The Effect of TISSEEL® on Colorectal Anastomosis Healing Process in a Diabetic Animal Experimental Model

KONSTANTINOS STERGIOS1, MAXIMOS FROUNTZAS1, VASILIOS PERGYALIOITIS1, LASKARINA MARIA KOROU1, KONSTANTINOS KONTZOGLOU1, KONSTANTINOS STEFANIDIS1, NIKOLAOS NIKITEAS1, DESPINA N. PERREA1 and GEORGE VAOS2

1Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, Athens Medical School, Athens, Greece; 2Department of Paediatric Surgery, “ATTIKON” University General Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Abstract. Background/Aim: Diabetes mellitus is an established risk factor of colorectal anastomosis failure. The purpose of the present study was to evaluate the effect of TISSEEL® in anastomotic healing. Materials and Methods: Forty male, Sprague-Dawley rats were used. Diabetes was induced in half of them by intraperitoneal injection of Streptozotocin, 60 mg/kg. One week after the injection, animals were operated and a 1 cm segment was removed and an end-to-end hand sewn anastomosis was performed. TISSEEL® was applied in each group (diabetic, non-diabetic) following randomization. Results: The pathology analysis revealed improved tissue remodeling in the TISSEEL® group, both for the normoglycemic and the diabetic group. Specifically, the extent of inflammation was decreased (p<0.001), whereas fibroblast and collagen formation were improved (p=0.040 and p=0.008). Neovascularization was also improved (p=0.047). Conclusion: Application of TISSEEL® on colorectal anastomoses improves healing in rats that suffer from severe hyperglycemia.

Surgical operation is currently the definitive treatment option both for colorectal cancer and a variety of benign colorectal modalities, such as inflammatory bowel disease (IBD), inflammatory strictures, diverticulosis-diverticulitis, obstructive defecation, volvulus, fistulae etc. (1). Despite the fact that colorectal surgeons undergo a high-level training and specialization in advanced techniques, colorectal operations still demonstrate serious complications (2). The most frightening and dramatic complication of colorectal resections with restorative anastomoses is anastomotic dehiscence (3). Anastomotic leakage remains a relatively frequent complication of colorectal operations even in high volume specialized centers, with reported rates of 2.5%-15% for rectal cancer resections and 3%-7% after colon cancer surgery (4). The consequences of this complication are devastating as it has been related to higher recurrence rates, increased morbidity and mortality rates, elevated treatment costs and negative influence in the quality of life of patients (5, 6). Despite technological advances, including transanal total mesorectal excision (TME), laparoscopic and robotic approach, and the new trends followed during post-operative management of patients that undergo colorectal resection, such as enhanced recovery after surgery (ERAS), there are several risk factors that still exert a significant impact on the outcome of colorectal anastomoses (7, 8). So far, patient-related factors (male sex, ASA score>II, radiotherapy, immunosuppressive therapy, bevacizumab intake), tumor-related factors (distal size>3 cm, advanced stage, emergency surgery, metastatic disease), comorbidities (diabetes, cardiovascular disease, poor nutrition) and operation-related factors (operative time, blood loss, need for transfusion) have been considered as determinants of failed anastomotic healing and leakage (9). Diabetes mellitus has a special position among the previously mentioned risk factors, as it is a well-established independent factor for anastomotic leakage, that has been associated to increased mortality after anastomotic dehiscence as well (10).

Previous studies have suggested that the negative impact of diabetes mellitus on tissue healing is based on the exacerbated inflammatory processes (11, 12). Diabetes also dysregulates the transformation of macrophages from their...
inflammatory-state into their healing-state (13). Furthermore, the disease results in the formation of extracellular neutrophilic traps that contain chromatin and cytotoxic proteins, a process called NETosis, that damages healthy tissues (14). Peripheral angiopathy is another factor that is frequently encountered in diabetic patients which per se results in impairment of the integrity of colorectal anastomoses (15). Diabetes affects a large number of physiological factors involved in the healing process, such as growth factor production, angiogenic response, collagen concentration, tissue granulation and extracellular matrix accumulation and remodeling by matrix metalloproteinases (16). However, fibrin sealants have been used as hemostatic factors and enhancers of the wound healing process in various surgical procedures including gastrointestinal anastomoses, plastic surgery, gynecologic and urologic procedures (17, 18).

The aim of the present study was to investigate the effect of TISSEEL®, which is a fibrin sealant that simulates the final stages of the coagulation cascade, in tissue healing of colorectal anastomoses in diabetic rats.

Materials and Methods

Animals. Forty male, Sprague-Dawley rats (Hellenic Pasteur Institute, Department of Animal Models for Biomedical Research, Greece) were transferred in the Laboratory of Experimental Surgery “NS Christeas” of the National and Kapodistrian University of Athens. The animals remained in atmosphere-controlled chambers (temperature 20±1°C, humidity 55±5%) and under controlled light (12 h per day) for 7 days in order to adapt to their new environment. Full nutrient supplementation was provided ad libitum using ELVIZ 510 food pellets. Animal care, surgical operations and postoperative care were approved by the Athens University Medical School Ethics Committee and by the Veterinary Directorate of the Ministry of Agriculture in agreement with the EU Directive 2010/63/EU for animal experiments. The animals were not given food the night before the surgery.

Research involving human participants and/or animals. The present study was conducted in accordance to the Declaration of Helsinki concerning animal and Human Rights and approved by the Athens University Medical School Ethics Committee and by the Veterinary Directorate of the Ministry of Agriculture in agreement with the European Union directive 86/609.

Diabetes induction. Type I diabetes was induced by intraperitoneal injection of Streptozotocin, 60mg/kg of body weight, one week following the admission of animals. Streptozotocin or Streptozocin is a naturally occurring alkylating antineoplastic agent, which is especially toxic to the insulin-producing pancreatic β-cells in mammals. Verification of the increased blood glucose levels was performed during the 3rd and 7th day post injection by collecting blood samples from the vascular plexus of the outer canthus. Animals having blood glucose levels above 200 mg/dl were considered diabetic. Following computer generated randomization, animals in each group were sub-grouped to receive TISSEEL® or not. Four groups were, therefore, formed as depicted in Figure 1.

Experimental protocol and surgical procedures. Anesthesia was performed using Xylazine (7 mg/kg) and Ketamine (70 mg/kg). Xylazine is an analogue of clonidine and an agonist at the α-2 adrenergic receptors. Ketamine is a drug mainly used for inducing and maintaining anesthesia. It induces a trance-like state while providing analgesia, sedation, and memory loss. The anterior abdominal surface was prepared and draped, using povidone iodine solution, alcohol and single-use sterile drapes. A 4 cm midline
incision was performed, starting 1 cm above the external genitalia. After entering the peritoneal cavity, the left colon was recognized and a 1 cm segment, 3 cm above the peritoneal reflection, was removed. An end-to-end hand sutured anastomosis, with interrupted 5-0 monofilament absorbable (Poly-L-lactide-co-caprolactone) sutures was performed. The groups DM+S+ TISSEEL® and S+ TISSEEL® received 1 ml/cm² dose of TISSEEL® on the anastomosis site. Closure of the abdomen was performed using a mass closure 4-0 multifilament (90% glycolide, 10% L-lactide) Vicryl continuous suture and the skin was closed with 4-0 monofilament non-absorbable, nylon continuous suture. All animals, following the operation received analgesia with subcutaneous Tramadol, at a dose of 0.01 mg/kg. Post-operatively the animals had free access to food and water, as per ERAS, and were euthanized on postoperative day 10 to minimize the possibility of false positive results concerning the integrity of anastomoses. At that time, an 1 cm segment of the colon, 0.5 cm above and 0.5 cm below the anastomosis was removed and histopathologically analyzed. We considered not to include the tensile strength nor the bursting pressure measures in our experiment, since we needed intact peri-anastomotic segments for healing evaluation and since the clinical result was already evaluated prior to biopsy.

**Fibrin sealant.** The fibrin sealant (TISSEEL®; Baxter Healthcare Corporation, Deerfield, IL, USA) is a biocompatible agent that contains a mixture of coagulation factors, the active ingredients of which include two sterile, deep-frozen solutions: the sealer protein solution and thrombin solution, each in a separate preloaded double-chamber syringe in a mixture of coagulation factors. The sealer protein solution consists of synthetic aprotinin, factor XIII, and fibrinogen while the thrombin solution contains human thrombin and calcium chloride as active ingredients, fractionated from pooled human plasma. After thawing and warming to 37°C, the two solutions were mixed and approximately 0.4 ml was applied to the colorectal anastomosis.

**Pathology analysis.** Tissue specimens were processed using standard procedures. Diagnosis was based on 4 μm thick formalin fixed, paraffin embedded hematoxylxin and eosin stained sections and in Masson's trichrome staining. The latter staining helps determine the extent of collagenous connective tissue fibers. The Ehrlich-Hunt model was used to evaluate tissue healing by assessing inflammation, fibroblastic activity, neovascularization and collagen formation in a 5-point scale (0: no evidence, 1+: occasional evidence, 2+: light scattering, 3+: abundant evidence, 4: confluent cells or fibers) (19).

---

### Table I. Baseline and Timepoint 1 weight and glucose values of enrolled animals.

| Studies parameter | Group 1 | Group 2 | Group 3 | Group 4 | p-Value |
|-------------------|---------|---------|---------|---------|---------|
| Baseline weight (g) | 211±17  | 216±16  | 207±16  | 208±18  | 0.631   |
| Baseline glucose (mg/dl) | 104±17  | 98±15   | 103±17  | 108±19  | 0.836   |
| Timepoint 1 weight (g) | 240±19  | 248±16  | 239±23  | 245±12  | 0.239   |
| Timepoint 1 glucose (mg/dl) | 321±59  | 309±66  | 96±12   | 121±74  | <0.001  |

**Statistical analysis.** Intention-to-treat analysis was performed. Continuous variables are presented as mean and standard deviation (±SD) and as median (range) values. The normality of the distributions was assessed with Kolmogorov-Smirnov’s test and graphical methods. Quantitative variables are presented with absolute and relative frequencies. Student’s t-test or nonparametric Mann-Whitney test were used to compare means between groups. For the comparisons of proportions, we used the chi-square and Fisher’s exact tests. Post-hoc analysis was performed in quantitative variables of the pathology analysis using the chi square and Fisher’s exact tests. All reported p-values are two-tailed. Statistical significance was set at p<0.05. All analyses were conducted using the SPSS statistical software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

### Results

Overall, 40 rats were included in the present study. All animals underwent resection of a part of the colon and end-to-end anastomosis was performed. The two groups were sub-stratified to those that had TISSEEL® applied at the anastomotic site and those that did not. The basic characteristics of rats prior to the onset of the randomization (baseline) and prior to the onset of the procedure (Timepoint 1) are presented in Table I. No differences were observed at baseline in terms of animal weight and glucose values, whereas at Timepoint 1 significant differences were observed in glucose values.

The procedure was uncomplicated in all but two rats that ultimately developed significant hematochezia at post-operative day 2 (one in the normoglycemic group that did not receive TISSEEL® and another one in the diabetic group that did not receive TISSEEL®) (Figure 1). Both rats were re-operated at which point we observed that both had partial bowel necrosis. The first one had a complete recovery following the procedure; whereas the second one succumbed to the procedure.

The pathology analysis revealed improved tissue remodeling in the TISSEEL® group, both for the normoglycemic and the diabetic group as the Ehrlich-Hunt model was significantly better in the TISSEEL® group compared to the group that did
not receive TISSEEL®. Specifically, the extent of inflammation was decreased, whereas fibroblast and collagen formation were improved among animals receiving TISSEEL® (fibroblast formation was very close to statistical significance among diabetic rats with TISSEEL® compared to those without TISSEEL®) (Table II, Figure 2). Neovascularization was not different between control animals that received TISSEEL® and those that did not receive treatment; however, the effect was significant in diabetic rats, favoring the TISSEEL® group.

**Discussion**

The reduction of morbidity and mortality following colorectal resections due to benign and malignant modalities would be of great socioeconomic importance. Several factors seem to affect the integrity of colorectal anastomoses including smoking, excessive blood loss and need for transfusion, the use of immunosuppressive therapy as well as the site of anastomosis (20). Diabetes mellitus is one of the most widely studied risk factors for colorectal anastomoses, with a proven destructive effect on the tissue healing process (10). Our study demonstrated an improvement in tissue remodeling after colorectal anastomosis following application of TISSEEL® both for diabetic and non-diabetic subjects. Specifically, inflammatory response and fibroblast accumulation were diminished for both groups after application of TISSEEL®, and those that did not receive treatment; however, the effect was significant in diabetic rats, favoring the TISSEEL® group.

Despite the proven effect of several risk factors related to colorectal anastomoses on specific molecular pathways, fibrin glue has been studied only in animal models without additional risk factors (21). On the other hand, several experimental studies have suggested that the implementation of biological sealants may be effective as an adjunct factor that could ensure the integrity of colorectal anastomoses (22). Vakalopoulos et al. have evaluated the efficacy of several biological fibrin sealants on sutureless repair of colonic defects. They have observed that Histoacryl Flex® exhibited significantly higher collagen formation at day 10 compared to other sealants (23). In addition, a previous systematic review produced by the same study group, has revealed that application of fibrin sealants on colonic defects is promising (24). However, the most recent systematic review relevant to this field failed to show a clear benefit from the use of fibrin glue on colorectal anastomoses (25).
Moreover, van der Vijver et al. have argued in favor of the beneficial effect of fibrin sealants on patent anastomoses in low risk conditions (26). Nevertheless, to date, none of the aforementioned fibrin sealants has been studied in severely diabetic colorectal patients who require anastomosis.

To the best of our knowledge, this is the first study, which evaluates the effect of a fibrin sealant on the proven destructive role of diabetes mellitus during the healing process of a colorectal anastomosis. Another major strength of the current study is the randomization of the animals during the second stage of the experiment prior to the application of TISSEEL®. Furthermore, all experiments were performed by the same operator and the pathologist that conducted the histopathologic analysis was blinded to the application or not of the agent. A potential limitation of the present study is the relatively small sample size of animals.

Figure 2. Description of the procedure. A: Bowel exteriorization and site selection for excision; B: application of TISSEEL® in site of end to end bowel anastomosis; C: extensive inflammation and thickening of the muscularis layer (H&E×4) in a diabetic animal that did not receive TISSEEL®; D: neovascularization (H&E×20) in a diabetic animal that received TISSEEL®; E: extensive inflammation (H&E×4) in a non-diabetic animal that did not receive TISSEEL®; F: TISSEEL® fragments in serosal macrophages (H&E×20) in a non-diabetic animal that received TISSEEL®.
used. However, its clinical importance is not diminished as it may serve as a pilot for future experimental and clinical studies in the field. Furthermore, bursting pressures were not applied; however, the clinical efficacy of the experiment may be proven by our decision to implement ERAS guidelines and by the number of postoperative days that exceed the time of anastomosis failure.

Experimental and clinical studies demonstrate that the application of fibrin sealants may have an effect on healing of colorectal anastomoses. In addition, the improvement of the healing process seems to be crucial for anastomatic stability in diabetic patients that undergo colorectal anastomoses. The findings of our study could be the basis for the design of further experimental studies in order to examine the effect of other agents on diabetic colorectal anastomoses, as well as on the safety of application of such agents. The next large step would be the application of fibrin sealants on colorectal anastomoses of diabetic human patients in order to identify their possible effect on diminishing morbidity and mortality following colonic resections.

In summary, application of TISSEEL® on the colorectal anastomoses improves healing in rats that suffer from severe hyperglycemia. This effect is mainly attributed to improved fibroblastic activity and collagen formation as well as a decrease in inflammation. Vascularization may also be improved, although the sample size of our study did not suffice to reach statistical significance. Therefore, our study may serve as a pilot for future research in larger animals, as well as in clinical trials to reach firm conclusions regarding the beneficial effect of TISSEEL® in diabetic patients that undergo colectomy.

Conflicts of Interest
The Authors report no conflict of interest regarding this study.

Authors’ Contributions
Konstantinos Stergios and Vasilios Pergialiotis: conceived the idea, designed the protocol, performed the pilot study and revised the manuscript. Konstantinos Stergios, Maximos Frountzas, Laskarina Maria Korou, and Ioannis Thivaio performed the procedures and were responsible for animal care, Nikolaos Nikiteas, Despina N. Perrea and George Vaos wrote the manuscript. All Authors critically revised the manuscript and approved it prior to submission.

References
1 Bae SU, Saklani AP, Hur H, Min BS, Baik SH, Lee KY and Kim NK: Robotic and laparoscopic pelvic lymph node dissection for rectal cancer: short-term outcomes of 21 consecutive series. Ann Surg Treat Res 86(2): 76-82, 2014. PMID: 2476141210. DOI: 4174/astu.2014.86.2.76
2 Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, Mills S and Stamos MJ: Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 148(1): 65-71,2013. PMID: 22986932. DOI: 10.1001/2013.jamasurg.2
3 Halawani HM, Faraj W, Khoury G, Khalifeh F and Deeba S: Colorectal anastomotic leaks: a brief review of current literature. World J Colorectal Surg 4(4): 4, 2015.
4 McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL and Winter DC: Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg 102(5): 462-479, 2015. PMID: 25703524. DOI: 10.1002/bjs.9697
5 Krarup PM, Nordholm-Carstensen A, Jorgensen LN and Harling H: Anastomatic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. Ann Surg 259(5): 930-938, 2014. PMID: 24045445. DOI: 10.1097/SLA.0b013e318d2abc892
6 Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P and Finan P: Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 253(5): 890-899, 2011. PMID: 21394013. DOI: 10.1097/SLA.0b013e3182128929
7 Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, McNaught CE, Macfie J, Liberman AS, Soop M, Hill A, Kennedy RH, Lobno DN, Fearon K and Ljungqvist O: Enhanced Recovery After Surgery (ERAS®) Society, for Perioperative Care; European Society for Clinical Nutrition and Metabolism (ESPEN); International Association for Surgical Metabolism and Nutrition (IASMEN): Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®)) Society recommendations. World J Surg 37(2): 259-284, 2013. PMID: 30426190. DOI: 10.1007/s00268-012-1772-0
8 Khan AA, Wheeler JM, Cunningham C, George B, Kettlewell M and Mortensen NJ: The management and outcome of anastomotic leaks in colorectal surgery. Colorectal Dis 10(6): 587-592, 2008. PMID: 18070185. DOI: 10.1111/j.1463-1318.2007.01417.x
9 Lin X, Li J, Chen W, Wei F, Ying M, Wei W and Xie X: Diabetes and risk of anastomotic leakage after gastrointestinal surgery. J Surg Res 196(2): 294-301, 2015. PMID: 25890436. DOI: 10.1016/j.jss.2015.03.017
10 Ziegler MA, Catto JA, Riggs TW, Gates ER, Grodsky MB and Wavarry HJ: Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: analysis from a statewide surgical quality collaborative. Arch Surg 147(7): 600-605, 2012. PMID: 22430091. DOI: 10.1001/archsurg.2012.77
11 Brownrigg JR, Hinchliffe RJ, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, Reekers J, Shearman CP, Zierler RE and Schaper NC; International Working Group on the Diabetic Foot: Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. Diabetes Metab Res Rev 32: 128-135, 2016. PMID: 25634219. DOI: 10.1002/dmr.2704
12 Wong SL, Demers M, Martinod K, Gallant M, Wang Y, Goldfine AB, Kahn CR and Wagner DD: Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. Nat Med 21(7): 815-819, 2015. PMID: 26076037. DOI: 10.1038/nm.3887
13 Mirza RF, Fang MM, Novak ML, Urao N, Sui A, Ennis WJ and Koh TJ: Macrophage PPARgamma and impaired wound healing in type 2 diabetes. J Pathol 236(4): 433-444, 2015. PMID: 25875529. DOI: 10.1002/path.4548
14 Rajendran V and Uppoor A: A perspective on NETosis in diabetes and periodontal diseases. J Indian Soc Periodontol 22(4): 290-293, 2018. PMID: 30131618. DOI: 10.4103/jisp.jisp_230_18

15 Gallagher KA, Liu ZJ, Xiao M, Chen H, Goldstein LJ, Buerk DG, Nedeauc A, Thom SR and Velazquez QC: Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha. J Clin Invest 117(5): 1249-1259, 2007. PMID: 17476357. DOI: 10.1172/JCI29710

16 Hayden DM, Mora Pinzon MC, Francescatti AB and Saclarides TJ: Patient factors may predict anastomotic complications after rectal cancer surgery: Anastomotic complications in rectal cancer. Ann Med Surg (Lond) 4(1): 11-16, 2015. PMID: 25685338. DOI: 10.1016/j.amsu.2014.12.002

17 Jung MS, Choi CH and Yu MS: Comparison of the effect of aerosolized fibrin sealant and biodegradable synthetic polyurethane foam on hemostasis and wound healing after endoscopic sinus surgery: a prospective randomized study. Int Forum Allergy Rhinol 7(11): 1089-1094, 2017. PMID: 28859245. DOI: 10.1002/alr.22011

18 Stergios K, Kontzoglou K, Pergialiotis V, Korou LM, Frountzas M, Lalude O, Nikiteas N and Perrea DN: The potential effect of biological sealants on colorectal anastomosis healing in experimental research involving severe diabetes. Ann R Coll Surg Engl 99(3): 189-192, 2017. PMID: 27917665. DOI: 10.1308/rcsann.2016.0357

19 Phillips JD, Kim CS, Fonkalsrud EW, Zeng H and Dindar H: Effects of chronic corticosteroids and vitamin a on the healing of intestinal anastomoses. Am J Surg 163(1): 71-77, 1992. PMID: 1733376. DOI: 10.1016/0002-9610(92)90255-P

20 Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC and Lee WY: Risk factors of anastomotic leakage and long-term survival after colorectal surgery. Medicine 95(8): e2890-e2890, 2016. PMID: 26937928. DOI: 10.1097/MD.0000000000002890

21 Senol M, Altintas MM, Cevik A, Altuntas YE, Barisik NO, Bildik N and Oncel M: The effect of fibrin glue on the intensity of colonic anastomosis in the presence and absence of peritonitis: an experimental randomized controlled trial on rats. ISRN Surg 2013: 521413, 2013. PMID: 23401799. DOI: 10.1155/2013/521413

22 van der Ham AC, Kort WJ, Weijma IM, van den Ingh HF and Jeeckel J: Effect of fibrin sealant on the healing colonic anastomosis in the rat. Br J Surg 78(1): 49-53, 1991. PMID: 1998864.

23 Vakalopoulos KA, Wu Z, Kroese LF, Jeeckel J, Kleinrensink GJ, Dodou D, Lam KH and Lange JF: Sutureless closure of colonic defects with tissue adhesives: an in vivo study in the rat. Am J Surg Res 180(2): 290-300, 2013. PMID: 23384970. DOI: 10.1016/j.amjsurg.2016.05.009

24 Vakalopoulos KA, Daams F, Wu Z, Timmermans L, Jeeckel JJ, Kleinrensink GJ, van der Ham A and Lange JF: Tissue adhesives in gastrointestinal anastomosis: a systematic review. J Surg Res 180(2): 290-300, 2013. PMID: 23384970. DOI: 10.1016/j.jss.2012.12.043

25 Nordentoft T, Pommeggaard HC, Rosenberg J and Achiam MP: Fibrin glue does not improve healing of gastrointestinal anastomoses: a systematic review. Eur Surg Res 54(1-2): 1-13, 2015. PMID: 25247310. DOI: 10.1159/000366418

26 van der Vijver RJ, van Laarhoven CJ, de Man BM, Lomme RM and Hendriks T: The effect of fibrin glue on the early healing phase of intestinal anastomoses in the rat. Int J Colorectal Dis 27(8): 1101-1107, 2012. PMID: 22398458. DOI: 10.1007/s00384-012-1435-5

Received October 26, 2019
Revised December 6, 2019
Accepted December 10, 2019