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ORIGINAL ARTICLE

Clinical Feasibility of Large Gastrotomy Closure Using a Flexible Tissue Glue Based on N-Butyl-2-Cyanoacrylate: Experimental Study in Pigs

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Abstract

Background The use of synthetic adhesives such as cyanoacrylates has been established previously for a wide range of clinical indications. However, more research is necessary to evaluate their use in digestive closures or anastomosis. New chemical formulations developed to achieve more flexibility of synthetic adhesives (i.e., based on n-butyl-2-cyanoacrylate) could be an alternative to achieve this purpose. The aim of this study was to investigate the feasibility of using flexible cyanoacrylate adhesives for large gastric incision closure in an animal model.

Methods Twelve farm pigs were divided in two groups depending on the type of closure method applied. In all cases, extra-large seven centimeters gastrostomies were performed. Braided absorbable hand-sewn interrupted suture versus n-butyl-2-cyanoacrylate with softener closure were compared during a 3-week follow-up period. Histopathological aspects, hematologic and inflammatory biomarkers, and endoluminal pressure tolerated until leakage were assessed. The time spent on both closing procedures was compared.

Results No differences between the two groups were found in any of the histopathological and inflammatory variables evaluated. The glued group tolerated a significantly higher pressure than the manual suture group. A reduction of surgery time was also observed.

Conclusions Our results suggest that flexible cyanoacrylates could be a feasible alternative to improve the clinical outcome of the closure of hollow viscera through more efficient sutureless procedures.

Keywords Gastrotomy · Surgical anastomosis · Anastomotic leak · Tissue glue · Cyanoacrylates · Histoacryl · General surgery

Introduction

Common practices in general surgery are often faced with a hollow viscera closure or a resection followed by an anastomosis procedure. The success of those surgical procedures requires avoiding complications such as bleeding or leakage. Technical skills, host characteristics, and local conditions become crucial aspects for good results. It is worth noting that after a gastric surgery suture dehiscence occurs in about 4.2% of patients increasing morbidity and mortality.[1–3] Different substances have been used as an alternative or as a reinforcement to hand-sewing or mechanical suturing. Besides biological compounds, synthetic adhesive materials, particularly cyanoacrylates (CA), have become especially popular as an easy, safe, and feasible option.[4,5] An additional benefit of the gluing technique is that it prevents the undesired micro-ischemia caused by the suture stitch on the sewn tissue.

Cyanoacrylates (CA) is the generic name of the well-known n-alkyl-2-cyanoacrylate family, consisting of the alkyl esters of 2-cyanoacrylic acid. The exothermic reaction of n-alkyl-2-cyanoacrylates occurs in the presence of weak bases such as water to form solid polymers, poly (alkyl-2-cyanoacrylates), that strongly adhere to a variety of substrates including soft tissue. Although the medical use of CA has been object of controversy due to this cytotoxic potential,[5–7] it has been found that toxicity is

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reduced with increased carbon numbers in the alkyl chains. Thus, the use by practitioners of CA monomers with short alkoxycarbonyl group side chains, such as in methyl-2-cyanoacrylate and ethyl-2-cyanoacrylate, has been discontinued, unlike n-butyl-2-cyanoacrylate (NBCA) and octyl-2-cyanoacrylate (OCA), whose use has been widespread in the clinical field.

Due to its fast action and excellent bonding properties, the use of CA has been progressively extended in the clinical practice from skin closure to most surgical disciplines as an alternative to conventional treatments in vascular,[8,9] nerve,[10] and more recently, in gastrointestinal anastomosis.[10–13] NBCA, in particular, has been widely used in embolization of gastrointestinal varices and in hernia mesh repairs.[14–25]

The research of new CA indications in pre-clinical studies has been intense through time. Recently, some advanced surgical groups using surgical glues have introduced the use of CA as sealants in liver surgery in order to minimize the occurrence of biliary fistulae and to reduce the postoperative axillar seroma after axillary lymphadenectomy. CA glues have not only been used as a reinforcement of sutures but also as a viable alternative to them. Several authors have reported the use of NBCA in animal models to achieve, for instance, cartilage and bone grafting[26–29] in the repair of damaged ossicles,[30–32] and as coating of corneal ulcers.

The role of CA in gastric closure remains unclear due to lack of clinical and experimental reports. In addition to this, the clinical experience with CA in the gastroesophageal area is limited to gastrojejunal anastomosis[33] and postoperative leak or cutaneous fistulae.[34–36]

CA have been used in experimental colonic anastomosis showing promising results in terms of safety and feasibility in both small and large animals.[11–13] However, a recent systematic review summarizing the research regarding CA application in intestinal anastomosis noted poor methodological aspects, especially with regard to dosage optimization.[37]

Histoacryl® Flexible (HF), B. Braun Surgical, S.A. Rubí (Spain), is a synthetic adhesive consisting of NBCA and a softener. The softener is added to Histoacryl® Flexible formulation in order to improve its pliability of skin closure. When exposed to tissue moisture, HF polymerizes within seconds resulting in a flexible layer that maintains both sides of the wounds sealed.

A recent study by our group in a small animal sample proved that a flexible adhesive (Histoacryl® Flexible) can provide a permanent and feasible closure in gastric incisions. Nonetheless, more experimental studies are necessary to assess the role of CA in gastric closure, particularly in large gastric gastrotomies.[38]

Our hypothesis is that similar results can be reproduced in a big animal sample, by performing an extra-large gastrotomy of about 7 cm. The main end-point was defined as the clinical absence of leakage 3 weeks postoperative, as well as the demonstration of anastomotic integrity, both macroscopically and histologically. Clinical and analytical test surveillance, liver and kidney toxicity, and development of adhesions in the abdominal cavity were also assessed. In addition, the period of time performing gastric closure procedures and the bursting pressure endured until leakage were compared.

Material and Methods

Materials

Large gastric closure was performed either with Histoacryl® Flexible (HF), B. Braun Surgical, S.A. Rubí (Spain), or a PGLA braided absorbable suture (Novosyn® USP 2/0, B. Braun Surgical S.A. Rubí, Spain). A Novosyn® USP 0 suture was used for abdominal wall closure. The procedure was completed using a stapler (Manipler® AZ, B. Braun Surgical, S.A. Rubí, Spain) for skin closure (Fig. 1)

Animals

The study was carried out on 12 common farmed male pigs, *Sus scrofa domesticus* species and "Large white x Landrace strain," of around 5 months old (80–90 kg weighed; Specipig S.L., Barcelona, Spain). This breed of mammal was considered the most appropriate considering its anatomical and physiological similarity to humans. The number of specimens included in the study was in accordance to The European Guidelines for Ethical Care of Experimental Animals.[39]

All animals received standard care, with free access to food and water. Local (Catalonian Directive D214/1997) and European Union Guidelines for Ethical Care of Experimental Animals (EC Directive 86/609/EEC for animal experiments) were strictly followed. Permission was obtained from the Local Ethics Committee for Animal Experimentation as well. Animals were divided into two groups, HF ($n = 6$) and manual stitch suture ($n = 6$). To minimize the effects of subjective bias, animals were randomized, no blinded methods were used. All animals were individually identified and housed 7 ± 2 days prior to the study. Surgeries were performed in groups of 2–3 pigs per day. A blood sample was obtained during the quarantine period to be used as a baseline data.

Anesthetic Schedule

The animals received neither diet nor liquids for 24 h prior to surgery and a liquid diet was supplied after 6 h post surgery. Solid diet was supplied after 24 h. All animals were weighed prior to surgery for medication dose adjustment. Premedication included Atropin 0.04 mg/kg, to avoid oropharyngeal secretions, and Dexmedetomidine 0.03 mg/kg + Midazolame 0.2 mg/kg + Butorfanole 0.2 mg/kg based sedo/

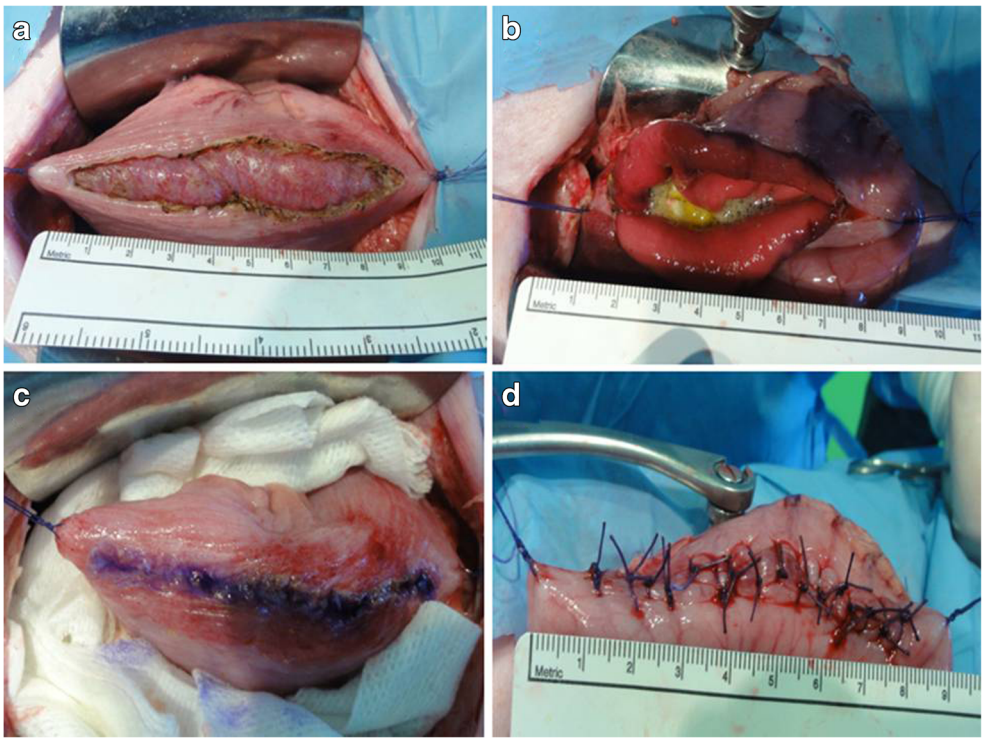

Fig. 1 Picture showing large gastrotomy being performed. Serosa and muscular layer opened (**a**). Complete open gastrotomy (**b**). Histoacryl® Flexible closure (**c**). Manual interrupted 2/0 braided absorbable suture (**d**)

analgesia. After pre-oxygenation (oxygen 100% for 3 min), a venous catheter, in auricular pavilion or saphenous vein, was inserted. Anesthesia was induced with Propofole 1.5–5 mg/kg and orotracheal intubation was immediately placed in all animals. Isofluorane 1.5–2.4% maintained the anesthesia effect and fluid therapy was guaranteed with Ringer lactate solution (LacRinger®, B. Braun Melsungen, Germany).

Surgical Procedure

A midline laparotomy was performed under standard aseptic conditions. An 8-cm longitudinal gastrotomy was placed afterwards at about 3 cm far from the greater curvature in the anterior wall of the gastric body. Surgical incisions of about 8 cm were made but after stomach opening, the incisions measured about 7 cm due to muscular retraction. Two different types of closures were performed: polyglactin braided absorbable suture and HF closure.

HF was applied directly onto the wound in a dropwise manner using a 1-mL polypropylene syringe (approximately 50 μL of HF was applied). According to literature and studies performed by our group in controlled settings, the polymerization reaction results in a slight increase in temperature of about 3 °C. Wound edges were fastened for a period of 60 s with three equidistant fixating sutures to facilitate tissue approximation. Fixating sutures were removed immediately after glue polymerization (Fig. 1). It is worth emphasizing that in order to keep both sides of the gastric wall joined together, a thin layer of glue was applied to the surface of the wound. The objective was to avoid glue penetration within the two inner faces of the gastric wall, keeping only the outer layer glued. Blood samples were obtained via direct vena cava puncture after the surgical procedure. The abdominal wall was closed with a 0 braided absorbable suture using a stapler for skin closure (Fig. 1).

Follow-Up

After the surgical intervention, all animals were kept in individual cages with free access to a liquid and solid diet after six postoperative hours. Later, IM Butorphanol (0.15–0.3 mg/kg) analgesia was added every 12 h during the first 2 days as well. Meloxicam (im) as anti-inflammatory and Enroflocaxin as antimicrobial prophylaxis, both every 24 h for 5 days. All animals were weighed after 48 h and every week until the study termination. Each animal was evaluated daily in order to record clinical and behavioral changes during the postoperative period. Two peripheral blood samples were obtained from cranial veins, 9 ± 2 and 15 ± 2 days after surgery, in order to detect indirect signs of anastomotic leakage and to determine the leukocyte count as well as to analyze the glucose, sodium and potassium plasma levels, and C-reactive protein as inflammatory biomarker.

Day 23 after surgery, all animals were sacrificed by means of a lethal overdose of sodium pentobarbital and underwent an iterative laparotomy. Liver and kidney tissue samples and the surrounding gastric area involved in the suture were removed for histopathological analysis. Additionally, the incidence, extension, and consistency of adhesions were all evaluated as were other macroscopic findings (intra-abdominal liquid or

collections, suture dehiscence of hemorrhagic foci). Finally, blood samples from vena cava were obtained during the surgical procedure, before completing euthanasia.

Blood Samples

Central and peripheral venous samples (1 mL) were collected in a standard laboratory tube with ethylendiamine tetra-acetic acid (0.4 mL) in order to perform a standard blood test (leukocytes, platelets, and hematocrit), the remaining quantity (0.6 mL) was centrifuged (300 cycles for 10 min), collected, and preserved until analysis. The amount of blood used was determined according recommendations of the EU and National Regulations for animal experimentation.

Histopathological Examination

Anastomotic segments, parts of stomach plus liver and kidney samples were fixed in a 10% formaldehyde solution and embedded in paraffin for hematoxylin eosin and Masson's trichrome staining. Samples were examined with optical microscopy at × 20 and × 200 magnification by the same pathology specialist who was blinded to group assignments.

The modified Ehrlich-Hunt score[39] was used to assess anastomotic healing: Inflammatory cell infiltration (leukocyte count), fibroblast activity, angiogenesis de novo, and collagen content were calculated for each of these parameters, and stratified into presence of monomorphic or polymorphic cells (Table 3). The Zühlke grading scale was used for the evaluation of the inflammation. We stratified it into four grades, grade A was defined as weak connective tissue, rich cells, and thin reticulin fibers; grade B was classified as connective tissue with cells and capillaries, and few collagen fibers; grade C was characterized by firmer connective tissue, fewer cells, more vessels, and few elastic and smooth-muscle fibers; and grade D was defined by firm granulation tissue which was cell poor and serosal layers which were hardly distinguishable (Table 3).

Statistical Analysis

Numerical variables are expressed as medians (25th–75th percentile). The non-parametric tests (Kruskal-Wallis and Mann-Whitney *U*) were employed and a 95% confidence level was considered significant. *P* values less than 0.05 were considered significant. Statistical analysis was carried out using the Statgraphics Plus 5.1 package (Statpoint Technologies, Inc., Warrenton, VA, USA) for Microsoft Windows.

Results

No significant changes in animal weights were found between both groups during the follow-up period. Manual suture vs. HF glue, preoperative (86.2 ± 3.8 kg vs. 84.6 ± 2.1); after 2 weeks (84.3 ± 1.6 kg vs. 83.8 ± 1.3 kg); and at sacrifice (85.6 ± 0.8 kg vs. 85.2 ± 1.2 kg), respectively. Kruskal-Wallis test, $P = 0.13$.

No differences between experimental groups were found in any of the laboratory tests performed. Kruskal-Wallis test (Table 1).

Histopathological Findings

After histological examination, neither signs of anastomotic leakage nor disruptions were observed. Moreover, no differences in acute or chronic inflammatory aspects, foreign body inclusions, granulation tissue or liver and kidney damage were identified in either study group.

The presence and extension of adhesions was slightly higher in closures performed with HF when compared to manual suture (only in the category of small adhesions, see Table 1), although no significant differences were found. Mann-Whitney *U* test, $P = 0.06$ (Table 2).

The degree of fibrosis was predominantly type C, an immature collagenous matrix, but still in the process of fibrosis and with the connective tissue vascularization relatively stabilized.

There were some areas, focal and generally more common in inner layers (serosa), of immature tissue, poor in collagenous matrix and neovascularization process (type B fibrosis). In every case, mature connective tissue type D was found (Fig. 2). Zühlke grade and Ehrlich-Hunt scale score[40] for inflammatory infiltration evaluation between both groups are represented as follows (Table 3).

Significant differences were observed with regard to the time spent on closure between manual and HF closure (12.5 ± 0.6 vs. 6.5 ± 0.5 min, respectively; $P < 0.05$) Kruskal-Wallis test (Fig. 3). We have included the time to place and remove the edges sutures to facilitate the closure in the HF group.

Discussion

Although the use of CA has been progressively extended in the surgical field and it has been the subject of wide clinical research, its role in gastric surgery has been poorly studied.[41] Previous experiences in gastrointestinal anastomosis in animal samples comparing NBCA and manual suture closures reported no significant differences in terms of anastomotic leakage, adhesion incidence and histopathological changes. Ozmen et al. studied the use of glues in colon anastomosis by comparing NBCA with monofilament sutures.[13] According to the results reported, the use of the glue was associated with a higher incidence of stenosis in the anastomosed area, higher adhesion formation but without significant differences in such parameters between both closure procedures. However, the authors concluded that the glue was not suitable for colon anastomosis. They reported that the bursting pressure was lower but the

Table 1 No differences between experimental groups were found in any of the laboratory tests performed

	Normal range values	Manual suture ($n = 6$)	Histoacryl® Flexible ($n = 6$)	P
Hematocrit (%)				
Preoperative	32.0–53.0	34.6 ± 3.5	35.5 ± 4.3	0.26
3 weeks		33.4 ± 1.9	34.2 ± 1.6	0.32
Hemoglobin (g/dL)				
Preoperative	10.0–17.3	10.8 ± 1.2	11.5 ± 0.3	0.28
3 weeks		11 ± 0.7	11.2 ± 0.5	0.21
Leukocyte count (10^3/mL)				
Preoperative	6.6–22.0	22.8 ± 4.5	21.0 ± 5.5	0.16
3 weeks		25.3 ± 5.1	25.1 ± 6.5	0.18
Platelet count (10^3/mL)				
Preoperative	200.0–680.0	425.5 ± 93.2	432 ± 147.7	0.45
3 weeks		462 ± 82.4	503.3 ± 144.6	0.31
Glucose plasma (mg/dL)				
Preoperative	43.0–153.0	68.4 ± 31.4	62.6 ± 25.0	0.08
3 weeks		83.3 ± 15.6	83.1 ± 14.3	0.12
Bilirubin (g/dL)				
Preoperative	36.0–123.0	11.8 ± 8.6	21.8 ± 12.9	0.09
3 weeks		67.0 ± 29.5	53.9 ± 42.8	0.08
ALT (U/L)				
Preoperative	5.0–106.0	50.3 ± 9.7	54.9 ± 34.4	0.20
3 weeks		67.6 ± 9.2	54 ± 13.5	0.23
Urea (mg/dL)				
Preoperative	9.0–32.4	33.9 ± 3.5	33.7 ± 5.4	0.12
3 weeks		38.9 ± 7.8	40.0 ± 4.6	0.14
Creatinine (mg/dL)				
Preoperative	0.5–2.7	1.6 ± 0.1	1.3 ± 0.2	0.09
3 weeks		1.8 ± 0.4	1.2 ± 0.3	0.11
Albumin (g/dL)				
Preoperative	0.5–5.6	3.4 ± 0.2	3.7 ± 0.4	0.18
3 weeks		3.6 ± 0.3	3.5 ± 0.3	0.13

Results are expressed as mean ± SD; P = non-significant (ns); ALT, alanine aminotransferase. Normal range values according to DJ. Weiss et al. Schalm's Veterinary Hematology, 6th ed. 2010

incidence in inflammatory changes on the anastomotic surface was higher. In the same way, the study carried out by Nursal and cols, compared Dermabond® (OCA based skin adhesive) with monofilament closure in rats and under high-risk anastomosis.[42] The authors concluded that the tested adhesive was not suitable for colonic anastomoses, as it presented lower resistance to pressure and higher incidence of inflammatory changes over the anastomosis surface in CA groups. Furthermore, other authors report a higher level of fistula incidence when using CA.[43] On the other hand, Ozmen and Nursal reported that glued anastomosis showed lower resistance to the progressive increment of intraluminal pressure.

Table 2 The presence and extension of adhesions was slightly higher in closures performed with HF when compared to manual suture

	Manual suture ($n = 6$)	Histoacryl® Flexible ($n = 6$)
No adhesions	0	0
Minimal adhesions	4	3
Small adhesions	1	2
Enhanced adhesions	1	1

Considering that recent commercially available formulations are intended to provide the resulting CA adhesive layer with increased flexibility,[38] we wondered if they could be used as the only closure agent in gastrointestinal surgery, specifically in gastric surgery. We noted that the rigidity of CA after polymerization might lead to small cracks in the glue layer that could explain the presence of intestinal leaks. It was hypothesized that the increased pliability of the flexible glue layer should result in additional security to the sealing line.

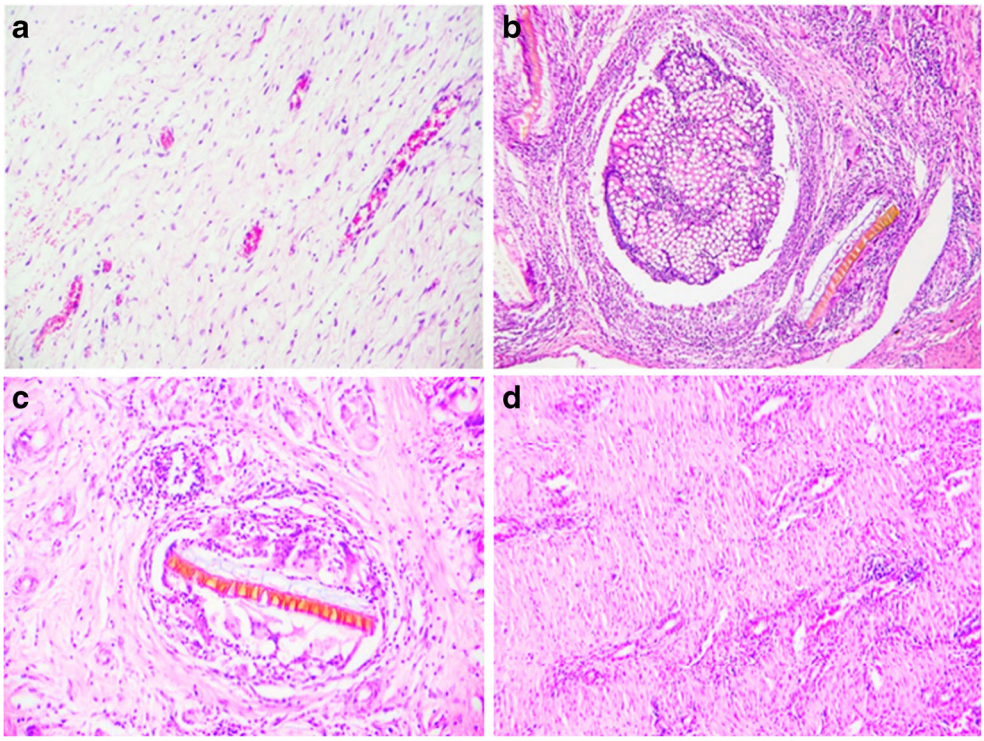

Fig. 2 Comparative picture showing microscopic findings. Fibrosis type B in HF glue closure 20× (**a**). Gastric wall acute inflammation signs in manual suture 10× (**b**). Granuloma involving silk manual suture 10× (**c**). Fibrosis type C in manual suture 20× (**d**)

It should be pointed out that in order to achieve an appropriate performance, the application of a thin layer of glue is recommended, thus minimizing the risk of cracks as well as a poor adhesion to the underlying tissues.

Earlier research by our group evaluated two different flexible NBCA formulations in a small animal sample in order to close gastrostomies and longitudinal colon holes.[38] Good results obtained in terms of efficacy, safety and easy handling led us to evaluate their use in a sample closer to human beings. We selected an animal sample based on large animals (pigs) as the length of the gastrotomy, up to 7 cm, was defined to simulate a surgery in humans. It was considered extra large and only possible to be performed on a large animal such as a pig. Additionally, to the best of our knowledge, such a long gastrotomy using only CA as a closure agent had not at that time been reported in the medical literature.

Our present experimental work demonstrates that primary gastric closure using only a flexible glue is feasible, safe and reproducible. To determine if there were differences related to the healing process and the surgical process, a braided absorbable suture, frequently used in gastric surgery, was compared to flexible NBCA tissue adhesive (Histoacryl® Flexible). The results, of the two methods, are similar with the only exception being a slightly higher but not significant incidence of adhesions in the glued closure group. Histologic analysis showed no significant differences either in the scarring process or in the foreign body reaction that would be demonstrated through inflammatory cell infiltration (leukocyte count), fibroblast

Table 3 Inflammatory cell infiltration (leukocyte count), fibroblast activity, angiogenesis de novo, and collagen content were calculated for each of these parameters, and stratified into presence of monomorphic or polymorphic cells

	Manual suture ($n = 6$)		Histoacryl® Flexible ($n = 6$)		P
Zühlke grade					0.18
A	0		0		
B	1		2		
C	5		4		
D	0		0		
Ehrlich-Hunt score	Polymorph	Monomorph	Polymorph	Monomorph	0.21
Minimum	0	0	0	0	
Low	6	1	5	1	
Moderate	0	5	1	5	
Severe	0	0	0	0	

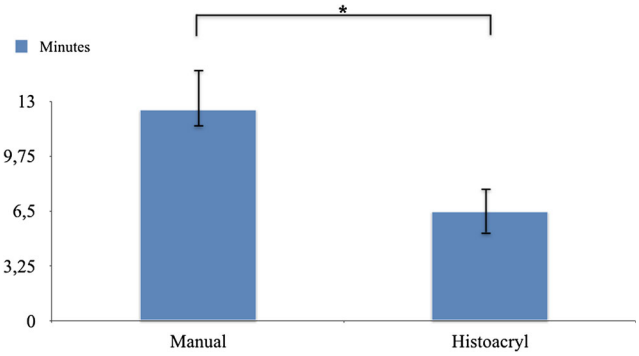

Fig. 3 Comparison of surgery time spent on the closure (minutes). $P < 0.05$; Kruskal-Wallis test

activity, neoangiogenesis and collagen content. Neither open abscesses nor necrosis were found after termination.

The results of this work suggest new opportunities for the use of flexible CA formulations in the case of gastrointestinal perforations, particularly in cases of peptic ulcers.[43] NBCA tissue adhesives have been successfully used in rat models to close gastric perforations with good results in terms of healing and safety, but with only a slight increase in adhesions around the wound.[44] In this study, compared with standard suture, cyanoacrylate achieved similar results in terms of safety and histopathological profile but with significantly increased adhesion formation. In contrast to our study, the NBCA was employed as a reinforcement and sealer rather than as a substitute for suture material. The significantly increased presence of adhesions has not been observed in our study, most likely because the wound was created as a clean longitudinal cut and was repaired immediately. The procedure intends to avoid the contamination of the wound and the risk of gastric fluid leakage that could result in an incremental inflammatory process and finally in adhesion formation. Additionally, the glue has a bacteriostatic effect that helps to avoid contamination of the wound.[45] However, up to now, there is no knowledge about the performance of NBCA in a septic environment and more research is necessary in that field.[44]

In this study, we suggest that closure performed with CA are faster than manual suture. One limitation of our results was to choose an interrupted closure that takes longer period of time opposed to a running suture. Although differences in closure time are significatives, this feature should be take into account for future studies.

Results attained in the present study open the door to the use of flexible CA in NOTES (Natural Orifice Transluminal Endoscopic Surgery) surgery with the purpose of reinforcing the closure opening needed to intervene in the interior of the abdominal cavity, giving the closure greater tightness and safety to the closure. Our results confirm that gastric closure with CA does not affect the normal wound healing in terms of integrity of gastric wall cicatrization, as reported with other surgical options.[43,44,46] Despite the fact that some authors point out that NBCA could affect the plasticity of the vagal afferent nerves, toxicity after their use has not been described at either renal, hepatic nor pulmonary level.[46–48] This fact should be taken into consideration when the conditions altering the gastric motility (i.e., diabetes mellitus).

Conclusion

This study is the first to perform an extra-large gastric closure, up to 7 cm, without manual suture in an experimental animal sample. Our results confirm that the HF glue does not affect the normal process of healing in terms of closure integrity, granulation mechanism, foreign body reaction, adhesions and clinical safety. Additionally, in terms of efficiency, surgical procedures using glues could be faster compared to manual sutures after a suitable training. Factors depending on the surgeon's technique in hand-sewn anastomosis could probably be avoided which would additionally result in less tissue damage than mechanical procedures.

Authors' Contribution JF. Julian and J. Fernández-Llamazares participated in the conception, design, surgical procedures in pigs and final critical revision.

P. Turon, AM Rodríguez, LF. del Castillo and E. Díaz participated in the conception, design, execution and final critical revision.

F. Espin and I. Vorisova contributed to analysis, interpretation of data, structure and drafting.

J. Navinés and J. Tarascó participated in the acquisition, analysis and interpretation of data.

Compliance with Ethical Standards

The authors declare that the Investigational Review Board and the Ethical committee of our institution approved the study and that they have no conflict of interest.

Conflict of Interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The present work has been developed under agreement between B. Braun Surgical, S.A. and The Catalonian Public Health Institute (ICS), Barcelona, Spain. The authors disclosed that Histoacryl® Flexible was employed for investigational use. Histoacryl® Flexible is not approved for internal use, only for skin closure.

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