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Original Article

Effects of Duraseal® and Fibrin Glue on healing of normal and ischemic colon anastomosis

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ABSTRACT

Background and Aims: Anastomotic leaks represent a major complication of colorectal surgery. This study, involving a rat model of normal and ischemic colon anastomosis, aims to compare the effects of Duraseal® with those of Fibrin Glue (FG).
Methods: Fifty adult male Wistar Albino rats were divided into six groups; normal colon anastomosis, ischemic colon anastomosis, FG on normal colon anastomosis, Duraseal® on normal colon anastomosis, FG on ischemic colon anastomosis, Duraseal® on ischemic colon anastomosis. After scarification, bursting pressure were measured and samples were collected for histopathological examination and hydroxyproline assays.
Results: While the mean bursting pressure was statistically higher in groups treated with Duraseal® when compared to controls ($p<0.05$), no significant differences between Duraseal® and FG were detected ($p>0.05$). The mean hydroxyproline level was significantly lower in the Duraseal® groups than in the FG groups ($p<0.05$). However, significant differences between Duraseal® and control groups were found only in ischemic colon anastomosis ($p<0.05$). Histopathological examinations did not show any differences in wound healing.
Conclusion: Considering the advantages associated with the use of Duraseal®, we may assume that it may play role in gastrointestinal surgery with respect to prevention of anastomotic leaks. However, data is limited, and further studies are warranted to better define its place in surgery.

Keywords: Duraseal, surgical anastomosis, fibrin glue, rat, ischemia

INTRODUCTION

Anastomotic leaks represent a major complication of traditional or laparoscopic colorectal surgery that are associated with increased morbidity, risk of reoperation, prolonged hospitalization, and reduced quality of life (Raptis, Pramateftakis, & Kanellos, 2018). Although the reported rates of anastomotic leaks vary between 1% and 24%, this figure is approximately 5% in experienced centers (McArdle, McMillan, & Hole, 2005; Raptis et al., 2018; ; Vakalopoulos et al., 2017b), while it may increase up to 30% to 40% in ischemia, where wound healing is poor, and in patients with inflammatory bowel disease (Wu et al., 2015). Anastomotic leaks following curative surgery for colorectal cancer have been shown to have an adverse impact on the overall survival (McArdle et al., 2005).

Systemic factors influencing anastomotic healing include age, nutritional status, cigarette smoking, chemoradiation, and diabetes, while local factors include the ischemia at the site of anastomosis as well as the surgical technique utilized (Raptis et al., 2018).

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Until now, a variety of surgical techniques, drugs, and adhesion barriers have been investigated in experimental studies of colon anastomosis in an attempt to identify effective means of leakage prevention. In addition to agents such as 5-fluorouracil and hydrocortisone that have been shown to negatively affect the anastomotic healing, others, including tacrolimus and iloprost, have exerted positive effects (Raptis et al., 2018). In recent years, tissue adhesives have been increasingly used for the prevention of upper gastrointestinal leaks (Fullum, Aluka, & Turner, 2009). Their effects have also been tested in a number of studies involving lower gastrointestinal procedures, although they are not used in clinical practice. While fibrin glue (FG) is one of the most frequently investigated agents in experimental studies of colonic anastomosis (Aghayeva et al., 2017; Daglioglu, Duzgun, Sarici, & Ulutas, 2018; Raptis et al., 2018; Senol et al., 2013; Torres-Melero, Motos-Mico, Lorenzo-Linan, Morales-Gonzalez, & Rosado-Cobian, 2016; Vakalopoulos et al., 2017a), Duraseal® has also been subject to some research (Karagoz Avci et al., 2011; Wu et al., 2015).

In this study involving a rat model of normal and ischemic colon anastomosis, we compared the effects of Duraseal® with those of FG, which has been previously shown to have positive effects on the healing of colonic anastomosis in a number of studies.

MATERIALS AND METHODS

Tissue adhesives in current clinical practice can be classified into four categories based on their chemical structure: cyanoacrylates (CA), FG, polyethylene glycol (PEG) adhesives and, biological adhesives, which contain albumin and/or gelatin (Vakalopoulos et al., 2017a). In this study, FG was compared with Duraseal®, which is a modified PEG.

Duraseal®

Duraseal® (Confluent Surgical, Inc., Waltham, MA) is an FDA-approved surgical sealant that is generally used to prevent cerebrospinal fluid leaks in cranial and spinal surgery as well as for improved anastomotic safety in cardiovascular surgery (Jeon et al., 2017; Nishimura, Kimura, & Morita, 2012; Osbun et al., 2012; Pereira, Grandidge, Nowak, & Cudlip, 2017; Strong et al., 2017).

This hydrogel system consists of two solutions; the first contains modified PEG and very low concentrations of FD&C Blue #1 dye, while the second solution contains a low molecular weight, water soluble trilysine amine at very low concentrations. When sprayed onto the tissues, these two solutions react and form cross-links within a few seconds, leading to the formation of a strong hydrogel (90% water) without measurable increases in local temperature and without requiring the application of any external source of energy (Preul, Bichard, & Spetzler, 2003). FD&C Blue #1 dye, on the other hand, provides a measure of the extent and thickness of the application (Preul et al., 2003), and diffuses out of the wound site to be finally excreted via the renal route without being incorporated into the hydrogel structure (Preul et al., 2003).

The hydrogel formed by the above-described reaction leads to the formation of a barrier impermeable to fibroblasts, and remains on site for 4 to 8 weeks. Subsequently, it is broken down into water soluble PEG molecules, and is excreted primarily through the kidneys.

Some advantages of Duraseal® include storage at room temperature, absence of a requirement for heating or external source of energy, easy preparation, good mechanical strength and elasticity, usability in moist conditions, good adaptation to irregular surfaces, good tissue adhesion, and clear visibility due to the blue dye content.

Care should be practiced when using Duraseal® in patients with severe impairment of kidney or liver function, pregnant women, patients with immune suppression or autoimmune conditions, and in individuals allergic to FD&C Blue #1 dye. Also, concomitant use with other tissue adhesives or hemostatic agents should be avoided, and it should not be used in patients who have active infection at the site of surgery.

Fibrin glue

FG is a biological adhesive derived from human fibrinogen concentrates, and has been reported to provide strong tissue adhesion for wound healing, in addition to hemostatic properties at the wound site (Raptis et al., 2018; Senol et al., 2013; Wu et al., 2015).

Fibrin adhesives contain thrombin and aprotinin, and mimic the final step of the coagulation cascade (Karagoz Avci et al., 2011), leading to the conversion of fibrinogen to fibrin with the effect of thrombin. On the other hand, Factor XIII is responsible for the formation of a stable clot thanks to the formation of covalent bonds between fibrin monomers. In order to prevent excessive and sudden fibrinolysis, aprotinin is added into fibrin adhesives. Fibrin adhesives trigger the clotting cascade on the site of application, resulting in the conversion of fibrinogen to fibrin and formation of a gel-like adhesive.

Fibrin glues have positive effects on wound healing, reduce hematoma formation due to their hemostatic effects, and stimulate the migration of macrophages that are involved in the maturation of fibroblasts and in angiogenesis (Karagoz Avci et al., 2011).

Contraindications to the use of fibrin glues include arterial or severe venous bleeding and hypersensitivity to bovine proteins or to any of the ingredients. Data on their use during pregnancy or breastfeeding is insufficient.

In this experimental study, Beriplast® P combi-set (Farma-Tek, Istanbul, Turkey) was used as the fibrin glue.

Design of the study

This experimental study was performed at Istanbul University, Cerrahpasa Medical Faculty, Experimental Medicine Research Institute after approval of the Institutional Review Board.

Fifty adult male Wistar Albino rats 10-12 weeks of age and weighing 200-250 g, were obtained from Istanbul University Cerrahpasa Medical Faculty Experimental Animals Research Laboratory. The rats were cared for in accordance with the "Guide for the Care and Use of Laboratory Animals" prepared by the In-

stitute of Laboratory Animals Resources and published by the National Institute of Health; maintained in colony cages (five rats per cage) under controlled conditions of temperature (28°C), light (10 h light: 14 h dark) and humidity (50°F 5%). The rats were not permitted ad libitum access to standard lab chow and tap water starting from 12 hours before the surgery until the end of the experimental procedures to decrease fecal contamination.

The rats were placed under general anesthesia using intraperitoneal administration of 50 mg/kg Ketamine HCl (Ketalar® vials, Eczacibasi). After the site of surgery was shaved, skin was cleansed with povidone iodine. Experimental animals were categorized into six groups based on the procedure and type of adhesion barrier to be applied (Table 1). Beriplast P® and Duraseal® were prepared in accordance with the instructions of the manufacturers.

Table 1. Procedures and adhesion barriers applied to the groups.

Group	Procedure	Adhesion barrier	Number of subjects (n)
Group 1	Segmenter colon resection + end-to-end anastomosis	-	5
Group 2	Segmenter colon resection + end-to-end anastomosis at ischemic colon segment	-	5
Group 3	Segmenter colon resection + end-to-end anastomosis	Fibrin Glue	10
Group 4	Segmenter colon resection + end-to-end anastomosis	Duraseal®	10
Group 5	Segmenter colon resection + end-to-end anastomosis at ischemic colon segment	Fibrin Glue	10
Group 6	Segmenter colon resection + end-to-end anastomosis at ischemic colon segment	Duraseal®	10

In all animals, the abdomen was accessed with a four cm standard midline incision. After the descending colon was released, a 0.5 cm segment was resected. End-to-end anastomosis was performed by 6-8 interrupted sutures using 5/0 polypropylene suture material. In Group 1, no procedures were carried out on the anastomotic line, while FG was applied on anastomosis in Group 3, and Duraseal® in Group 4. In Groups 2, 5, and 6, the free ends of the colonic segments were devascularized up to a distance of 0.5 cm from the end, followed by anastomosis with the same method to allow for the formation of ischemic colonic anastomoses (Portilla-de Buen et al., 2014). In Groups 5 and 6, FG and Duraseal® were applied on the anastomosis, respectively. In all groups, for the closure of the midline incision, fascia and skin were closed separately using 3/0 silk sutures.

The rats were sacrificed at postoperative day four using high dose ether inhalation. Then, the bursting pressure were measured at anastomosis sites, and samples were collected for histopathological examination and hydroxyproline assays.

Bursting pressure

Bursting pressures were measured in mmHg. Adhesions around the anastomoses were not released after opening the abdominal cavity, as these were thought to reflect an effect on anastomotic healing.

A catheter was advanced 1 cm distally into the left colon through the anal canal of the rats and was fixed using 3/0 silk sutures. The rats were sunk into a bowl filled with water. Air insufflation was performed at a stable speed of 6 ml/min, and the bursting pressure was measured using a sphygmomanometer. Bursting pressure was defined as the highest reading at the sphygmomanometer with simultaneous visualization of air bubbles in the water.

After bursting pressure measurements, the anastomoses were released from the surrounding adhesions. A 1-cm segment encompassing the proximal and distal parts of the anastomotic line was removed. One part of the segment was fixed in 10% formaldehyde for histopathological examinations, and the other was wrapped into aluminum folios for hydroxyproline assays and was stored at -22°C.

Hydroxyproline quantification

Hydroxyproline is a part of collagen that was demonstrated to be positively correlated with the amount of collagen formation and healing of colonic anastomosis. Hydroxyproline quantification was performed at the Biochemistry Laboratory, Cerrahpasa Medical Faculty, Istanbul University. After weighing, the colonic samples were treated with the modified Bergman and Loxley method for quantification of hydroxyproline, which was expressed as mg/g in wet tissue (Karagoz Avci et al., 2011; Lee et al., 2005).

Histopathological examination

Half of the 1 cm colon segment removed after bursting pressure measurements that included the line of anastomosis was fixed in 10% formaldehyde. Then, cross-sections obtained from colonic segments were embedded in paraffin blocks as to expose all layers of the colon. Samples were stained with hematoxylin and eosin. Inflammatory cells, neutrophils, extent of neovascularization, fibroblastic activity, and collagen fibrils were examined microscopically to assess the healing (Ersoy et al., 2016).

Statistical evaluation

All the values were expressed as the mean ± standard deviation (SD). The data of the bursting pressure and the hydroxyproline content were analyzed by ANOVA (Analysis of Variance) test. Post-hoc analyses were performed with the Tukey test. Values were considered as significant when $p<0.05$.

RESULTS

Although the surgical procedures and anesthesia were well tolerated by the animals, one rat in each of Groups 1 and 6, and two rats in each of Groups 3, 4, and 6 died in their cages before postoperative day 4. However autopsy in these eight rats showed no signs of macroscopic anastomotic leak or peritonitis.

None of the rats sacrificed at postoperative day four using high dose ether inhalation had macroscopic leaks. All bursts occurred in the line of anastomosis during the measurement of bursting pressures. Average bursting pressures in the study groups are shown in Table 2.

Table 2. Mean bursting pressure and Hydroxyproline levels.

Experimental group	Mean bursting pressure (mmHg)	Mean Hydroxyproline level (mg/g wet tissue)
Group 1	98.75±15.47	1.85±2.13
Group 2	87.00±16.80	12.14±8.44
Group 3	115.62±23.21	13.61±15.94
Group 4	129.37±20.07	0.21±0.04
Group 5	107.77±22.33	8.72±9.10
Group 6	122.50±19.45	0.29±0.15

values are given as mean ± SD

Rats undergoing Duraseal® and FG treatment were found to have significantly higher mean bursting pressures both in ischemic and normal colon anastomoses as compared to rats in the other groups ($p<0.05$). Although the mean bursting pressure in the Duraseal® groups (Groups 4 and 6) were higher than in the FG groups (Groups 3 and 5), the difference was not statistically significant ($p>0.05$).

The mean hydroxyproline levels were significantly lower in the Duraseal® groups (Groups 4 and 6) than in the FG groups (Groups 3 and 5) ($p<0.05$). When the Duraseal® groups (Groups 4 and 6) were compared with the control groups (Group 1 and 2), the difference was significant only between the ischemic colonic anastomosis groups (Groups 2 and 6) ($p<0.05$).

Comparison of inflammatory cells, neutrophils, neovascularization, fibroblastic activity, and collagen fibers showed no significant differences between groups. However, despite similar collagen content between the Duraseal® and the control groups, these groups were found to have irregular collagen alignment.

DISCUSSION

Anastomotic leaks are a major complication of colorectal surgery that lead to increased morbidity and mortality (McArdle et al., 2005; Raptis et al., 2018; ; Vakalopoulos et al., 2017b). Although the reported rates of anastomoses range between 1% and 24%, this figure may rise up to 30% to 40% in the presence of conditions that lead to poor wound healing, such as ischemia (McArdle et al., 2005; Raptis et al., 2018; Vakalopoulos et al., 2017b; Wu et al., 2015). Due to the recent increase in the use of cytoreductive surgery together with hyperthermic intraperitoneal chemotherapy (HIPEC), concerns have been expressed regarding the effect of chemotherapeutic agents on anastomotic healing, with a consequent emphasis on the prevention of such leaks (Raptis et al., 2018).

Although a variety of surgical techniques, drugs, and adhesion barriers have been utilized in experimental studies of colonic anastomoses, no ideal algorithms for the prevention of anastomotic leaks have been established until now (Aghayeva et al., 2017; Daglioglu et al., 2018; Demiryas et al., 2019; Raptis et al., 2018; Senol et al., 2013; Torres-Melero et al., 2016; Vakalopoulos et al., 2017a). Advances in technology have allowed the introduction of adhesion barriers in a wide spectrum of procedures (Vakalopoulos et al., 2017a). Despite the confirmed efficacy of adhesion barriers, the ideal molecule, particularly for the lower gastrointestinal system, has not been defined (Daglioglu et al., 2018; Fullum et al., 2009; Raptis et al., 2018; Senol et al., 2013; Torres-Melero et al., 2016; Vakalopoulos et al., 2017a, 2017b; Wu et al., 2015). An ideal barrier should have certain characteristics such ease of preparation, low cost, sterility, pliability, biochemical inertness and harmlessness, and minimal or no inflammatory properties as well as causing no adhesions or infections.

Duraseal® is an FDA-approved synthetic hydrogel that is commonly used in cranial and spinal surgery, and in this study, its effects on ischemic and normal colonic anastomoses have been investigated and compared with an established product, i.e. FG, in the current study.

The efficacy of FG has been shown in many previous studies (Fullum et al., 2009; Raptis et al., 2018; Senol et al., 2013; Vakalopoulos et al., 2017a; Wu et al., 2015). While experimental and retrospective studies have shown negative effects of HIPEC on colon anastomoses, others have reported positive effects for the fibrin glue on colorectal anastomosis following HIPEC (Aghayeva et al., 2017; Piso et al., 2019; Raptis et al., 2018; Torres-Melero et al., 2016). Buen et al. (Portilla-de Buen et al., 2014) showed a positive effect of the fibrin glue on bursting pressure in an ischemic left colon anastomosis model, while

Fullum et al. (Fullum et al., 2009) suggested a possible reduced risk of leakage with the use of FG in the anastomosis and stapler lines, following laparoscopic Roux-en-Y gastric bypass. In another experimental model, FG provided improved anastomotic safety in anastomoses performed in both clean abdominal wounds as well as in the presence of peritonitis (Senol et al., 2013). Despite these reported positive effects of FG on anastomosis, a major drawback is its aprotinin content, which may be associated with certain complications such as renal failure, myocardial infarction, and anaphylaxis (Zoegall, 2008). Furthermore, FG requires storage in cold temperatures, and absence of a dye precludes estimation of the extent of application. Also, the surgical site should be dry for effective use of FG.

Duraseal® adhesion barrier is a practical synthetic hydrogel free of infection-risk. Some of its advantages over FG include storage in room temperature, easy preparation, good pliability, suitability for moist conditions, good tissue adhesion, and blue stain showing the extent of the application.

Several previous studies have compared Duraseal® with FG. In an experimental rat study by Avci et al. (Karagoz Avci et al., 2011), it was not significantly different from the fibrin glue in duodenal perforation, while it showed no superiority over the conventional repair. In the study by Wu et al. (Wu et al., 2015) the effects of FG, CA, and Duraseal® were compared in the presence of experimental colitis, and a lower bursting pressure was found in the control group, than in the CA and Duraseal® groups. Conversely, in two separate experiments by Vakalopoulos et al. (Vakalopoulos et al., 2017a; 2017b) involving colonic anastomoses and suture-free colonic repair, Duraseal® did not show superiority over the fibrin glue.

In the current study, although the bursting pressure was statistically higher in groups treated with Duraseal® adhesion barrier when compared to controls, no significant differences between Duraseal® and fibrin glue could be detected ($p>0.05$). Hydroxyproline was significantly lower in the Duraseal® groups. Histopathological examinations did not show any differences in wound healing.

Thus, although Duraseal® offered certain advantages such as ease of use, reduced risk of side effects, and less restrictive use as compared to fibrin glue, it was found to have a negative impact on the hydroxyproline level. However, increased bursting pressure in the Duraseal® groups, higher than in the controls, suggests that it may still hold some promise in gastrointestinal surgery.

CONCLUSION

Although Duraseal® was clinically superior in normal and ischemic colon anastomosis in comparison with other approaches, it failed to provide biochemical superiority. Considering the advantages associated with the use of Duraseal® adhesion barrier, we may assume that it may play a role in gastrointestinal surgery with respect to prevention of anastomotic leaks. However, the data is limited, and further studies are warranted to better define its place in such surgery.

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REFERENCES

- Aghayeva, A., Benlice, C., Bilgin, I. A., Atukeren, P., Dogusoy, G., Demir, F., Baca, B. (2017). The effects of hyperthermic intraperitoneal chemoperfusion on colonic anastomosis: an experimental study in a rat model. *Tumori Journal, 103*(3), 307–313.
- Daglioglu, Y. K., Duzgun, O., Sarici, I. S., & Ulutas, K. T. (2018). Comparison of platelet rich plasma versus fibrin glue on colonic anastomoses in rats. *Acta Cirurgica Brasileira, 33*(4), 333–340.
- Demiryas, S., Hatipoğlu, E., Orhan, A., Demiryas, S., Süzer, Ö., Bülbül Doğusoy, G., İpek, T. (2019). Effects of Calcium Dobesilate on Colonic Anastomosis Healing: An Experimental Study. *Turkish Journal of Colorectal Disease, 29*, 146–152.
- Ersoy, O. F., Ozkan, N., Ozsoy, Z., Kayaoglu, H. A., Yenidogan, E., Celik, A., Lortlar, N. (2016). Effects of melatonin on cytokine release and healing of colonic anastomoses in an experimental sepsis model. *Ulusal Travma ve Acil Cerrahi Dergisi, 22*(4), 315–321.
- Fullum, T. M., Aluka, K. J., & Turner, P. L. (2009). Decreasing anastomotic and staple line leaks after laparoscopic Roux-en-Y gastric bypass. *Surgical Endoscopy, 23*(6), 1403–1408.
- Jeon, S. H., Lee, S. H., Tsang, Y. S., Jung, T. G., Moon, K. H., Choi, G., & Dilip, K. D. (2017). Watertight Sealing Without Lumbar Drainage for Incidental Ventral Dural Defect in Transthoracic Spine Surgery: A Retrospective Review of 53 Cases. *Clinical Spine Surgery, 30*(6), E702–E706.
- Karagoz Avci, S., Yuceyar, S., Aytac, E., Bayraktar, O., Erenler, I., Ustun, H., Erturk, S. (2011). Comparison of classical surgery and sutureless repair with DuraSeal or fibrin glue for duodenal perforation in rats. *Ulusal Travma ve Acil Cerrahi Dergisi, 17*(1), 9–13.
- Lee, H. S., Shun, C. T., Chiou, L. L., Chen, C. H., Huang, G. T., & Sheu, J. C. (2005). Hydroxyproline content of needle biopsies as an objective measure of liver fibrosis: Emphasis on sampling variability. *Journal of Gastroenteroolgy and Hepatology, 20*(7), 1109–1114.
- McArdle, C. S., McMillan, D. C., & Hole, D. J. (2005). Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. *British Journal of Surgery, 92*(9), 1150–1154.
- Nishimura, K., Kimura, T., & Morita, A. (2012). Watertight dural closure constructed with DuraSeal TM for bypass surgery. *Neurologia Medico-Chirurgica (Tokyo), 52*(7), 521–524.
- Osbun, J. W., Ellenbogen, R. G., Chesnut, R. M., Chin, L. S., Connolly, P. J., Cosgrove, G. R., Wilberger, J. E. (2012). A multicenter, single-blind, prospective randomized trial to evaluate the safety of a polyethylene glycol hydrogel (Duraseal Dural Sealant System) as a dural sealant in cranial surgery. *World Neurosurgery, 78*(5), 498–504.
- Pereira, E. A. C., Grandidge, C. A., Nowak, V. A., & Cudlip, S. A. (2017). Cerebrospinal fluid leaks after transsphenoidal surgery - Effect of a polyethylene glycol hydrogel dural sealant. *Journal of Clinical Neuroscience, 44*, 6–10.

- Piso, P., Nedelcut, S. D., Rau, B., Konigsrainer, A., Glockzin, G., Strohlein, M. A., Pelz, J. (2019). Morbidity and Mortality Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Data from the DGAV StuDoQ Registry with 2149 Consecutive Patients. *Annals of Surgical Oncology, 26*(1), 148–154.
- Portilla-de Buen, E., Orozco-Mosqueda, A., Leal-Cortes, C., Vazquez-Camacho, G., Fuentes-Orozco, C., Alvarez-Villasenor, A. S., Gonzalez-Ojeda, A. (2014). Fibrinogen and thrombin concentrations are critical for fibrin glue adherence in rat high-risk colon anastomoses. *Clinics (Sao Paulo), 69*(4), 259–264.
- Preul, M. C., Bichard, W. D., & Spetzler, R. F. (2003). Toward optimal tissue sealants for neurosurgery: use of a novel hydrogel sealant in a canine durotomy repair model. *Neurosurgery, 53*(5), 1189-1198.
- Raptis, D., Pramateftakis, M. G., & Kanellos, I. (2018). Our 20-year experience with experimental colonic anastomotic healing. *Journal of Medicine and Life, 11*(1), 5–14.
- Senol, M., Altintas, M. M., Cevik, A., Altuntas, Y. E., Barisik, N. O., Bildik, N., & Oncel, M. (2013). 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 Surgery, 2013*, 521413.
- Strong, M. J., West, G. A., Woo, H., Couture, D. E., Wilson, J. A., Munoz, L. F., Asher, A. L. (2017). A Pivotal Randomized Clinical Trial Evaluating the Safety and Effectiveness of a Novel Hydrogel Dural Sealant as an Adjunct to Dural Repair. *Operative Neurosurgery (Hagerstown), 13*(2), 204–212.
- Torres-Melero, J., Motos-Mico, J. J., Lorenzo-Linan, M., Morales-Gonzalez, A., & Rosado-Cobian, R. (2016). Use of absorbable fibrin sealant patch to strengthen the gastrointestinal anastomosis performed on patients with peritoneal carcinomatosis treated with intention to cure by debulking surgery and intraoperative hyperthermic intraperitoneal chemotherapy. *Cirrugia Cirujanos, 84*(2), 102–108.
- Vakalopoulos, K. A., Wu, Z., Kroese, L. F., Jeekel, J., Kleinrensink, G. J., Dodou, D., Lange, J. F. (2017a). Sutureless closure of colonic defects with tissue adhesives: an in vivo study in the rat. *American Journal of Surgery, 213*(1), 151–158.
- Vakalopoulos, K. A., Wu, Z., Kroese, L. F., van der Horst, P. H., Lam, K. H., Dodou, D., Lange, J. F. (2017b). Clinical, mechanical, and immunohistopathological effects of tissue adhesives on the colon: An in-vivo study. *Journal of Biomedical Materials Research Part B: Applied Biomaterials, 105*(4), 846–854.
- Wu, Z., Boersema, G. S., Kroese, L. F., Taha, D., Vennix, S., Bastiaansen-Jenniskens, Y. M., Lange, J. F. (2015). Reducing colorectal anastomotic leakage with tissue adhesive in experimental inflammatory bowel disease. *Inflammatory Bowel Diseases, 21*(5), 1038–1046.
- Zoegall, S. G. (2008). New clinical perspectives from nurses on aprotinin and fibrin sealants. *Journal Vascular Nursing, 26*(4), 100.