pigs. The animals were divided into two equal groups. In both groups, the sigmoid colon was transected. An intestinal anastomosis was constructed with a modified circular stapler (all staples were withdrawn) and cyanoacrylate tissue adhesives. Glubran 2® was used in group A and Dermabond® was applied in group B. Fourteen days after the first operation, a follow-up surgery was performed in both groups. The glued section of the colon was resected, processed with the standard paraffin technique and stained with haematoxylin–eosin. The finished specimens were examined under light microscopy. Assessments were made for the presence of fibroblasts, neutrophils, giant polynuclear cells, neovascularisation and collagen deposits. Adhesions, anastomotic dehiscence, peri-anastomotic inflammation and intestinal healing were assessed peri-operatively.
Results All anastomoses in group A healed with no signs of pathology. In group B, fibrotic adhesions and stenoses tended to occur in areas surrounding the anastomoses. Histological examinations confirmed increased fibrosis.
Conclusion The tissue adhesive Glubran 2 appears to be (under experimental conditions) a promising synthetic adhesive for colonic anastomosis construction; conversely, the tissue adhesive Dermabond was unsuitable for suture-free anastomosis construction.

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J. Paral (✉) · Z. Subrt · P. Lochman · L. Klein
Department of Field Surgery, Faculty of Military Health Sciences, University of Defense,
Trebesska 1575,
50001 Hradec Kralove, Czech Republic
e-mail: jiri.paral@seznam.cz

J. Paral · Z. Subrt · P. Lochman · L. Klein
Department of Surgery, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic

D. Hadzi-Nikolov
Department of Pathology, University Hospital, Hradec Kralove, Czech Republic

Z. Turek · M. Vejbera
Department of Anesthesiology, University Hospital, Hradec Kralove, Czech Republic

Keywords Colon · Anastomosis · Suture-free · Cyanoacrylate · Adhesive

Introduction

Correct technical execution is the fundamental prerequisite for success in any surgical procedure. Anastomotic dehiscence is one of the most serious post-operative complications in colorectal surgery. Anastomotic dehiscence occurs in 2–7% of patients after planned colon resection operations[1–4] and in 7–15% of patients after planned rectal surgeries.[5–7] This complication contributes substantially to morbidity and mortality rates associated with colorectal surgery.[1,3,7] The occurrence of dehiscence depends on a range of factors that have long been the subject of research and analyses. Surgical technique, tension in the area of anastomosis, type of sewing material, previous therapy, patient's overall health and nutritional status and the

erudition of the surgeon have been explored as potential impacting factors.[4,5,8–10]

Parallel to the research on factors that might negatively impact anastomosis healing, researchers are also exploring new materials and techniques that could prevent or minimize the risk of anastomosis dehiscence. The basic and seemingly simple aim of sutured or stapled anastomosis construction is to secure an appropriate edge-to-edge apposition for healing. It is necessary to achieve optimal distance, freedom from tension and suitable suture or staple tightness to ensure appropriate blood perfusion to the connected parts of the intestine.[11]

Cyanoacrylate tissue adhesives provide another option and alternative approach to traditional suture techniques. Considering their mechanical, physical and biological properties, tissue glues should facilitate an optimal bond between anastomosed sections of the intestine with negligible negative effects on intestinal wall perfusion.[11,12]

The aim of this experimental study was to explore the technical and biological potential of two types of cyanoacrylate tissue glues used for large intestine anastomosis construction (sigmoid colon). We compared their properties and ascertained their reliability when used as a single supportive element in intestinal anastomosis.

Materials and Methods

Experimental Animals

The study involved 12 experimental animals: female domestic pigs of medium weight (average 32.7 kg). The animals were divided into group A (six animals) and group B (six animals).

The experiments were conducted in accordance with the Protection of Animals against Cruelty Act No. 246/92 Coll. as amended. The experiments were approved by the joint Departmental Committee of the Faculty of Military Health Sciences and Faculty of Medicine, Charles University in Hradec Kralove, Czech Republic.

Anaesthesia

The animals were fasted 1 day prior to surgery but were allowed fluid intake. Fluid intake was stopped on the day of operation. Animals were pre-medicated with ketamine, 15 mg/kg of body weight delivered intramuscularly (IM; Narkamon, Zentiva, Prague, Czech Republic); azaperone, 1.0 mg/kg IM (Stresnil, Janssen, Beerse, Belgium) and atropine, 0.02 mg/kg IM (Atropin, Hoechst-Biotika, Martin, Slovakia). Next, an orotracheal intubation was performed; subsequently, the animal was artificially ventilated with managed volume ventilation (Cirrus-Trans, Datex-Ohmeda, GE Company, Fairfield, CT, USA).

General anaesthesia was maintained by titration with midazolam, 0.05 to 0.1 mg/kg delivered intravenously (Dormicum, Roche, Prague, Czech Republic), combined with propofol, 2 to 4 mg/kg/h (Diprivan, Astra Zeneca, Cheshire, UK) and metamizol, 5 mg/kg/h (Novalgin, Aventis Pharma, Frankfurt on Main, Germany). Muscle relaxation during the surgery was maintained with pipecuronium, 40 mg/kg, delivered intravenously (Arduan, Budapest, Gedeon Richter, Hungary). The blood pressure was monitored invasively via an axillary artery cannulation.

A single intramuscular bolus dose (‘one shot’) of Betamox LA at 15 mg/kg (amoxicillin, Norbrook Laboratories, Newry, UK) was administered as an antibiotic prophylaxis after the induction of anaesthesia. Continual volume maintenance therapy consisted of a combination of crystalloids (Infusio Hartmanni, Medicamenta, Vysoke Myto, Czech Republic) and colloids (Hemohes 6%, Braun, Melsungen, Germany). The electrocardiogram, O_2 saturation and end-tidal CO2 were monitored throughout surgery.

Surgical Procedure

A midline laparotomy was conducted after standard aseptic preparation of the surgical field. A urine catheter was introduced into the urinary bladder through a small incision at the bladder apex and fixed with a circular suture to ensure derivation of urine and management of diuresis throughout surgery.

The sigmoid colon was transected. Circular monofilament sutures (Prolene 3/0, Johnson & Johnson, division of Ethicon, Somerville, NJ, USA) were placed on the ends of the disconnected intestinal tubes. An intestinal anastomosis was constructed with a modified circular 25 mm stapler (Circular Stapler CDH25, Johnson & Johnson, division of Ethicon, Somerville, NJ, USA). All staples were withdrawn from the stapler, and only the circular blade and mechanical part of the stapler was used. A stapler anvil was placed into the oral section of the intestine and secured in place with a circular suture. Following sphincter divulsion, the main part of the stapler was inserted transrectally into the sigmoid colon. The metal shaft of the stapler was ejected and the aboral part of the intestine was fixed to the stapler with a purse-string suture (Fig. 1). Then, cyanoacrylate tissue glue was sparingly applied to both ends of the connected intestine (Fig. 2). One millilitre of Glubran 2 (*N*-butyl-2-cyanoacrylate + methacryloxysulpholane, GEM s.r.l., Viareggio, Italy) was used in group A and 1 ml of Dermabond (2-octyl-cyanoacrylate, Johnson & Johnson, division of Ethicon, Somerville, NJ, USA) was applied in group B. The subsequent procedures were identical in both groups.

The circular stapler was closed in order to achieve tight apposition of the glued surfaces. Any remaining glue was cleared away from the glued surfaces with a gauze swab.

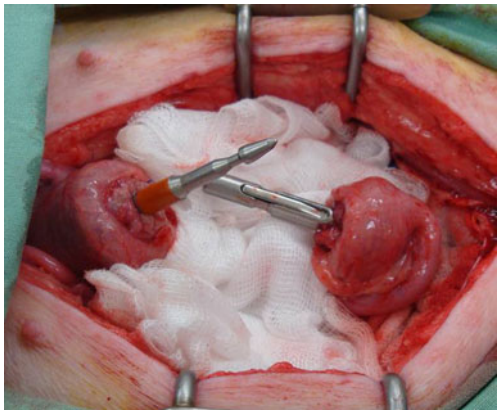

Fig. 1 Intestinal sections fixed on the stapler with circular sutures

After 90 s (time to glue polymerisation), the stapler was fired, opened with two turns and withdrawn from the intestine. Anastomosis was visually checked over the entire diameter and the tightness was verified by 'water test'. The abdominal cavity was lavaged with 10% Betadine solution (Povidonum iodinatum, Egis Pharmaceutical Ltd., Budapest, Hungary) and then dried. The abdominal cavity was closed in one layer, similar to a 'mass closure', with an absorbable monofilament suture PDS-loop (polydioxanon, Johnson & Johnson, division of Ethicon, Somerville, NJ, USA). The abdominal skin was closed by stapling (Stapler PMR 35, Johnson & Johnson, division of Ethicon, Somerville, NJ, USA). Following surgery, the experimental animal was extubated and placed into a warm end-of-anaesthesia booth.

Post-surgery Period

The animals were started with liquid feed the second day after surgery. Standard granulated feed was started on the third day after surgery. The skin staples were left in place until the follow-up operation.

Fourteen days after the first operation, a follow-up surgery was performed in both groups to evaluate the integrity of the anastomosis (Fig. 3) and uncover any potential strictures or leaks. We also reviewed the presence of abscesses or other forms of inflammation in the area of anastomosis, other pathological processes in the abdominal cavity and the incidence and the extent of adhesions. A scale modified by Houston and Rotstein[13] was used to assess adhesions: 0 = no adhesions; 1 = minimal adhesions, mainly between the small part of omentum and intra-abdominal organs or abdominal wall or freely separable adhesions between organs; 2 = small adhesions, i.e. between omentum and anastomotic site or between anastomosis and small bowel, oviducts, urinary bladder or other organs and 3 = extensive adhesions with partial obliteration of abdominal cavity.

The glued section of the intestine was resected to include at least 5 cm of the intestine on both sides of the anastomosis. Resected segments were cut lengthwise and macroscopic evaluation was performed on the mucosal side of the anastomosis. The animals were euthanized by intravenous administration of T61 (Hoechst, Frankfurt on Main, Germany) at the end of the operation.

Histopathological Examination

The resected parts of the intestine were fixed in a 10% formalin solution, processed with the standard paraffin technique and stained with haematoxylin–eosin. The finished specimens were examined under light microscopy. Assessments were made for the presence of fibroblasts, neutrophils, giant polynuclear cells, neovascularisation and collagen deposits. Collagen deposit area was evaluated with Masson's trichrome stain. Semi-quantitative histopathological evaluation of the presence of cell elements in the glued area of the anastomosis was performed according to the Ehrlich–Hunt numeric scale.[14]

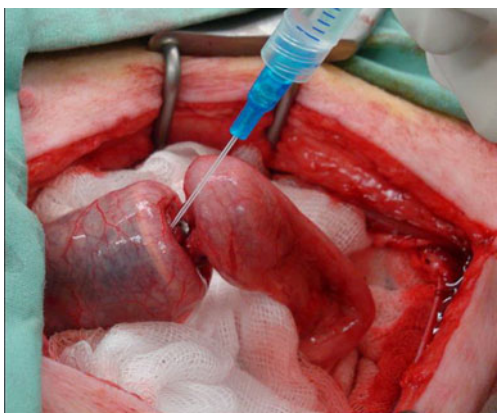

Fig. 2 Application of the cyanoacrylate adhesive on the intestinal sections

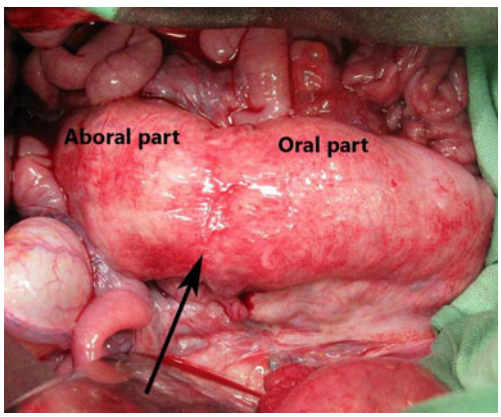

Fig. 3 Healed anastomosis 2 weeks after it was glued with Glubran 2. The *arrow* shows the anastomosis

For fibroblasts and neutrophils, one to 40 cells in ten high-power fields was graded as 1+, 41 to 80 as 2+ and 81 to more as 3+. One to 3 giant polynuclear cells or vessels in neovascularisation or collagen deposits areas in ten high-power fields was graded as 1+, four to six as 2+ and seven to more as 3+. The histopathologist who assessed the specimens was blinded to the type of glue used on the evaluated specimens.

Variables were expressed as medians (25th percentile, 75th percentile), and Wilcoxon two-sample test was used to compare them. Probability values were two-tailed and were considered significant if <0.05 (Table 2).

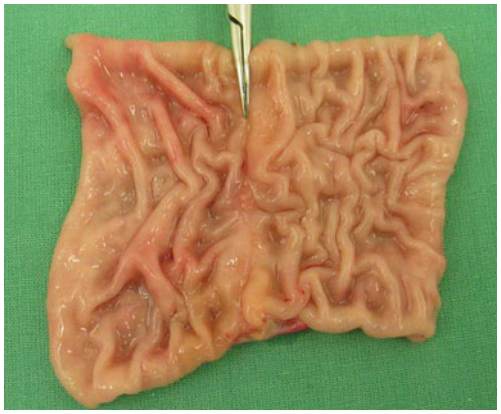

Fig. 4 Healed mucosal layer of anastomosis 2 weeks after it was glued with Glubran 2

Results

Macroscopic Picture—Group A (Glubran 2)

All anastomoses created with Glubran 2 healed, and no dehiscence or leaks were observed. Adhesions were minimal or small in all cases. The adhesions mostly involved adhesions of the omentum to the abdominal wall, but in one animal, the small intestinal loop had adhered to the abdominal wall. It is likely that these adhesions were related more to the laparotomy than to the method of constructing the anastomosis. Peri-anastomotic adhesions mostly involved freely separable adhesions of the oviducts. The presence of these adhesions was attributable to the anatomic arrangement of the female pig pelvis; the bicornuate uterus and the adjacent oviducts pressed ventrally and laterally upon the sigmoid colon. In one animal, the wall of the urinary bladder was drawn up against the anastomosis (Table 1).

No abscesses or other inflammatory changes to the abdominal cavity were identified, but one subcutaneous abscess was observed in one animal. Macroscopic assessments of the resected anastomoses revealed nearly complete healing of the mucosal layers in all specimens (Fig. 4). No stenosis was found.

Macroscopic Picture—Group B (Dermabond)

Complete healing of the anastomosis occurred in four animals in the Dermabond group. One animal had to be euthanized the third day after surgery due to signs of acute peritonitis; an autopsy revealed dehiscence of 1/3 of the perimeter of the anastomosis. During the planned follow-up surgery performed 2 weeks later, one animal displayed a small peri-anastomotic abscess and a small covered dehiscence of the posterior anastomotic wall. The incidence and extent of adhesions within the abdominal cavity were more extensive (Table 1). Peri-anastomotic adhesions were, compared to group A, more fibrotic. The most frequent adhesions were observed in the oviducts, and in two animals, the wall of the urinary bladder was tightly fixed to the anastomosis. Apart from the one case of a local abscess at the anastomosis, no signs of peritonitis were observed in any of the surviving animals.

Resections of the anastomoses revealed fibrotic restructuring of the mucosal layer (Fig. 5). The anastomoses were characterized by a partially stenotic ring and intestinal dilatation above the anastomosis, exceeding the diameter of the intestine below the anastomosis by 1/3 to 1/2 in all the cases. The narrowing was consequent to protuberance of the fibrotic tissue into the lumen of the intestine within the area of glued anastomosis.

Microscopic Picture—Group A (Glubran 2)

The histological findings in the area of the glued anastomosis were virtually uniform in all animals in group A. The adhesive was spread evenly over the entire perimeter of the anastomosis and was surrounded by a wide layer of granulated tissue with mixed inflammatory infiltrate rich

Table 1 The incidence and the extent of adhesions

Extent of adhesions		Group A Glubran 2 (N=6)	Group B Dermabond (N=5)
0	No adhesions	0	0
1	Minimal adhesions	4	0
2	Small adhesions	2	5
3	Extensive adhesions	0	0

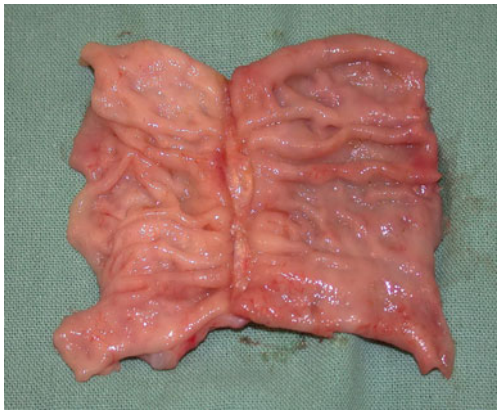

Fig. 5 Healed mucosal layer of anastomosis 2 weeks after it was glued with Dermabond fibrous restructuring of mucosal lining and narrowing of the lumen at anastomosis is evident macroscopically

in neutrophils. A fresh thin layer of cellular fibrous tissue was evident at the periphery. Giant polynuclear cells were either absent or infrequent (Fig. 6). Part of the mucosal surface was replaced with granulated tissue of mixed inflammatory infiltrate, and the other part showed a tendency towards complete healing. The presence of cellular elements, vascularisation and collagen deposits was assessed semi-quantitatively (Table 2).

Microscopic Picture—Group B (Dermabond)

An even, thin layer of the adhesive was found within the entire perimeter of the anastomoses in group B specimens. This was surrounded by a very thin border of granulated tissue with acute or mixed inflammatory infiltrate rich in neutrophils and encircled with a wide layer of cellular fibrous tissue containing numerous polynuclear cells that are common in

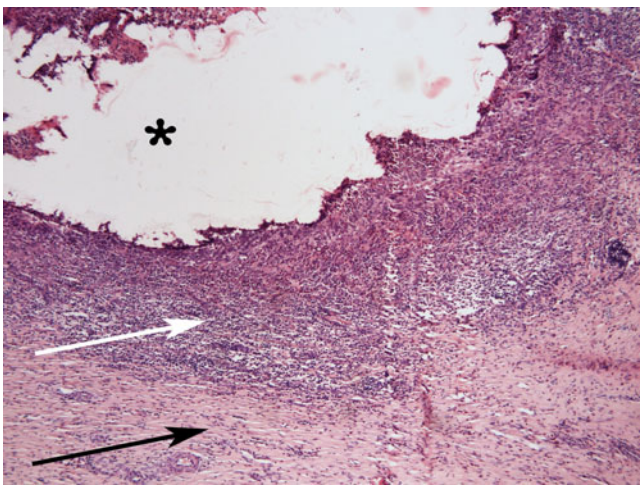

Fig. 6 Glubran 2. The amorphous mass of tissue adhesive (*asterisk*) encircled with granulation tissue layer with mixed inflammatory infiltrate rich in neutrophils (*white arrow*). Fresh thin layer of cellular fibrous tissue is present on the periphery (*black arrow*; enlarged ×10)

response to a foreign body (Fig 7). The mucosal tissue above the anastomosis was ulcerated and replaced with granulated tissue with inflammatory infiltrate. Also, fibrous hypertrophy was evident in the serous layer. The presence of cellular elements, vascularisation and collagen deposits was assessed semi-quantitatively (Table 2).

Discussion

Tissue glues are biological, semi-synthetic or synthetic substances. The basic feature of tissue glue is a strong adherence to living tissue surfaces. Tissue glues are classified as those with haemocoagulation factors (biological glues), including fibrin and thrombin glues, and those without haemocoagulation factors, i.e. cyanoacrylates, polyethyleneglycols, albumin with glutaraldehyde, cellulose, gelatine and collagen.[15,16]

Initially, abdominal surgery was predominantly associated with fibrin glues. These adhesives mimic the last step in the haemocoagulation cascade, i.e., conversion of fibrinogen into fibrin. Concentrated fibrinogen forms the primary component of these glues, and minor components include fibronectin, factor VIII and plasminogen.[16]

At present, research regarding tissue adhesives focuses mostly on cyanoacrylate-based agents. With this type of tissue glue, a firm bond between tissues occurs as a result of the transformation of monomer cyanoacrylate components (clear, colourless liquids) into polymer chains. The polymerization process is induced by anions (I−, CH3COO−, OH−), weak organic bases and amino acids.[17] Polymerization induced by the amino acids in the proteins of living tissues results in the formation of a thin polymer film firmly fixed to the tissue surface. Consequently, when polymerization takes place between two apposed tissue sections, they become firmly attached.[18] The polymerized film is then biodegraded by the gradual hydrolysis of alkyl-group bonds by esterases contained in cellular lysosomes. The by-products of degradation (polycyanoacrylate acids) are water-soluble and are excreted renally.[17,18]

Methyl-cyanoacrylate was the first glue used for medical purposes in 1964; it was used to close a 3-cm-long cystostomy in a dog. However, this derivative was not widely used in practice due to its rapid biodegradation and tissue toxicity.[18]

It was not until the 1990s, when derivatives with long polymer chains had become available, that wider utilisation of cyanoacrylates was reported in experimental and clinical practices. Currently, the most widely used cyanoacrylate is 2-octyl-cyanoacrylate (Dermabond®, Nexaband®, Liqui-Band®, SurgiSeal®). This derivative is now routinely used to form suture-free closers in skin injuries, predominantly in paediatric and plastic surgery practices.

Table 2 Semi-quantitative histopathological score of the presence of cellular elements, neovascularisation, and collagen deposits; examined under light microscopy

	Glubran 2 (N=6)					Dermabond (N=5)					p value
Grading	0	1+	2+	3+	–[c]	0	1+	2+	3+	–[c]	
Fibroblasts [a]	–	4	2	–	1 (1, 2)	–	–	3	2	2 (2, 3)	<0.05
Neutrophils [a]	–	–	2	4	3 (2,3)	–	3	2	–	1 (1, 2)	<0.05
Giant polynuclear cells[b]	4	2	–	–	0 (0, 1)	–	–	2	3	3 (2, 3)	<0.05
Neovascularisation[b]	–	4	2	–	1 (1, 2)	–	3	2	–	1 (1, 2)	NS
Collagen deposits[b]	4	2	–	–	0 (0, 1)	–	3	2	–	1 (1, 2)	<0.05

[a] For fibroblasts and neutrophils, one to 40 cells per ten high-power fields (HPF) was graded as 1+, 41 to 80 as 2+ and 81 to more as 3+

[b] One to three giant polynuclear cells, neovascularisation or large collagen deposits per ten HPF was graded as 1+, four to six as 2+ and seven to more as 3+

[c] Variables are expressed as median (25th percentile, 75th percentile). Wilcoxon two-sample test was used to compare them. Probability values were two-tailed and were considered significant if <0.05

2-Octyl-cyanoacrylate (Dermabond®) was successfully used in in vivo experiments with pigs to create closures of urinary bladder incisions. Two comparative studies demonstrated healing of 7.5-cm-long incisions made through the entire thickness of the bladder wall.[19,20]

Only two experimental studies focusing on creating suture-free colonic anastomosis with cyanoacrylate glues have been conducted so far. Both studies involved laboratory rats. Similar experiments on a large laboratory animal (domestic pig) have not been performed so far.

The first study compared colonic closures created with a monofilament fibre (polypropylene) and cyanoacrylate tissue glue *n*-butyl-2-cyanoacrylate (Histoacryl Blue®).[21] The comparisons between the cyanoacrylate glue and the suture groups were made with respect to outcome measures including anastomotic leakage, anastomotic stricture, peritonitis and wound infection. Also, histological appearance of tissue samples from anastomotic site was evaluated, and anastomotic bursting pressure was measured. The measurement was made on the third and seventh post-operative day.

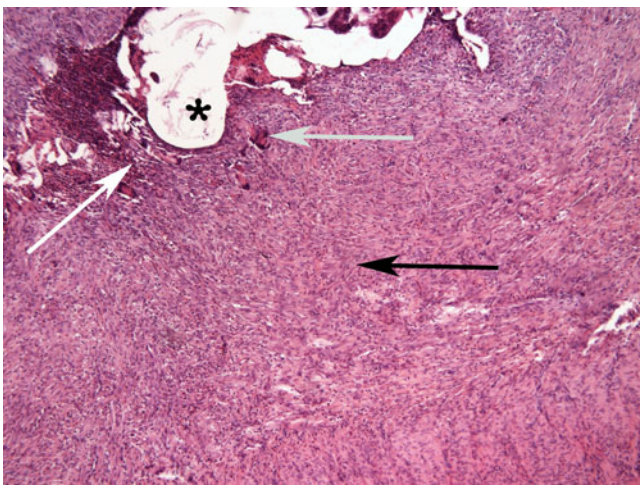

Fig. 7 Dermabond. The glue (*asterisk*) is surrounded by a thin layer of granulation tissue rich in neutrophils (*white arrow*) with evidence of giant polynuclear cells (*grey arrow*). This layer is surrounded by a wide layer of cellular fibrous tissue (*black arrow*; enlarged ×10)

The authors concluded that the use of Histoacryl Blue® in rat colonic anastomosis does not improve the healing process due to significantly higher incidence of anastomotic stricture, adhesion formation and higher bursting pressure in the suture group. There were no significant differences in histological scores.

The second study investigated the effects on healing in high-risk experimental intestinal anastomosis rats. The colonic closures created with a monofilament fibre (polypropylene) and 2-octyl-cyanoacrylate (Dermabond®) were compared under standard and high-risk conditions, where the intestinal wall was intentionally bruised with a Pean clamp.[22] The investigated end-points were mechanical strength, gross adhesion formation, hydroxyproline concentration and histological healing parameters. The study demonstrated a comparable degree of intestinal healing on the third and seventh post-surgery day. No differences between the groups regarding gross peri-anastomotic changes and hydroxyproline concentration were identified on the seventh post-operative day, representing a late phase of healing in a rat. Compared to the third post-operative day, there were fewer general inflammatory changes; granulocyte infiltration level, representing the acute inflammatory reaction, was still increased in the high-risk and octyl-cyanoacrylate groups compared to the normal anastomosis group. Also in these groups, the presence of necrosis, exudate and peritonitis was more evident. Regarding to mechanical strength, there were no differences between the groups on the third post-operative day, but on the seventh day, the sewn anastomoses resisted higher pressure during the bursting pressure test.

The authors concluded that the tested adhesive was not suitable for construction of colonic anastomoses, due to the lower resistance to pressure and the higher (but not significant) incidence of inflammatory changes in the area

of anastomosis compared to sewn anastomoses.[22] Both studies used cyanoacrylates intended primarily for skin closures, not for organ adhesions; in our opinion, this is the likely explanation for the unsatisfactory results with the cyanoacrylate tissue glues.

Currently, the only commercially manufactured cyanoacrylate that is intended primarily for surgical bonding of organs is Glubran 2 (GEM S.r.l., Viareggio, Italy), which is a combination of *N*-butyl-2-cyanoacrylate and methacryloxysulpholane. The product conforms to the European Directive on Medical Devices 93/42/CEE for internal and external surgical use.[23] *N*-Butyl-2-cyanoacrylate alone is available under various brand names (Indermil®, Histoacryl®, Xoin®, GluStitch®) as a tissue glue intended for suture-free skin closures or sclerotisations of esophageal varices.[24–26] The second component of the adhesive, methacryloxysulpholane monomer provides the adhesive with important properties; it reduces the temperature needed for exothermic polymerization (approximately 45°C), increases the elasticity of the glue after polymerization, reduces tissue toxicity and prevents microbial invasion. These properties may play a crucial role in the healing process of the glued tissue. The proportions of the two substances in the glue and its particular biological, physical and mechanical properties are subject to the manufacturer's trade secret. In the present study, the combination of *N*-butyl-2-cyanoacrylate and methacryloxysulpholane contained in Glubran 2 provided significantly better healing of anastomoses, as assessed macro- and microscopically. Our microscopic evaluations corresponded to physiological healing of the colon in the second week post-surgery.[27,28]

In contrast to Glubran 2, 2-octyl-cyanoacrylate (Dermabond) was associated with pronounced fibrosis of the anastomosis and a relatively high incidence of peri-anastomotic adhesions. These results are in line with the results of previous studies and provide evidence for some degree of organ toxicity. However, these complications did not occur when the glue was used for its original purpose, i.e. for skin closures.[29]

Wider use of cyanoacrylate adhesives in gastrointestinal tract surgery has been hindered by reports of relatively unreliable outcomes and, as already mentioned, various extents of histological toxicity. Our study found statistically significant difference in the occurrence of fibroblasts, neutrophils, foreign-body giant polynuclear cells and collagen deposits; this likely results from the different responses of the organism to the type of the applied glue. Dermabond, in comparison to Glubran 2, causes greater fibrosis. This leads to formation of scar-like fibrous stenosis in the area of anastomosis, representing an important negative adverse effect of the glue. The presence of foreign-body polynuclear cells is expected in areas where a foreign material is present. Glue is a foreign material that gradually disintegrates; this disintegration is proportional to the pace of glue fragmentation, i.e. reduction into smaller sections that cause increase in the number of polynuclear cells. Another mechanism contributing to the polynuclear cell elevation includes direct tissue toxicity that causes destruction of the nearby cells—their necrosis. Therefore, it can be assumed that Dermabond is associated with faster fragmentation and possibly higher biological toxicity. This is most probably the reason for greater presence of giant cells associated with Dermabond use compared to Glubran 2.

Previous experimental studies on the use of cyanoacrylate glues for intestinal anastomoses frequently focused, apart from macroscopic and microscopic assessment of anastomotic healing, on measuring the maximal intraluminal pressure ('bursting pressure') that could be resisted by the glued anastomosis. These experiments on laboratory rats demonstrated that glued anastomoses did not resist the same pressures as sewn anastomoses.[21,22] The focus of the present study was to determine whether the use of an adhesive facilitated primary healing of an intestinal anastomosis. We chose not to measure bursting pressures on incompletely healed anastomoses because high pressures would negatively impact the integrity of the anastomosis. Consequently, the damaged anastomosis would require reapplication of the adhesive, and this could bias the results of the experiment. This might cause significant damage to the pigs and result in the devaluation of this challenging research work involving large experimental animals. Bursting pressure measurement was not performed during the follow-up surgery as it is very likely that, after 2 weeks, a healed anastomosis is so strong that it is not important what technique or material was used to make it. Nonetheless, intra-luminal pressure resistance values and comparisons represent valuable information. Therefore, in future phases of this research project and in a wider time frame, it is the authors' intention to systematically measure resistance of glued anastomoses to intra-luminar pressure at different stages of anastomosis healing.

Hand-sewn and stapled anastomoses are well-established and reliable techniques but may also be associated with certain risks. In order for the intestinal tissue to be joined, its structure is partly disturbed with a needle or a staple. This results in tissue microtraumas and might cause mild bleedings and haematomas in the area of anastomosis. Intestinal wall disruption with a suture or a staple might theoretically facilitate bacterial contamination. Hand-sewn anastomosis also depends on an individual surgeon's technique. Tight and dense sutures may result in local ischemia, necrosis and dehiscence. When a stapler with unsuitable staple length is used, the intestinal wall connection may be too tight and lead to ischemia or may be too loose. These, together with other factors, may contribute to development of a leak and dehiscence.

It is advantageous that tissue glue is active only on the intestinal wall (generally any glued organ) surface and that the entire glued area is being joined; its activity is thus not limited to restricted junctures as with the classical anastomoses. The tight interconnection with a cyanoacrylate polymer chain does not in any way affect internal structure or integrity of the connected tissue. This is the main reason why the authors are researching the use of tissue glue in colorectal surgery.

The present study aims not only to compare two glues, i.e. Dermabond, a skin glue that had been previously applied in a similar study,[22] and Glubran 2 intended for gluing organs and not previously investigated in a similar study, but it also seeks to answer whether it is of value to continue researching glued anastomoses. According to our results and in case of Glubran 2, it seems to be justifiable to continue. Obviously, it will be necessary to perform further experiments focusing on comprehensive comparisons of glues with classical suture materials. It is a view of the authors that rational use of glues in colorectal and gastrointestinal surgery, respectively, could at first be achieved through a combination of classical, sparsely sutured (i.e. less traumatic for the tissue) stitched anastomosis and tissue glue or a combination of a stapled anastomosis (possibly with a lower number of staples) and tissue glue.

Conclusion

The combination of *N*-butyl-2-cyanoacrylate and methacryloxysulpholane in Glubran 2® appears to be (under experimental conditions) a promising synthetic adhesive for colonic anastomosis construction. It demonstrated a high level of reliability, with minimal impact on the surrounding organs or the entire abdominal cavity throughout the course of anastomotic healing. It did not facilitate adhesion formation. Further studies are needed to determine the long-term effects of the adhesive on intestinal wall tissue.

Our results also showed that 2-octyl-cyanoacrylate (Dermabond®), used to glue organs in recent experimental studies, was unsuitable for suture-free anastomosis construction. We found that its organ toxicity led to intensive inflammatory reactions and intestinal wall fibrosis.

References

1. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 2009;208:1152–1153.
2. Platell C, Barwood N, Dorfmann G, Makin G. The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis 2007;9:71–79.
3. Buchs NC, Gervaz P, Secic M, Bucher P, Mugnier-Konrad B, Morel P. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2008;23:265–270.
4. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006;202:439–444.
5. Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjödahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462–469.
6. Kanellos I, Vasiliadis K, Angelopoulos S, Tsachalis T, Pramateftakis MG, Mantzoros I, Betsis D. Anastomotic leakage following anterior resection for rectal cancer. Tech Coloproctol 2004;8 (Suppl 1):79.
7. Eberl T, Jagoditsch M, Klingler A, Tschmelitsch J. Risk factors for anastomotic leakage after resection for rectal cancer. Am J Surg 2008;196:592–598.
8. Choi HK, Law WL, Ho JW: Leakage after resection and intraperitoneal anastomosis for colorectal malignancy: analysis of risk factors. Dis Colon Rectum 2006;49:1719–1725.
9. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg 2006;76:579–585.
10. Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002;26:499–502.
11. Waninger J, Kauffmann GW, Shah IA, Farthmann EH. Influence of the distance between interrupted sutures and the tension of sutures on the healing of experimental colonic anastomoses. Am J Surg 1992;163:319–323.
12. Byrne DJ, Hardy J, Wood RA, McIntosh R, Hopwood D, Cuschieri A. Adverse influence of fibrin sealant on the healing of high-risk sutured colonic anastomoses. J R Coll Surg Edinb 1992;37:394–398.
13. Houston KA, Rotstein OD. Fibrin sealant in high-risk colonic anastomoses. Arch Surg 1988;123:230–234.
14. Ehrlich HP, Tarver H, Hunt TK. Effects of vitamin A and glucocorticoids upon inflammation and collagen synthesis. Ann Surg 1973;177:222–227.
15. Shekarriz B, Stoller ML. The use of fibrin sealant in urology. J Urol 2002;167:1218–1225.
16. Jönsson K, Jiborn H, Zederfeldt B. Comparison of healing in the left colon and ileum. Changes in collagen content and collagen synthesis in the intestinal wall after ileal and colonic anastomoses in the rat. Acta Chir Scand 1985;151:537–541.
17. Leonard F, Kulkarni RK, Brandes G, Nelson J, Cameron IJ. Synthesis and degradation of poly (alkyl-cyanoacrylate). J Appl Polymer Sci 1966;10:259.
18. Vauthier C, Dubernet C, Fattal E, Pinto-Alphandary H, Couvreur P. Poly(alkylcyanoacrylates) as biodegradable materials for biomedical applications. Adv Drug Deliv Rev 2003;55:519–548.
19. Marcovich R, Williams AL, Rubin MA, Wolf JS Jr. Comparison of 2-octyl cyanoacrylate adhesive, fibrin glue, and suturing for wound closure in the porcine urinary tract. Urology 2001;57:806–810.
20. Seifman BD, Rubin MA, Williams AL, Wolf JS. Use of absorbable cyanoacrylate glue to repair an open cystotomy. J Urol 2002;167:1872.
21. Ozmen MM, Ozalp N, Zulfikaroglu B, Abbasoglu L, Kacar A, Seckin S, Koc M. Histoacryl blue versus sutured left colonic anastomosis: experimental study. ANZ J Surg 2004;74:1107–1110.
22. Nursal TZ, Anarat R, Bircan S, Yildirim S, Tarim A, Haberal M. The effect of tissue adhesive, octyl-cyanoacrylate, on the healing of experimental high-risk and normal colonic anastomoses. Am J Surg 2004;187:28–32.
23. Glubran 2—Technical Card [Internet]. GEM s.r.l. [cited 2008] Available from: http://www.gemitaly.it/cms/index.php?lang=english.

24. Charters A. Wound glue: a comparative study of tissue adhesives. Accid Emerg Nurs 2000;8:223–227.
25. Wang YM, Cheng LF, Li N, Wu K, Zhai JS, Wang YW. Study of glue extrusion after endoscopic N-butyl-2-cyanoacrylate injection on gastric variceal bleeding. World J Gastroenterol 2009;15:4945–4951.
26. Seewald S, Ang TL, Imazu H, Naga M, Omar S, Groth S, Seitz U, Zhong Y, Thonke F, Soehendra N. A standardized injection technique and regimen ensures success and safety of N-butyl-2-cyanoacrylate injection for the treatment of gastric fundal varices (with videos). Gastrointest Endosc 2008;68:447–54.
27. Braskén P. Healing of experimental colon anastomosis. Eur J Surg Suppl 1991;566:1–51.
28. Hendriks T, Mastboom WJ. Healing of experimental intestinal anastomoses: parameters for repair. Dis Colon Rectum 1990;33:891–901.
29. Bernard L, Doyle J, Friedlander SF, Eichenfield LF, Gibbs NF, Cunningham BB. A prospective comparison of octyl cyanoacrylate tissue adhesive (Dermabond) and suture for the closure of excisional wounds in children and adolescents. Arch Dermatol 2001;137:1177–1180.
30. Golub R, Golub RW, Cantu R Jr, Stein HD. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. J Am Coll Surg 1997;184:364–372.