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Basic Study

Effects of albumin/glutaraldehyde glue on healing of colonic anastomosis in rats

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Abstract

AIM

To evaluate the effect of local surgical adhesive glue (albumin/glutaraldehyde-Bioglu) on the healing of colonic anastomoses in rats.

METHODS

Forty Albino-Wistar male rats were randomly divided into two groups, with two subgroups of ten animals each. In the control group, an end-to-end colonic anastomosis was performed after segmental resection. In the Bioglu group, the anastomosis was protected with extraluminal application of adhesive glue containing albumin and glutaraldehyde. Half of the rats were

sacrificed on the fourth and the rest on the eighth postoperative day. Anastomoses were resected and macroscopically examined. Bursting pressures were calculated and histological features were graded. Other parameters of healing, such as hydroxyproline and collagenase concentrations, were evaluated. The experimental data were summarized and computed from the results of a one-way ANOVA. Fisher's exact test was applied to compare percentages.

RESULTS

Bursting pressures, adhesion formation, inflammatory cell infiltration, and collagen deposition were significantly higher on the fourth postoperative day in the albumin/glutaraldehyde group than in the control group. Furthermore, albumin/glutaraldehyde significantly increased adhesion formation, inflammatory cell infiltration, neoangiogenesis, and collagen deposition on the eighth postoperative day. There was no difference in fibroblast activity or hydroxyproline and collagenase concentrations.

CONCLUSION

Albumin/glutaraldehyde, when applied on colonic anastomoses, promotes their healing in rats. Therefore, the application of protective local agents in colonic anastomoses leads to better outcomes.

Key words: Adhesions; Bursting pressure; Bioglue™; Albumin/glutaraldehyde; Collagen; Colonic anastomosis

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Core tip: The present study was designed to investigate the effect of local surgical adhesive glue composed of albumin/glutaraldehyde in the healing of colonic anastomoses in rats. The application of adhesive glue promotes the healing of colonic anastomoses in rats as it significantly increases the bursting pressure in the early period, but it also causes more adhesions and an enhanced inflammatory reaction.

Despoudi K, Mantzoros I, Ioannidis O, Cheva A, Antoniou N, Konstantaras D, Symeonidis S, Pramateftakis MG, Kotidis E, Angelopoulos S, Tsalis K. Effects of albumin/glutaraldehyde glue on healing of colonic anastomosis in rats. *World J Gastroenterol* 2017; 23(31): 5680-5691 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i31/5680.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i31.5680>

INTRODUCTION

Anastomosis dehiscence is a serious postoperative complication, and the risk of anastomotic leakage is higher in large intestine surgery compared with other gastrointestinal anastomoses^[1,2]. Different techniques of using additive materials such as omentum and several types of fibrin sealants to cover

the anastomosis have been proposed^[3,4], and in experimental studies, various protective methods such as endoluminal latex prostheses, stents, biofragmental rings, and local application of bioadhesives have been used, with promising results^[5-9]. Tissue glues and fibrin adhesives, which are biodegradable and biocompatible, have been used to seal suture lines for haemostasis and/or to strengthen and reinforce fragile tissues by tissue adherence and replacement or support of sutures by biomaterial gluing^[9,10]. The goal is to reduce the incidence of dehiscence by increasing the strength of anastomoses, covering the anastomotic line, and stimulating healing^[11]. The possibility of direct influence of extraluminal contents and the substance's biological compatibility, as well as the adhesive and tension strength of the glue, has as a result in the critical healing phase: an increase in the force needed for anastomosis bursting^[12].

Local application of albumin/glutaraldehyde (Bioglue™), a haemostatic and adhesive agent, has received approval for many vascular, pulmonary and soft tissue repairs, and its use is already established in cardiothoracic surgery^[13,14]. So far, however, there have been no published experiments using this glue in colonic anastomosis. The aim of this experimental study was to investigate the effects of surgical adhesive glue during the healing process of colonic anastomosis in rats.

MATERIALS AND METHODS

Laboratory animals

The animal protocol was designed to minimize pain and discomfort to the animals. Forty male Wistar rats weighing 200-300 g were used in this study. The research protocol was approved by the Ethical Committee of the Department of Veterinary Services of the Prefecture of Thessaloniki (S.N.: 13/11872/11-09-08). Principles of laboratory animal care were followed. Animals were housed individually and had unrestricted access to the standard laboratory diet and water pre- and postoperatively. They were kept in our laboratory for seven-ten days before the experiment on a 12-h light and dark cycle and did not receive any course of chemoprophylaxis. At the sacrifice, all animals were euthanized by intracardiac administration of KCL 10% for tissue collection.

Anaesthesia, operative technique and experimental groups

The rats were weighed on the day of operation as well as before the sacrifice, and changes in weight were recorded. Operations were performed through a 3-cm midline incision under intraperitoneal thiopental anaesthesia (40 mg/kg bodyweight). After resection of a 1-cm segment of the colon and 5 cm from the rectum, an end-to-end anastomosis was created using a single layer of eight interrupted extramucosal 6-0 polypropylene sutures. Rats were randomly assigned

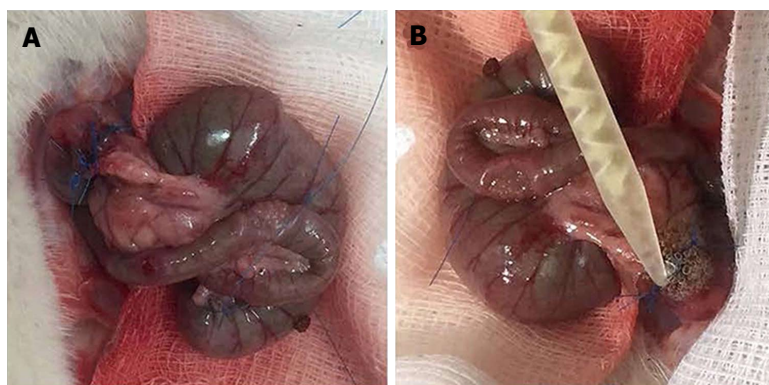


Figure 1 Control and Bioglue group. A: Creation of end-to-end anastomosis using a single layer of eight interrupted extramucosal 6-0 polypropylene sutures; B: Application of the Bioglue on the colon edges after taking precautions to avoid dispersion of the glue in the peritoneal cavity.

to two groups of 20 animals. In the CONTROL group, an end-to-end anastomosis was created (Figure 1A). In the BIOGLUE group, after creating the anastomosis, albumin/glutaraldehyde was applied around it (Figure 1B). The glue was applied on the colon's edges with an applicator. Holding the applicator was sufficient to place the liquid adhesive on the cut edges of the colon, taking precautions to avoid dispersion of the glue in the peritoneal cavity. The abdominal muscle layer and the skin were closed in one layer, using three sutures (3/0 silk). Each group was subdivided in two subgroups of ten animals each, with half of the animals being sacrificed on the fourth postoperative day (CONTROL4 and BIOGLUE4) and the other half being sacrificed on the eighth postoperative day (CONTROL8 and BIOGLUE8).

Macroscopic examination

On the day of sacrifice, the animals were anaesthetized again, and the anastomotic segments were isolated during relaparotomy. The anastomoses were examined macroscopically. Integrity of the anastomosis, existence of perianastomotic abscess or peritonitis, and adhesion formation were recorded. The evaluation was performed according to the scale of van der Ham *et al.*^[15], as has been described elsewhere. Briefly, anastomosis was given score 0 when no adhesions occurred; score 1 represented minimal adhesions mainly between the anastomosis and the omentum; score 2 corresponded to moderate adhesions, *i.e.*, between the omentum and the anastomotic site or between the anastomosis and a loop of small intestine; finally, score 3 represented severe and extensive adhesions, including abscess formation.

Bursting pressure

Bursting pressure was measured *ex vivo*. The anastomosis was removed along with a 2.5 cm segment of the colon on either side *en bloc* with the formed adhesions and cleared of stools. The proximal end was ligated using a 3/0 silk suture, and a catheter was secured into the distal end and fixed to the bursting

pressure apparatus as described elsewhere^[16-18]. Through this catheter, the bowel was infused with a continuous flow of physiological saline at a rate of 1 mL/min. The bursting pressure was defined as the pressure at which leakage of saline or gross rupture was noted and recorded in mmHg. The site of leakage during the bursting pressure measurement was also recorded, since in some rats, rupture occurred at the anastomotic site, and in others far from it.

Histological assessment

After the *ex vivo* measurement of bursting pressure, the anastomotic segment of the colon was cleared of the surrounding mesentery and fat and rinsed with saline. The anastomosis was resected along with a 0.5 cm segment of the colon on either side and divided into two parts vertically. The first segment was placed in 4% formaldehyde solution for histopathological examination and stained with haematoxylin and eosin. The anastomosis was examined under a light microscope and graded histologically in a blind fashion, using a 0-4 Ehrlich and Hunt numerical scale as modified by Phillips *et al.*^[19]. The evaluated parameters were inflammatory cell infiltration (white blood cell count), neoangiogenesis (new blood vessel formation), fibroblast activity, and collagen deposition^[20]. Each studied parameter was evaluated individually using a numerical scale from 0 to 4 as follows: 0 (-) = no evidence; 1 (+) = occasional evidence; 2 (++) = light scattering; 3 (+++) = abundant evidence; and 4 (+++++) = confluent fibres or cells.

Hydroxyproline

Quantification of collagen in colonic anastomosis is synonymous with quantification of hydroxyproline. The second segment of the anastomosis was weighed and then divided into two parts vertically and stored at -20 °C. Determination of hydroxyproline tissue contents was performed as described in previous experiments, with some modifications^[13,21]. Briefly, after the specimens were lyophilized, a polytron homogenizer was used to homogenize the tissue sample in distilled

water. The acid-soluble collagen was extracted from the tissue sample by overnight incubation with acetic acid 0.5 mol/L at 4 °C. 70 µL of standard/test sample was hydrolysed in 30 µL NaOH 10.125 mol/L for 25 min at 120 °C by autoclaving. The hydrolysed sample was then mixed with a buffered (pH 7) chloramines-T reagent (0.056 mol/L), and at room temperature the oxidation was continued for 25 min. Following the development of chromophore was achieved with the addition of Ehrlich's reagent. The absorbance was measured at 550 nm using a Biotek µQuant™ spectrophotometer. Absorbance values were plotted against the concentration of standard hydroxyproline, and the presence of hydroxyproline in unknown tissue extracts was determined from the standard curve. The results were expressed in µg/g of tissue^[21].

Collagenase I

The concentration of collagenase I was estimated in another segment of the anastomotic site by using a commercial ELISA kit (USCNLIFE, E0212r). The test sample was added to the appropriate plate well pre-coated with anti-collagenase I antibody-microtiter with a biotin-conjugated polyclonal antibody specific to collagenase I. Then, avidin conjugated to HRP was added to the microplate well and incubated. The chromophore was then developed with the addition of TMB substrate solution, and the reaction stopped with sulphuric acid solution. The colour change was measured spectrophotometrically at 450 nm using a Stat Fax-210™ spectrophotometer (Awareness Technology Inc.). The concentration of collagenase I in unknown tissue samples was determined from the standard curve. The results were calculated as µg/g of wet tissue weight^[22].

Statistical analysis

Using statistical descriptive indices of central tendency and dispersion the experimental data were summarized. Data are presented as mean ± SD. After performing a normality test, if the data presented a normal distribution we used ANOVA to compare all four groups and the least significant difference criterion^[23] as *post hoc* analysis to make comparisons between groups. If the data didn't have normal distribution we used the non-parametric Kruskal-Wallis test to compare all four groups and performed the Mann-Whitney test to make comparisons between groups, with the significance level for the certain test adjusted to $P = 0.0125$ ($0.05/4$). The significance level of statistical hypothesis testing procedures concerning comparisons of means was pre-set at $P < 0.05$. All the statistical analyses were performed using the SPSS version 15.0 statistical package (SPSS Inc., Chicago, IL, United States) enhanced with the module Exact Tests^[24,25]. The statistical methods of this study were reviewed by Dr. Haidich AB, Assistant Professor

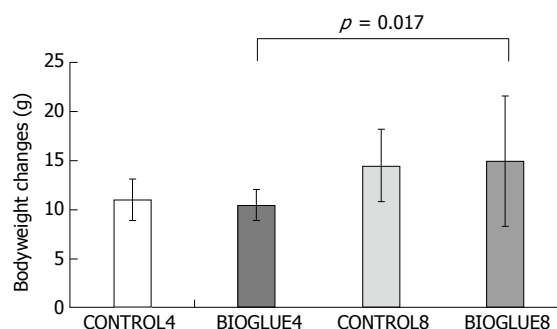


Figure 2 Bodyweight changes in grams in the two groups (mean ± SD). A statistically significant difference was found between subgroups BIOGLUE4 and BIOGLUE8.

in Hygiene-Medical Statistics, Aristotle University of Thessaloniki, Greece.

RESULTS

Mortality, infection, and anastomotic dehiscence

No deaths or wound infections occurred, and no anastomotic dehiscence was noted before the day of sacrifice.

Bodyweight change

In all the experimental groups, the bodyweight decreased from the day of the experiment till the day of sacrifice. Bodyweight changes differed significantly among the subgroups ($P = 0.03$). In particular, the only significant difference in bodyweight change was between subgroups BIOGLUE4 and BIOGLUE8 ($P = 0.017$), but there were no other differences between subgroups. The bodyweight changes are presented in Figure 2.

Adhesion Formation

On the fourth postoperative day, in subgroup CONTROL4, 90% of animals had no adhesions, and only 10% presented with grade 1 adhesions, while in subgroup BIOGLUE4, all animals had adhesions, and the adhesion formation score was grade 2 in all animals. On the eighth postoperative day, in subgroup CONTROL8, 90% of animals had no adhesions, and only 10% presented with grade 1 adhesions, while in subgroup BIOGLUE8, all animals had adhesions, and the adhesion formation score was grade 2 in all animals (Figure 3).

The adhesion formation score differed significantly between groups ($P < 0.001$). It was significantly higher in both Bioglue subgroups than in the two control groups ($P < 0.001$ in both cases). The adhesion formation scores are presented in Figure 4.

Bursting Pressure measurement

There was a significant difference in bursting pressure among groups ($P < 0.001$). Bursting pressure was significantly increased in the Bioglue subgroup



Figure 3 Moderate adhesion formation between the omentum and the anastomotic site in the Bioglue group.

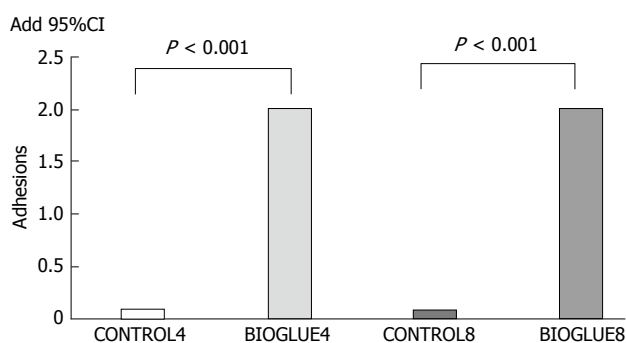


Figure 4 Comparative bar chart of adhesion formation (mean). The adhesion formation score was statistically significantly higher in both Bioglue subgroups compared to control.

compared to the control subgroup on the fourth postoperative day ($P = 0.017$) but not on the eighth postoperative day ($P = 0.545$). Furthermore, bursting pressure was statistically significantly higher on the eighth postoperative day in both the Bioglue and the control groups, with $P < 0.001$ in both cases. The differences in bursting pressures are presented in Figure 5.

Regarding the site of leakage during the measurement of bursting pressure, on the fourth postoperative day in both the control (CONTROL4) and the study (BIOGLUE4) groups, the rupture occurred in 50% of the animals at the anastomosis and in 50% far from it, while on the eighth postoperative day in both subgroups (CONTROL8 and BIOGLUE8), all ruptures occurred far from the anastomotic site.

Histological assessment

The histological assessment of the anastomotic healing included measurements of inflammatory cell infiltration, neoangiogenesis, fibroblast activity, and collagen deposition. In Figure 6, histology images of various degrees of inflammation, neoangiogenesis, fibroblast activity, and collagen deposition are presented,

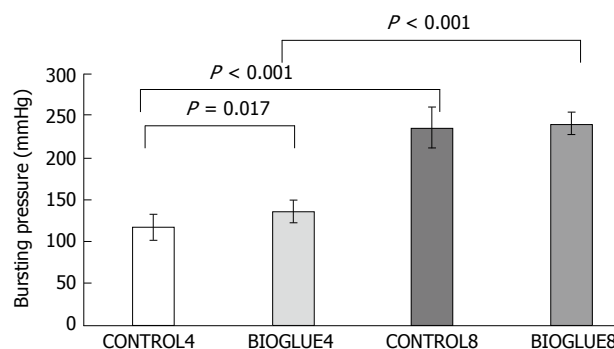


Figure 5 Comparative bar chart presenting bursting pressures (mmHg) (mean \pm SD). A statistically significant increase in the bursting pressure was noted on the fourth postoperative day in the Bioglue subgroup compared to the control.

respectively.

Statistical analysis revealed significant changes in all histological parameters: inflammation ($P < 0.001$), neoangiogenesis ($P < 0.001$), fibroblast activity ($P = 0.001$), and collagen deposition ($P < 0.001$).

The average inflammatory cell infiltration was significantly higher in the Bioglue subgroups than in the controls for both postoperative days, with $P < 0.001$ in both cases. There was also a significant difference between subgroups CONTROL4 and CONTROL8 ($P < 0.001$) and between BIOGLUE4 and BIOGLUE8 ($P = 0.001$). The changes in inflammatory cell infiltration among groups are presented in a histogram in Figure 7A.

Regarding neoangiogenesis, in the Bioglue group, there was an increase on the fourth and eighth postoperative days compared to the control group, but this difference was significant only on the eighth postoperative day (CONTROL4 vs BIOGLUE4 with $P = 0.2398$ and CONTROL8 vs BIOGLUE8 with $P = 0.039$). Neoangiogenesis was also statistically significantly higher on the eighth postoperative day in both Bioglue and control groups (CONTROL4 vs CONTROL8 with $P = 0.014$ and BIOGLUE4 vs BIOGLUE8 with $P = 0.002$). Changes in neoangiogenesis between groups are plotted in Figure 7B.

The fibroblast activity was similar in the Bioglue subgroups and in the control subgroups on both postoperative days (CONTROL4 vs BIOGLUE4, $P = 1$, and CONTROL8 vs BIOGLUE8, $P = 1$). However, there was a significant difference between subgroups CONTROL4 and CONTROL8 ($P = 0.002$) and between BIOGLUE4 and BIOGLUE8 ($P = 0.002$). The changes in fibroblast activity among groups are presented in a histogram in Figure 7C.

Collagen deposition was statistically significantly lower in the control subgroups than in the Bioglue subgroups (CONTROL4 vs BIOGLUE4 and CONTROL8 vs BIOGLUE8 with $P = 0.032$ and $P = 0.002$, respectively). There was also a significant increase in collagen deposition between subgroups CONTROL4 and CONTROL8 ($P < 0.001$) and between BIOGLUE4 and BIOGLUE8 ($P < 0.001$). Changes in collagen deposition between groups are presented in Figure 7D.

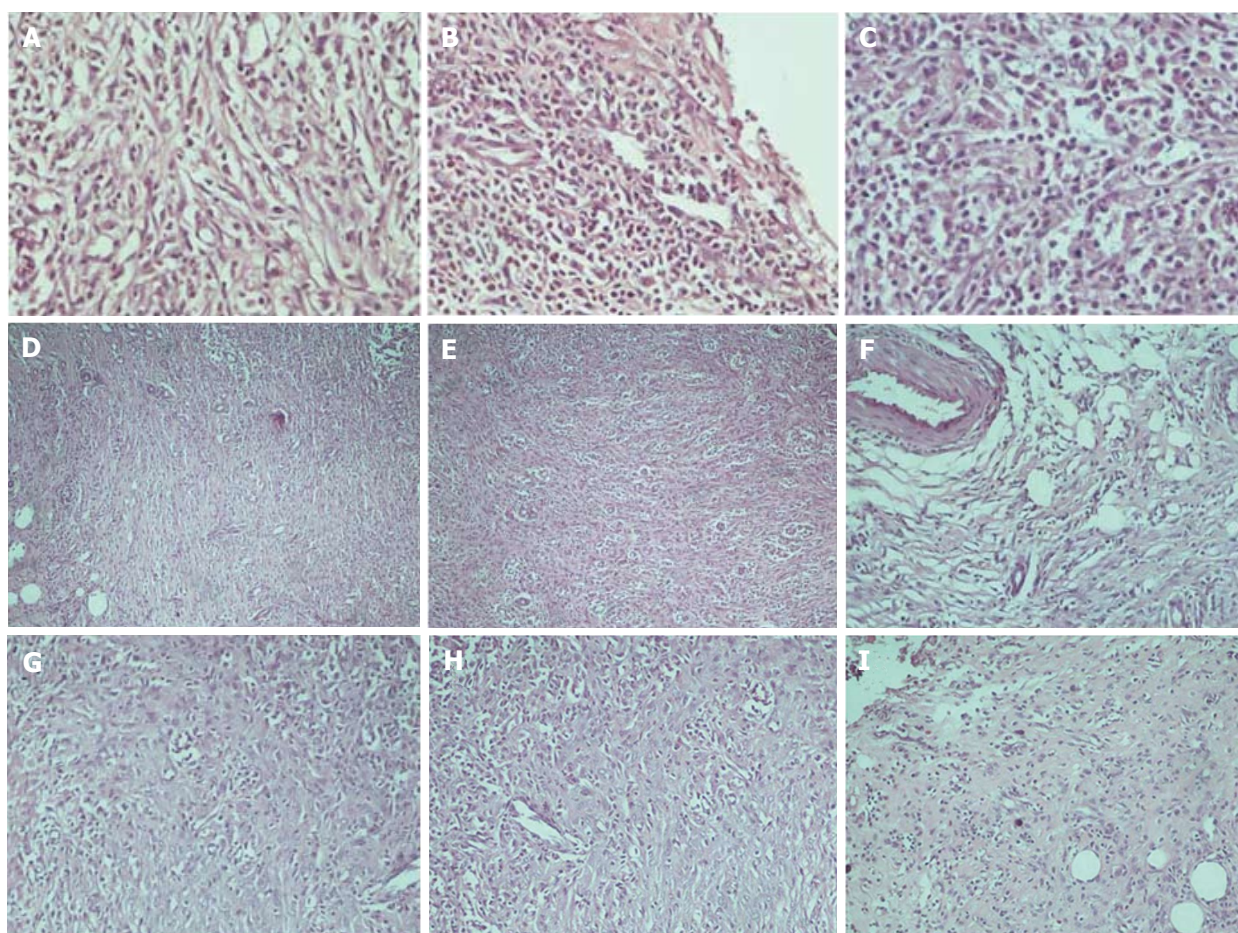


Figure 6 Representative haematoxylin-eosin histopathology images. A: Inflammatory cell infiltration revealing light scattering ($\times 400$); B: Abundant evidence ($\times 400$); C: Confluent cells ($\times 400$); D: Neoangiogenesis revealing light scattering (A, $\times 100$); E: Abundant evidence ($\times 100$); F: Fibroblast activity revealing light scattering ($\times 100$); G: Abundant evidence ($\times 200$); H: Collagen deposition revealing light scattering ($\times 200$); I: Abundant evidence ($\times 100$).

Hydroxyproline and collagenase I concentration

Hydroxyproline concentration differed significantly between groups. Specifically, it was similar on the fourth and eighth postoperative days between the two groups (CONTROL4 vs BIOGLUE4 with $P = 0.656$ and CONTROL8 vs BIOGLUE8 with $P = 0.309$), but there was a significant increase in the hydroxyproline tissue content of both groups (control and Bioglue) on the eighth postoperative day compared to the fourth (BIOGLUE4 vs BIOGLUE8 and CONTROL4 vs CONTROL8, with $P < 0.001$ in both cases). The results are presented in Figure 8A.

Collagenase I concentration was similar between the two groups and subgroups on the fourth and eighth postoperative days ($P = 0.959$). Specifically, CONTROL4 vs BIOGLUE4 ($P = 0.912$) and CONTROL8 vs BIOGLUE8 ($P = 0.796$). CONTROL4 vs CONTROL8 ($P = 0.684$) and BIOGLUE4 vs BIOGLUE8: ($P = 0.912$). The results are presented in Figure 8B.

DISCUSSION

Anastomotic leakage remains the most important cause of postoperative mortality and morbidity in colorectal surgery^[26,27]. Intestinal anastomoses are

complicated by leakages, even in the most experienced of hands and despite the development of new surgical techniques, suture materials, and stapling devices^[28,29].

Many factors affect the healing of anastomoses, divided into general and local ones^[30]. General factors include the patient's age and diet, hypovolemia, malignancy, medications (e.g., steroids, nonsteroidal anti-inflammatory drugs, and 5-FU), immunocompetence, blood transfusion, radiotherapy, diabetes, uraemia, anaemia, jaundice, and nutrient deficiencies (vitamin C, iron, zinc, methionine, cysteine, etc.)^[16,31-34]. Local factors include ischaemia at the anastomotic site, anastomotic tension, surgical technique, peritonitis, pre-operative bowel preparation, infection, and emergency or elective surgery^[34-36].

Bioglue surgical adhesive is a two-component surgical adhesive that confers enhanced bonding properties. It is composed of 45% purified bovine serum albumin and 10% glutaraldehyde. The advantage of Bioglue is that the bi-functional glutaraldehyde molecule covalently bonds the bovine serum albumin molecules to each other, as well as to lysine in proteins on the cell surface and in the extracellular matrix. This reaction is spontaneous, increasing tensile and shear strength. The albumin provides an extensive flexible network of bonds.

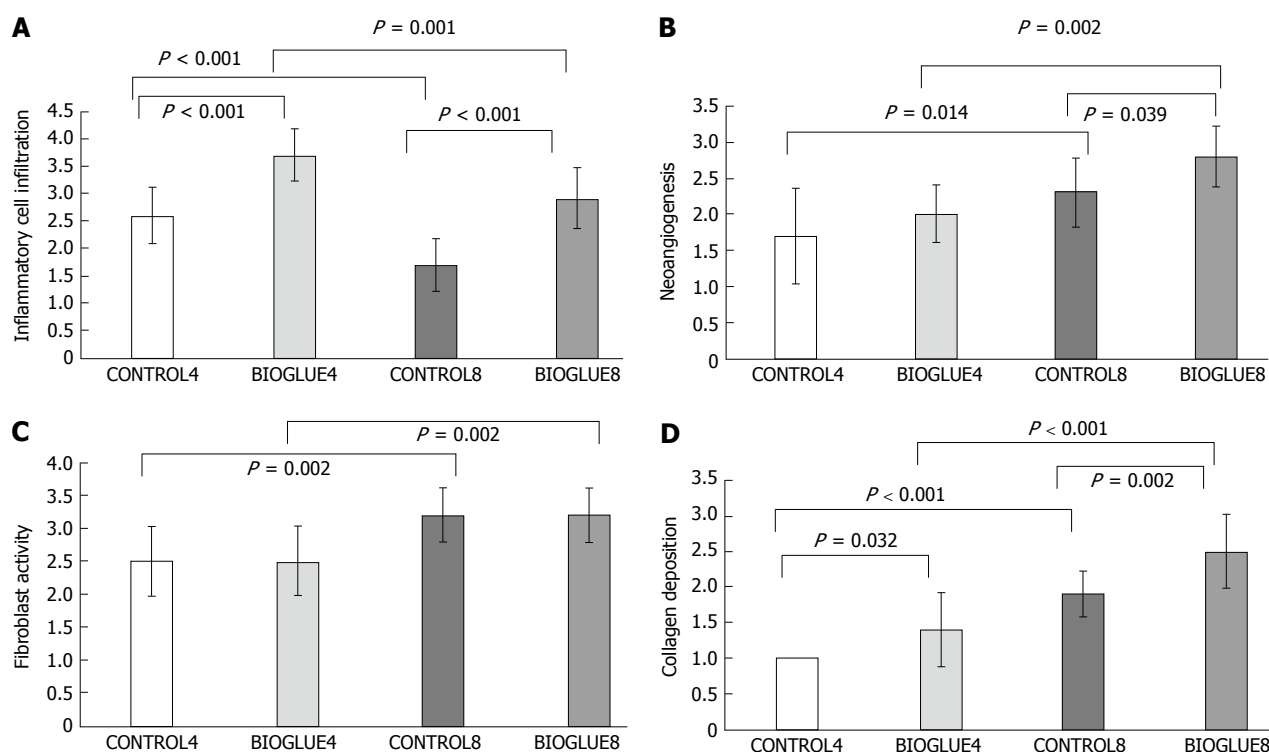


Figure 7 Comparative bar chart presenting the average inflammatory cell infiltration (A), new vessel formation (neoangiogenesis) (B), fibroblast activity (C) and collagen deposition (D), according to the scale of Ehrlich and Hunt, as modified by Phillips *et al*^[19] (0-4) (mean \pm SD). A: The average inflammatory cell infiltration was statistically significantly higher in the Bioglue subgroups on both the fourth and eighth days than in the controls. Also, in each subgroup, there was a statistically significant decrease in the average inflammatory cell infiltration from the fourth to the eighth day; B: The average neoangiogenesis was statistically significantly higher in the Bioglue subgroups on the eighth day than in the control. Also, in each subgroup, there was a statistically significant increase in neoangiogenesis from the fourth to the eighth day; C: The average fibroblast activity was statistically significantly higher in each subgroup from the fourth to the eighth day; D: The average collagen deposition was statistically significantly higher in the Bioglue subgroups on both the fourth and eighth days than in the control. Also, in each subgroup there was a statistically significant increase in collagen deposition from the fourth to the eighth day.

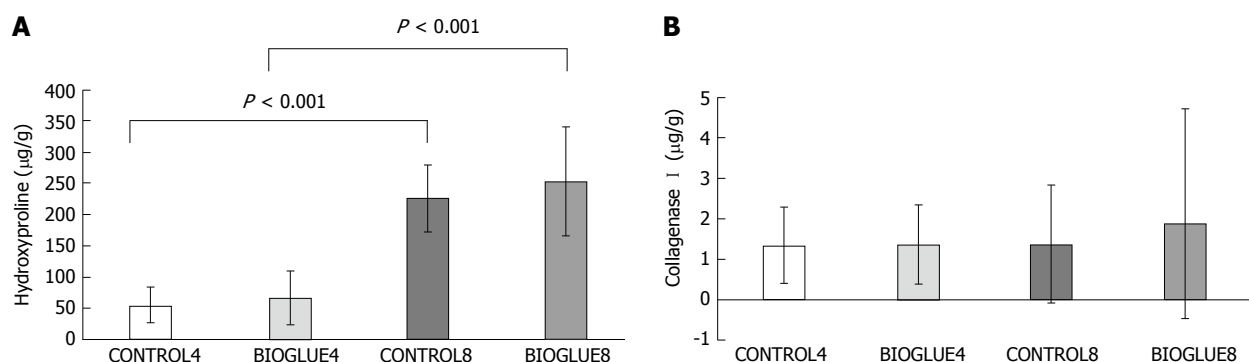


Figure 8 Comparative bar chart of hydroxyproline tissue contents (A), collagenase I tissue contents (B) ($\mu\text{g/g}$ tissue) at the anastomotic site (mean \pm SD). A: In each subgroup, there was a statistically significant increase in hydroxyproline tissue content from the fourth to the eighth day; B: No statistically significant difference was noted.

When applied to the repair site, it forms a watertight mechanical seal and holds sutures securely^[13]. It is necessary to dry the completed anastomosis as much as possible and to protect the area surrounding the target tissue with moist sterile gauze pads^[37]. Polymerisation commences rapidly within 20 to 30 s and reaches full bonding strength in two minutes^[38].

Patients with colorectal cancer usually lose weight, and malnutrition accompanying loss of bodyweight decreases the deposition of collagen and the anastomotic

strength^[39]. As expected following surgery, in our study, the mean postoperative bodyweight was lower both on the fourth and the eighth postoperative days in all subgroups compared to the beginning of the experiment. However, a comparison of the control and Bioglue subgroups revealed that there wasn't any statistically significant difference between their mean bodyweights. The only significant difference was a greater decrease in bodyweight in the Bioglue group on the eighth day compared to the fourth day.

Adhesions are fibrous bands that connect the peritoneal organs to each other or the peritoneum and could possibly seal any potential micro-leakages from the anastomosis and simultaneously enhance the local blood supply^[40,41]. The incidence of adhesion formation appears to be caused by many factors, such as sutures or staples that can potentially cause topical ischemia. The foreign material used can lead to an infected anastomosis followed by anastomotic leakage^[42]. Furthermore, adhesion formation is dependent on the severity of the intestinal serosal trauma, fibroblast activation, metalloproteinase activity, and the efficiency of the fibrinolytic mechanism^[43-45]. Adhesion formation is a serious problem to tackle when using glue for anastomosis. In the Bioglue group, there was an increase in the adhesion formation score that was statistically significant. Similar are the results of Ozel *et al.*^[46], who, in an experimental study in rats using a fibrin patch to support colonic anastomoses, found more adhesions of greater degree in the study group compared to the control. However, Kanellos *et al.*^[47] using a fibrin glue, didn't notice any difference in adhesion formation compared to the control group in rats with colonic anastomosis, while Haukipuro *et al.*^[48] demonstrated fewer adhesions using fibrin sealant. Detweiler *et al.*^[49] proposed the combination of absorbable stents and fibrin glue to avoid adhesion formation and intestinal obstruction.

The percentage of anastomotic leakage is the most important marker reflecting the efficacy of the healing mechanisms of intestinal anastomoses and ranges from 3% to 30%^[1,2,50,51]. In the present study, no anastomotic leakage was noted in either subgroup on the fourth or the eighth postoperative day, reflecting the efficacy of healing mechanisms in both groups. The mechanical strength of the anastomosis is determined by its bursting pressure. It is therefore a useful parameter to measure the healing process in the first week after anastomotic formation^[52]. Bursting pressure increases progressively after the formation of the anastomosis. In our study, the bursting pressures were significantly higher in both the control group and the Bioglue group on the eighth postoperative day than the fourth. Moreover, Bioglue significantly increased bursting pressures compared to the control on the fourth postoperative day but not on the eighth. Hjortrup *et al.*^[53] found that the bursting pressure of small bowel segments with fibrin anastomoses was similar to those with sutured anastomoses. Capitán Morales *et al.*^[54] compared three groups of rats: one with anastomoses sutured with silk 5/0, one with anastomoses sutured with polyglycolic acid 5/0, and one with suture-less fibrin adhesive anastomoses. They found that the greatest bursting pressure occurred in the last series. Additionally, Akgün *et al.*^[55] in an experimental study using a fibrin sealant to protect anastomoses in rats, demonstrated an increase in bursting pressure in the study group compared to the control.

A fundamental element in the assessment of bursting pressure and the efficacy of healing mechanisms is the part of the colon that ruptures during the measurement of bursting pressure^[10,56,57]. Rupture at the anastomotic site happens in mechanically weaker anastomoses or anastomoses at the early healing phase, between the third and fifth days. In contrast, rupture far from an anastomosis presents in mechanically very strong anastomoses or in anastomoses in the late healing phase, specifically in the remodelling phase^[2,28]. In the current study, there were no differences in the rupture sites among the subgroups.

Healing of anastomoses is a complicated process which is divided into four different phases: coagulation, inflammation, migration and proliferation, and remodelling. Inflammation is the second phase and is characterized by infiltration of the anastomosis by inflammatory cells, especially leukocytes^[58-60]. Macrophages, lymphocytes and thrombocytes produce and secrete cytokines and growth factors that regulate neoangiogenesis and collagen synthesis^[60-63] and have mitogenic, chemotactic, and cell movement stimulant functions^[62]. The crucial role of neutrophils in the early postoperative weakening of the anastomosis due to activation of metalloproteinases and collagen degradation is well established^[64-67]. The foreign bodies such as sutures, clips, and any biological substances (glues) which are used in the anastomosis are those that keep the anastomosis intact during the healing phase^[1,3,10]. In our study, inflammatory cell infiltration was statistically significantly higher in the Bioglue subgroups than in the control subgroups on both postoperative days. Ozel *et al.*^[46] noticed a significant increase in the inflammatory reaction in the fibrin patch group compared to the control, which was attributed to the increased activity of the inflammatory cells and metalloproteinases between the third and seventh postoperative days due to the presence of the fibrin patch.

After inflammation comes the proliferative phase of healing, characterized by the production of collagen by fibroblasts, which increases the strength of the anastomosis^[68-70]. The fibroblasts secrete hyaluronic acid and proteoglycans, which are important for cell movement, function, and tissue resilience, and collagen, promoting anastomotic healing^[71]. According to the results of our experimental study, fibroblast activity was similar between the subgroups both on the fourth and the eighth postoperative days. This finding is in contrast with Akgün *et al.*^[55], who demonstrated an increase of fibroblasts in the fibrin sealant group compared to the control.

Neoangiogenesis is the formation of new blood vessels from the endothelium of pre-existing ones and takes place in the third phase of healing, the proliferative phase, leading to the formation of granular tissue^[39,72-74]. It has been shown that this phase is affected by various angiogenic factors such as platelet derived growth factor, tumour necrosis factor- α , and

Vascular Endothelial Growth Factor family^[61,75]. In our study, the degree of neoangiogenesis was affected by the presence of Bioglue: neoangiogenesis was statistically significantly higher in the Bioglue group only on the eighth postoperative day. Ozel *et al.*^[46] also found that neoangiogenesis was higher in the fibrin patch group than in the control.

The production and deposition of collagen, which takes place during the third (proliferation) and fourth (remodelling) phases, is a significant marker of the efficacy of the anastomotic healing process^[45,65,68,76,77]. Collagen is mainly produced by fibroblasts and metabolized by certain metalloproteinases, called collagenases^[68,78,79]. In our study, collagen deposition was significantly higher in the Bioglue group on both the fourth and the eighth days, a finding similar to Ozel *et al.*^[46] who noticed increased collagen production in the fibrin patch group compared to the control.

Histological analysis of anastomotic colon wall samples demonstrated the favourable influence of Bioglue on the complex process of colon anastomosis healing, reflected in the stimulation of the proliferative response, promotion of neoangiogenesis, more abundant young collagen synthesis, and reduction of the duration of the critical healing period.

The mechanical strength of healing wounds depends on fibroblast proliferation and the synthesis of collagen molecules. Collagen determines the mechanical stability and healing capacity of connective tissue. The quantitative measurement of collagen deposited in the anastomosis is accomplished by the measurement of hydroxyproline in the anastomotic tissue^[45,80]. Hydroxyproline is one of the basic amino acids of collagen, and its presence is restricted exclusively to the collagen of connective tissue. Low hydroxyproline levels negatively affect the mechanism of colonic anastomosis healing^[44,81]. We found that there was a statistically significant increase in hydroxyproline tissue content in both groups (control and Bioglue) on the eighth postoperative day compared to the fourth but no difference between the groups on either the fourth or the eighth day. Ozel *et al.*^[46] also demonstrated an increased hydroxyproline concentration in the fibrin patch group compared to the control.

In the third phase of healing, the collagen is synthesized and degraded by a variety of collagenase enzymes from granulocytes, macrophages, and fibroblasts. The concentration of mature collagen in the early phase of healing is decreased up to 40%, an event that correlates with a reduction in the mechanical strength of the anastomosis at this phase and with possible anastomotic dehiscence^[45,77,80]. Many studies have shown that their activity is a major pathogenic factor in the postoperative decline of colonic anastomosis strength. Experimental studies have shown maximal collagenetic activity in the colon on the third postoperative day^[82]. Collagenase is responsible for the degradation of mature collagen, and its concentration maximizes on the third postoperative

day, when increased degradation of type III collagen and synthesis of type I collagen takes place^[44,70,71,83].

Furthermore, immunohistochemical studies have shown that collagenase and other matrix metalloproteinases (MMPs) are in close vicinity to the suture line in uncomplicated anastomotic healing^[71], so the measurement of collagenase concentration is a marker reflecting the balance of collagenogenesis and collagenolysis^[43,84,85]. It has been previously demonstrated that the MMP levels in the anastomotic line are very different from those in adjacent tissue, where the level of MMPs was measured at up to 0.15-0.2 cm from the anastomotic line^[86,87]. In the current experiment, collagenase was measured in a segment of 0.5 cm on both sides of the anastomosis in each animal. While the levels of collagenase vary at the anastomotic line and 0.5 cm from it, as tissue samples were the same in all animals, the measured collagenase activity in 1 cm of large intestine with the anastomosis in the middle reflects the total collagenase activity, which is comparable between groups. Collagenase I concentration was similar between the two groups and subgroups on the fourth and on the eighth postoperative days.

In the early period of anastomotic healing, Bioglue seems to support anastomotic integrity in rats, since it increases the bursting pressure. This effect of Bioglue has also been demonstrated in *ex vivo* porcine gastrojejunal anastomosis^[88]. However, it also causes an inflammatory reaction which may increase the time necessary for the healing process. This may represent a major disadvantage for this biomaterial. Regarding the safety of Bioglue, our study demonstrated that the application of Bioglue on the suture line is not associated with increased mortality or dehiscence, in contrast with the study of Slieker *et al.*^[89] where the application of Bioglue on sutured colonic anastomoses in mice caused a 100% mortality rate, compared with the 40% mortality rate in the control group. Further studies are most likely required in order to assess the effects of Bioglue on anastomotic healing after direct administration into the colon, as there is only one other study assessing Bioglue's effect in suture-less closure of colonic defects^[90].

COMMENTS

Background

Anastomosis dehiscence is a serious postoperative complication in gastrointestinal surgery, and anastomotic leakage remains the most important cause of postoperative mortality and morbidity in colorectal surgery. The risk of anastomotic leakage is higher in large intestine surgery compared with other gastrointestinal anastomoses. Intestinal anastomoses are complicated by leakages, even in the best and most experienced of hands and despite the development of new surgical techniques, suture materials, and stapling devices. The efficacy of biomaterial over intestinal anastomoses is still controversial in clinical practice.

Research frontiers

The replacement or support of sutures by biomaterial gluing procedures has been investigated for many years. Different techniques using additive materials such as omentum and several types of fibrin sealants to cover the anastomosis have been proposed. Out of a large number of experimental studies, various

protective methods such as endoluminal latex prostheses, stents, biofragmental rings, and local application of bioadhesives have been used, with promising results. Tissue glues have been used to seal suture lines for haemostasis and to strengthen and reinforce fragile tissues by tissue adherence. The main idea was to reduce the incidence of dehiscence by increasing the strength of anastomoses, covering the anastomotic line and stimulating healing.

Innovations and breakthroughs

The current study demonstrated the safety and efficacy of Bioglue application on a colonic anastomosis, as it promotes the healing process, especially in the early stages, and increases the bursting pressure. The increase in the mechanical strength of the colonic anastomosis in the early stages is a result of increased adhesion formation and increased collagen deposition and takes place in spite of increased inflammatory cell infiltration.

Applications

The application of biological glue on colonic anastomosis in clinical practice may reduce anastomotic dehiscence and leakage and decrease the related morbidity and mortality

Terminology

Bioglue is a two-component surgical adhesive that confers enhanced bonding properties. It is composed of 45% purified BSA and 10% glutaraldehyde. The advantage of Bioglue is that the bi-functional glutaraldehyde molecule covalently bonds the bovine serum albumin molecules to each other, as well as to lysine in proteins on the cell surface in the extracellular matrix. This reaction is spontaneous, increasing tensile and shear strength independently of the coagulation status of the patient. The albumin provides an extensive flexible network of bonds. When applied to the repair site, it forms a mechanical watertight seal and holds sutures securely.

Peer-review

An interesting paper on sealment of experimental anastomoses in a rat model.

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