REPUBLIC OF AZERBAIJAN

On the rights of the manuscript

ABSTRACT

of the dissertation for the degree Doctor of Philosophy

THE ROLE OF PLACENTAL HYDROLYZATE IN THE PREVENTION OF ANASTOMOTIC LEAKAGE AFTER LAPAROSCOPIC AND OPEN INTESTINAL RESECTIONS

Specialty: 3213.01 – Surgery

Field of science: Medicine

Applicant: **Tapdıg Eldar oglu Mammadov**

Baku – 2021

The work was performed at the Department of General Surgery of the Azerbaijan Medical University.

Scientific supervisor: Doctor of Medical Sciences, professor **Elcin Kamil Agayev**

Scientific consultants: Doctor of Medical Sciences, professor **Habil Kamil Muradov**

Official Opponents: Doctor of Medical Sciences, professor **Qurbanxan Fatali Muslumov**
Doctor of Medical Sciences, professor **Sahib Ahmad Huseynov**
Doctor of Medical Sciences, professor **Nizami Ahmad Veliyev**

Dissertation Council ED 2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University

Chairman of the Dissertation council: Doctor of Medical Sciences, professor **Surxay Ismayıl Hadıyev**

Scientific Secretary of the Dissertation council: Doctor of Medical Sciences, professor **Fariz Hidayat Camalov**

Chairman of the scientific seminar: Doctor of Medical Sciences, professor **Mahammad Mahammadali Karimov**

İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMİ KATİBİ
Tibb elmləri doktoru, professor
Nazim Adil oğlu Pənahov
„19" 10 2021-ci il

GENERAL DESCRIPTION OF THE WORK

Relevant. Laparoscopic and open bowel resections are widely used in surgery. Patients who have undergone urgent and emergency bowel resections for various reasons sometimes need to have primary intestinal anastomoses. In all this cases prognosis, prevention and early diagnosis of possible complications are one of the important aspects of abdominal surgery. The most dangerous of these complications is intestinal anastomotic leakage. Despite the introduction of many new technical capabilities, this problem remains relevant. This complication is more common, especially in the patients at the risk group. Therefore, it is more important to identify risk factors and improve prevention methods taking into account these factors. Conditionally, risk factors can be grouped according to the patient and to the operation. Obesity, diabetes mellitus, systemic diseases, cardiovascular disease, alcohol and nicotine use, intake of corticosteroids, immunosuppressants, and vascular endothelial growth factor inhibitors, preoperative radiotherapy, male sexuality, aging are among the risk factors according to the patient. The risk factors according to the operation include surgeon's degree of specialization, duration of surgical operation, hypoxia and use of vasopressors during anesthesia, blood transfusions, intestinal obstruction and peritonitis, and placement of distal rectal anastomosis[1,2,3]. It is possible to reduce the frequency of intestinal anastomotic leakage by choosing a more adequate method of prevention in accordance with the risk factors.

---

[1] Phillips B. Reducing gastrointestinal anastomotic leak rates: review of challenges and solutions // Open Access Surgery, -2016. Jan; V.9, P.5-14.

[2] McDermott F.D. Prevention, diagnosis and management of colorectal anastomotic leakage / F.D.McDermott, S.Arora, J.Smith [et al.] // Issues in professional practice, - 2016. Marc; - p.9-15.

[3] Li Y. Very Early Colorectal Anastomotic Leakage within 5 Post-operative Days: a More Severe Subtype Needs Relaparatomy / Y.Li, P.Lian, B.Huang [et al.] // Natureresearch journal, scientific reports, - 2017. p.1-7.

Various methods have been proposed to prevent intestinal anastomotic leakage. Some researchers have tried to increase the technical capabilities by preferring mechanical factors. For this purpose, they paid attention to sewing threads, sewing staples, the use of various adhesives[4,5,6]. Other researchers have preferred biological factors, such as the rheological properties of the blood, the local blood circulation and the increase in albumin density in the blood[7,8]. However, in spite of all this, the inconsistency of the intestinal anastomosis is noted in various literature data in 3,4-19,0%[2,9,10] cases. This leads to an increase in hospital stay, medical consumption, recurrence due to chemotherapy delay in cancer patients, prolonged recovery of working capacity, and the social isolation of patients. Also, mortality from postoperative peritonitis as a result of the corresponding complication ranges from 1,7% to 16,4%[3,11]. All this indicates the presence of relevant problems in the field of prevention of appropriate complications. Both, the patient and surgical related risk factors listed above eventually manifest themselves in disorders of collagen synthesis. This indicates the need for a well-founded prophylaxis method that can have a positive effect on the healing of the anastomosis at the cellular level in the prevention of intestinal anastomotic leakage. Drugs that may have such effects include human placental hydrolyzate, which is rich in growth factors.

---

[4] Vasquez G.C. Histopathological changes associated to an absorbable fibrin patch (Tachosil®) covering in an experimental model of high-risk colonic anastomoses / G.C.Vasquez, G.S. Heras, C.Pastor Idoate [et al.] // Histol Histopathol, - 2018. Mar; 33(3), - p.299-306.

[5] Pommergaard H.C. Decreased leakage rate of colonic anastomoses by tachosil coating; an experimental study / H.C.Pommergaard, M.P.Achiam, J.Burcharth [et al.] // Int Surgery, - 2014. Jul-Aug; 99(4), - p.359-363.

[6] Wu Z. Critical analysis of cyanoacrylate in intestinal and colorectal anastomosis / Z.Wu, G.S.Boersema, K.A.Vakalopoulos [et al.] // J Biomed Mater Res B Appl Biomater, - 2014. Apr;102(3), - p.635-42.

Human placental hydrolyzate has been used successfully in various fields of medicine, including liver and nerve damage, cartilage tissue repair, and other conditions, where regeneration is important. Studies have shown that human placental hydrolyzate reduces fibrosis in the liver tissue – in the sinusoidal tissue and oxidative stress in the perivascular areas, increases the regeneration of endothelial cells, increases "growth-associated protein" (GAP-43) and "cell division cycle 2 protein" (Cdc2) levels, leading to axon regeneration and Schwann cell proliferation in nerve cells, prevents the destruction of cartilage tissue by inhibiting metalloproteinasa-2 in osteoblasts[12,13,14]. In view of all this, we considered it expedient to study the effect of human placental hydrolyzate on the regeneration of intestinal anastomoses.

---

[7] Sümer A., Altınlı E., Senger S. Effect of pentoxifylline and vinpocetine on the healing of ischemic colon anastomosis: an experimental study // Ulus Trauma Acil Cerrahi Derg., 2011, v.17, No 6, p. 482-487.

[8] Hasanoğlu A. Sildenafil sitratın kolon anastomozundakı yara iyileşmesi üzerine etkisi / A.Hasanoğlu, S.Erkan, S.Temel [et al.] // Turkish Medical Journal, - 2007. 1, - p.66-75.

[9] Ağayev E.K. Bağırsaqların təcili və təxirəsalınmaz rezeksiyasından sonrakı erkən nəticələrin yaxşılaşdırılması yolları. Tibb elm. dokt. ... diss. avtoref. Bakı 2013.

[10] Kingham T.P., Pachter L.H. Colonic Anastomotic Leak: Risk Factors, Diagnosis, and Treatment // Journal of the American College of Surgeons, - 2009. feb; 208(2), - p.269–278.

[11] Uzun M. Salvage repair of anastomotic dehiscence following colon surgery using an expanded polytetrafluoro-ethylene graft / M.Uzun, N.Koksal, O.Ozkan [et al.] // Tech. Coloproctology, - 2012. 16(2), - p.169-173.

[12] Yamauchi A. Placental extract ameliorates non-alcoholic steatohepatitis (NASH) by exerting protective effects on endothelial cells / A.Yamauchi, A.Kamiyoshi, T.Koyama [et al.] // Heliyon.- 2017 Sep27; 3(9), :e00416.

[13] Seo T.B. Growth-promoting activity of Hominis Placenta extract on regenerating nerve / T.B.Seo, I.S.Han, I.C.Seol [et al.] // Acta Pharmacol sin. 2006 jan; 27(1), - p.50-58.

[14] Kim J.K. Protective effects of human placenta extract on cartilage degradation in experimental osteoarthritis / J.K.Kim, T.H.Kim, S.W.Park [et al.] // Biol Pharm Bulletin, - 2010. 33(6), - p.1004-1010.

The aim of the study is experimental research the effect of human placental hydrolyzate on the regeneration of intestinal anastomoses, substantiate and apply in clinical practice.

Objectives of the study:

1. Morphohistological study the reparative-regenerative processes in the primary intestinal anastomoses against the background of a one-day model of acute small bowel obstruction in the experiment.

2. To study the effect of intramuscular injection of human placental hydrolyzate on the reparative-regenerative processes in the primary intestinal anastomoses, placed on the background of a one-day model of acute small bowel obstruction in the experiment.

3. To study the effect of intramesenteric injection of human human placental hydrolyzate on the reparative-regenerative processes in primary intestinal anastomoses placed on the background of a one-day model of acute small bowel obstruction in the experiment.

4. In clinical practice selection and application of a based method of prophylaxis in order to prevent suture inconsistencies during primary intestinal anastomoses.

Scientific novelty of the study:

- In experimental studies, the effect of human placental hydrolyzate on the regeneration of primary intestinal anastomoses against the background of the model of acute intestinal obstruction was studied.

- In clinical practice, human placental hydrolyzate was used by us to prevent intestinal anastomotic leakage.

Theoretical and practical significance of the study:

- As a result of research, information about the regeneration processes in anastomoses against the background of acute intestinal obstruction has been increased.

- The effect of human placental hydrolyzate on the regeneration of intestinal anastomoses has been morphohistologically studied.

- It has been determined which method of use of human placental hydrolyzate is more effective.

- In clinical practice, intestinal anastomotic leakage was prevented using human placental hydrolyzate.

Application of the study to the clinical practice. In clinical practice at the General surgery, I, II and III Surgical diseases departments of the Education Surgical Clinic of AMU in order to prevent anastomotic leakage after laparoscopic and open resections of the intestine, human placental hydrolyzate was used.

The main provisions of the defense:

1. Experimentally, human placental hydrolyzate has a positive effect on the regeneration of the intestinal anastomosis.

2. In clinic practice the inclusion of human placental hydrolyzate in the treatment regimen for the prevention of intestinal anastomotic leakage has led to a reduction in the frequency of this complication.

3. Intramuscular use of human placental hydrolyzate to prevent anastomotic leakage in patients with primary intestinal anastomosis allows to obtain positive results. However, in high-risk patients, it is more appropriate to inject the drug through a catheter placed in the root of the mesenter.

4. Patients treated with human placental hydrolyzate can be earlier activated, fed and sent for outpatient follow-up.

The relationship of research to the problem plan of medical sciences. The subject of the dissertation is included in the plan of scientific-research studies of the Department of General Surgery of AMU (state registration number № 099).

Approbation of the study. The main provisions of the study were presented, discussed and reported at the XXII Republican Scientific Conference of Doctoral Students and Young Researchers (Baku 2018), XVIII International Congress of Eurasian Surgery and Gastroenterology (Baku 2019). The initial interdepartmental discussion of the dissertation was held on November 15, 2019 (Protocol №1). Dissertation was discussed at the Scientific Seminar

of the Dissertation Council (12.04.2021, Protocol №1) operating under the ED 2.06 of AMU.

The scope and structure of the study. The dissertation consist of an introduction, literature review, 3 chapters of personal research, conclusion, results and practical recommendations.

MATERIALS AND METHODS OF RESEARCH

The research was conducted in two directions - experimental and clinical. Experimental research was carried out at the Scientific Research Center of the Azerbaijan Medical University. The experiments were performed on 60 chinchilla rabbits weighing 3-4 kg.

Experimental studies were conducted in 2 groups, control and main. 20 rabbits were used in the control group and 40 in the main group. The main group also was divided into 2 subgroups, each with 20 rabbits. Human placental hydrolyzate was administered intramuscularly in the I subgroup of the main group, and to root of the mesenter in the II subgroup.

The experimental animals were kept at room temperature of $23\text{-}25^0$ C and fed with standard rabbit feed and water. Feeding was stopped 12 hours before the operation.

The following appropriate measures have been taken for anesthesia. For the purpose of premedication of anesthesia, 30 minutes before the surgery, all animals were analgin - 50% (50 - 70 mg/kg), dimedrol - 1% (1 - 1.5 mg/kg), atropine sulfate - 0.1% (0.1 – 0.2 mg/kg), droperidol – 0.25% (0.5 mg/kg) solutions intramusculary injected. Then a subcutaneous ear vein in rabbits was catheterized and intravenous caliposol (3 - 4 mg / kg) was used for non-inhalation anesthesia. During the operation, intravenous anesthesia with calipsol was continued.

All groups of experimental animals were fixed on the operating table, the operating area was cleaned with 10% betadine solution, and covered with sterile sheets. Laparotomy was performed by injecting 20 ml of 0.5% novocaine solution into the skin and

subcutaneous tissues. The terminal part of the small bowel was obtained at a distance of 15 - 30 cm from the ileocecal angle and with a sterile tourniquet a model of acute strangulation obstruction of the small bowel was created. The surgical wound was continuously sewn with 1 silk thread.

A day later relaparatomies were performed in all groups, and it was found that the area with intestinal obstruction had gangrene. In the control group of experimental animals, the gangrenous segment of the small bowel was resected within healthy tissues and an intermittent, side-by-side, single-row entero-entero anastomosis was performed using a adsorbable 4/0 polyglycolicaside thread. The abdomen was dried and the surgical wound was sutured continuously with 1 silk thread. After surgery, the animals were treated with traditional methods (40% glucose solution (500 mg / kg) intravenously, ceftriaxone (15 mg / kg), analgin 50% (50 - 70 mg / kg), dimedrol 1% (1 – 1.5 mg / kg) intramuscularly once a day). A day later, the experimental animals were fed with standard rabbit feed.

In experimental animals belonging to the I subgroup of the main group, the segment of the small bowel with gangrene was resected within the limits of healthy tissues too. As in the experimental animals of the control group in this subgroup also intestinal anastomoses was made and general treatment was performed. However, in this subgroup of experimental animals, human placental hydrolyzate was administered intramuscularly at a dose of 0.15 ml (8.4 mg) / kg once daily after operation. The course of treatment lasted 3, 5, 7, 15 days, correspondingly, until the next operation.

The same type of ischemia model was created in the experimental animals of the II subgroup of the main group, an intestinal anastomosis was made and traditional treatment measures were carried out. However, in experimental animals belonging to this subgroup, a microirrigator was inserted into the root of the small bowel and fixed. For this purpose, 5 ml of 0.5% novocaine solution was injected into the root of small bowel and a 0,5 cm incision was

made. A 6 Fr drainage catheter was placed into the root of the mesenter and fixed to the peritoneum with a 4/0 catgut thread. Permeability and tightness were checked by injecting 5 ml of 0.5% novocaine solution through the drain. The distal end of the catheter is fixed to the skin by removing out. After the operation, in addition to traditional treatment measures, human placental hydrolyzate was injected into the root of the mesenter at a dose of 0.15 ml (8.4 mg) / kg / day, diluted in 5 ml of saline. The intramesenteric infusion was continued once a day for 3, 5, 7 and 15 days, correspondingly, until the next operation.

Experimental animals in all groups on days 3, 5, 7, and 15 of the operation, were underwent relaparatomy. During the inspection, small bowel anastomoses were found and mobilized. Small bowel anastomoses were resected 3 cm proximal and 3 cm distally and taken for morphohistological examination. The taken anastomoses were hold in 12% formalin solution.

For the purpose of clinical research, we analyzed the results of surgical treatment and examination of 128 patients who underwent laparoscopic and open intestinal resection and anastomosis of the intestines at the Education Surgical Clinic of the Azerbaijan Medical University in 2014-2019. 68 patients of these formed the main group under our personal observation, and 60 patients formed the comparison group, the results of which were retrospectively examined.

In the comparison group, archival documents of 60 patients who underwent laparoscopic and open bowel resection and anastomosis were extensively examined, technical aspects of anastomoses, methods of prevention of anastomotic leakage and postoperative complications were analyzed. 29 (48.3%) of the patients in this group were women and 31 (51.7%) were men. Patients under 30 years of age - 9 (15%), 30-49 years of age - 10 (16.6%), 50 - 70 years of age - 31 (51.8%), over 70 years of age - 10 (16.6%) was.

In the comparison group 9 (15.0%) patient of the 60 patients underwent laparoscopic surgery and 51 (85.0%) patient underwent

open surgery. 8 (88.9%) of the patients who underwent laparoscopic surgery, had scheduled operation and 1 (11.1%) had emergency operation. Of the patients undergoing open surgery 32 (62.7%) underwent scheduled operation and 19 (37.3%) underwent emergency operation. Of the patients undergoing laparoscopic operation in 1 (11.1%) right hemicolectomy, ileotransverso anastomosis, in 6 (66.7%) subtotal colectomy ileosigma anastomosis, and in 2 (22.2%) Sigma resection, descendorecto anastomosis placement operations were performed. In 8 (88.8%) patients who underwent laparoscopic operation, the anastomosis was placed extracorporely by hand, and in 1 (11.1%) it was placed intracorporely through a linear stapler. Of the patients undergoing open surgical operation in 1 (1.9%) patient resection of the IV segment of the duodenum, duedonoyeyuno anastomosis, in 5 (9.8%) resection of small bowel, enteroentero anastomosis, in 15 (29.5%) right hemicolectomy, ileotransverso anastomosis, in 9 (17.6%) subtotal colectomy ileosigma anastomosis, in 1 (1.9%) resection of the transverse colon, transversotransverso anastomosis, in 6 (11.8%) left hemicolectomy, transversorecto anastomosis, in 8 (15.7%) Sigma bowel resection, descendorecto anastomosis and in 6 (11.8%) anterior resection of the rectum, sigmarecto anastomosis placement operations were performed. Of the patients in the comparison group 23 (38.3%) had end to end anastomosis and 37 (61.7%) had side by side anastomosis.

In the comparison group in 8 (13.3%) patients was noted intestinal anastomotic leakage. Of the patients with anastomotic leakage 4 (50.0%) underwent scheduled operation and 4 (50.0%) underwent emergency operation. In 7 of them (87.5%) the operation was performed openly, and in 1 (12.5%) it was performed laparoscopically. In the comparison group anastomotic leakage occurred in 5 (21.7%) of 23 patients with end-to-end anastomosis and in 3 (8.1%) of 37 patients with side-by-side anastomosis. In 7 (87.5%) patients with intestinal anastomotic leakage, the anastomosis was made by hand, and in 1 (12.5%) it was placed through a circular stapler. Of these, in 2 (25.0%) patients enteroentero, in 1 (12.5%)

ileotransverso, in 2 (25.0%) ileosigma, in 1 (12.5%) transversorecto, in 1 (12.5%) descendorecto and in 1 (12.5%) sigmarecto anastomoses were placed.

Of the 68 patients in the main group 34 (50.0%) were women and 34 (50.0%) were men. Under 30 years of age - 10 (14.7%), 30 - 49 years of age - 14 (20.6%), 50 - 70 years of age - 30 (44.1%), over 70 years of age - 14 (20.6%) was

In the main group 10 (14.7%) patient of the 68 patients underwent laparoscopic surgery and 58 (85.3%) patient underwent open surgery. Of the patients who underwent open surgery 39 (67.2%) had scheduled operation and 19 (32.8%) had emergency operation. All laparoscopic operations were performed as scheduled. Of the patients who underwent laparoscopic operation in 3 (30.0%) patient right hemicolectomy, ileotransverso anastomosis, in 3 (30.0%) left hemicolectomy, transversorecto anastomosis, in 3 (30.0%) Sigmoid and rectal resection, descendorecto anastomosis, and in 1 (10.0%) total colectomy, ileorecto anastomosis were performed. In 6 (60.0%) of the patients who underwent laparoscopic operation, the anastomosis was made by hand, and in 4 (40.0%) patients it was placed intracorporaly with circular staples. In all patients, the anastomoses were formed end-to-end. 62 anastomoses were performed in 58 patients who underwent open surgery (8 anastomoses in 4 patients: in 3 patients in parallel entero-entero and transversorecto, and in 1 patient ileoceko and descendorecto anastomosis). Of these, 1 (1.6%) had a duedonoyeyuno anastomosis due to arteriomesenteric duedonostasis, 6 (9.7%) had a small bowel resection, enteroentero anastomosis, 1 (1.6%) had a resection of the terminal part of the small intestine, ileoceco anastomosis, 8 (12.9%) had right hemicolectomy, ileotransverto anastomosis, 2 (3.2%) had transverse colon resection, transversotransverso anastomosis, 21 (33.9%) had subtotal colectomy, ileosigma anastomosis, 8 (12.9%) had left hemicolectomy, transversorecto anastomosis, 8 (12.9%) had Sigma bowel resection, descendorecto anastomosis, 5 (8.1%) had anterior resection of the rectum, sigmarecto anastomosis and 2 (3.2%) had resection of the rectum and Sigma, colorectal

anastomosis. In 24 (38.7%) of these patients anastomoses were formed end-to-end, and in 38 (61.3%) they were formed side by side.

In the main group 67 (98.5%) patients did not have any complications related to the anastomoses, and the patients were discharged on time in good condition. Intestinal anastomotic leakage was noted in only 1 (1.5%) patient. The patient complicated with anastomotic leakage was admitted to the clinic with a diagnosis of polyposis of the colon and underwent an open operation "Subtotal colectomy, side-by-side ileosigma anastomosis." However, 8 days after the operation, the patient was found to have anastomotic leakage, and relaparotomy “Resection of the anastomosis, ileostomi placement, abdominal cavity lavage and drenage” operation was performed. The patient was discharged home in good condition 13 days later.

In patients of the main group human placental hydrolyzate was used as a part of complex treatment measures to prevent intestinal anastomotic leakage. In 65 (95.6%) patients in the main group, human placental hydrolyzate was used 1-2 times a day, 2-4 ml intramuscularly for 7-10 days. In 3 (4.4%) patients human placental hydrolyzate were infused once a day with 4-6 ml of diluted in 0.9% - 50 ml of saline from a microirrigator placed at the root of the mesenter during operation.

Examination methods. During clinical trials in patients general blood analysis, coagulogram, blood albumin, total protein, creatinine levels, CRP, ECG, EXO-cardiography, chest X-ray, colonoscopy, gastroscopy and dual contrast computed tomography of the abdomen, abdomen review X-ray. irrigography, magnetic resonance imaging examinations were performed.

Morphological studies. Morphological studies were performed during experimental studies. Morphological researches were carried out at the Department of Histology, Embryology and Cytology of AMU by the following methods of cyto-histological and histochemical examination. In the anastomotic aera by the hematoxillin - eosin, van- Gizon by hematoxylin - picrofuxin, methyl blue - eosin, buffered 0.05% thionine, toluidine, hematoxylin -

sodium - fluorescein (uranine), by iron hematoxylin incubation methods mitotic index (ratio of dividing cells to non-dividing cells), fibroblastic activity, denovo formation of fibers (collagen), mucus secretion, muscle-cell response, microvascular density (angiogenesis) were studied. The obtained results are expressed in conventional units.

Statistical processing of the obtained results was carried out with the help of variation statistics by the methods of quadratic calculation, average mathematical error, determination of the Student's coefficient. Their technical execution procedure is described in detail in the relevant manuals and methodical works.

ANALYSIS OF THE OBTAINED RESULTS

In experimental studies, morphological examination of intestinal anastomoses taken 3 days after operation in the control group of experimental animals revealed that the mucosa was covered with necrotic masses, there was a strong spasm in the arteries and arterioles, and venous vessels were dilated. It was found that crypts, which are the main source of regeneration and renewal of the mucosal epithelium are not dense and the cell composition is polymorphic. Here the mitosis index, which is the main indicator of epithelial regeneration, was very low and most of the enterocytes covering the piles are in a state of necrobiosis. In a special layer of the mucous membrane hyperemia, total edema and fragmentation of fibers were found. The fibrous carcass of the submucous layer is severely deformed, most of its fibers have lost their normal coloring properties.

Morphological examination of intestinal anastomoses taken 5 days after surgery in the control group showed that severe edema, disorganization and dystrophic changes in the intestinal mucosa persisted and the folds lost their crescent shape and flattened. Lymphoid infiltration is high and covers a large area and in some areas there is so much that the epithelium of the mucous membrane is not selected. The base of the crypts was destroyed and in some

areas the epithelial cover was torn. The special plate of the mucous membrane is in the form of a thin layer and consists of dystrophic connective tissue structures, the fibrous carcass created by these structures has a porous, chaotic and irregular structure.

On the 7th day of the experiment, microscopic examination of intestinal anastomoses taken from control animals revealed signs of vacuolar dystrophy in the mucous membrane (Figure 1). Mitosis index is characterized by low values (1.0 - 2.0 c.u.). Although the epithelial layer is composed mainly of brush-edged enterocytes, which is found in a variety of functional conditions. So that, some cells are desquamated, but in the cytoplasm of another cells there are signs of destruction and karyolysis. Although the third part of the enterocytes retains its intact shape and size, it suffers from mucoid dystrophy..

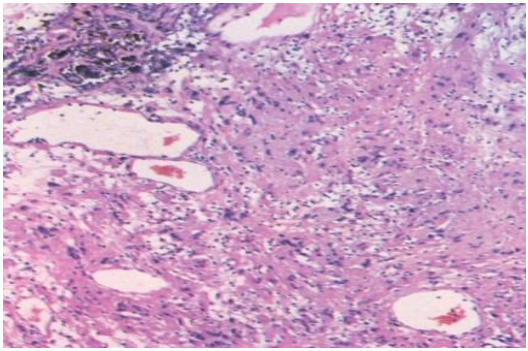

Figure 1. Symptoms of edema and vacuolar dystrophy in the epithelial layer of mucosa are distinguished. Fibroblast-type cells make up only 10-15% of the total cell volume.
Dye: hematoxylin-eosin, thionine.
Magnification: ok.12.5, ob.10

The special layer of the mucous membrane is diffuse edematic and partially hyperemic. Specific layer vessels are deformed, partially or completely thrombosed. Only 20% of microcirculatory vessels are free of thrombus masses. It should be noted that very few

fibroblast-type cells are found on this layer, which also make up only 10 - 15% of the total cell volume (Figure 1). The fibrous carcass of the submucousal layer is very thin.

Morphological examination of intestinal anastomoses taken from the control group of experimental animals on the 15th postoperative day revealed that the epithelial layer was composed of active mucus-secreting goblet cells and columnar cells with moderate mitosis activity (0.5 - 1.5 c.u.). Although the fibrous carcass is relatively dense, de-novo formation is in medium intensity.

Thus, in the experimental studies, morphohistochemical examination of intestinal anastomoses taken from experimental animals in the control group showed low levels of fibrillogenesis, and vascularity, prolonged persistence of inflammatory-infiltrate symptoms, rough fibrillar structures and lymphoid-epitheliode microgranulomas (Table 1).

Table 1.

Indications	3 day	5 day	7 day	15 day
Mucus secretion	4,0 (3,5-5,0)	3,5 (3,0-4,0)	3,0 (2,0-4,0)	2,0 (1,5-3,0)
Epithelial mitosis index (regeneration)	0,5 (0-1,0)	2,0 (1,0-3,0)	1,5 (1,0-2,0)	1,0 (0,5-1,5)
Fibroblastic activity	0,5 (0-1,0)	1,0 (0,5-1,5)	1,5 (1,0-2,0)	1,5 (1,0-2,0)
Muscle-cell response	3,0 (2,0-4,0)	4,0 (3,0-6,0)	3,0 (2,0-4,0)	2,0 (1,0-3,0)
De-novo fibers formation (collagen)	0,5 (0-1,0)	1,5 (1,0-2,0)	1,5 (1,0-2,0)	1,0 (0,5-2,0)
Density of microvessels (1mm^2) (angiogenesis)	25,0 (20,0-30,0)	30,0 (20,0-40,0)	25,0 (15,0-30,0)	20,0 (10,0-30,0)

Morphological parameters of control group experimental animals. The obtained results are expressed in conventional units.

Morphological examination of anastomoses taken 3 days after the operation from experimental animals of I subgroup in the main group showed that the epithelial layer of the mucous membrane was covered with fibrous exudate and sometimes signs of vacuolar-hydropic dystrophy. The number of crypts of the mucosal epithelium is not so much, but it has undergone hyperplasia. Mitotical active cells are recorded in moderate amounts and the mitosis index is characterized by values of 0.5 - 1.5 c.u. ($M = 1.0 \pm 0.06$; $p<0.001$). In the special layer of the mucous membrane edema, mucoid dystrophy in some of the fibers and foci of destruction are visible. The fibrous carcass of the subcellular base retains its normal tinctorial staining properties. Fibrillogenesis consists mainly of de-novo-type fibers, part of which is composed of precollagen fibers. The total volume of microcirculatory vessels with edema of the peripheral area is about 20 - 25% detected.

During the morphological examination of the anastomoses taken from the experimental animals of the I subgroup of the main group 5 days after the operation, it was noted that the mucous membrane folds were microscopically smoothed, elasticized and restored their crescent shapes. The depths of the crypts increased compared to the previous observation period (day III). Although the goblet cells, which are the source of regeneration are dominant, dissemination with lymphoid-plasmocytic-histiocyte cell aggregates is observed in the epithelial layer. Partial fragmentation and destruction of fibrin fibers observed on the previous day of examination were not detected in the specific layer of the mucosa. Collagenolysis and de-novo formation of fibers are clearly distinguished at the boundaries of the anastomosis.

In the I subgroup of the main group, on the 7th observation day of the experiment, there was an increase in the density and depth of crypts in the mucous membrane, as well as mitotic activity of cambial elements (2.0 - 4.0 c.u., $M = 3.0 \pm 0.12$; $p<0.001$) noted. The fibrous carcass of the special layer is loop-shaped and intensive fibrillogenesis is noted (Figure 2). Most of the microcirculatory vessels of the submucousal layer are free of thrombus masses and

dilated. In contrast to the control group, no signs of possible anastomotic leakage such as unsatisfactory tissue nutrition, bad fibrous carcass formation and deformative-dysfunctional microcirculatory vessel disorders were detected.

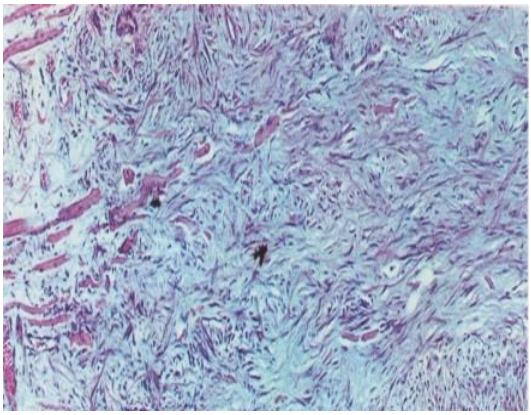

Figure 2. Intensive increase in the number of fibroblasts is observed in a special layer of the mucous membrane.
Dye: hematoxylin-eosin
Magnification: ok.12.5, ob.40

In the I subgroup of the main group, on the 15th day of observation, the intestinal anastomosis area, which was the object of examination, significantly accelerated the synthesis-recovery processes as a whole (3.0 - 5.0 c.u., $M = 4.0 \pm 0.12$; $p<0.001$) and characterized by extinction of inflammatory infiltration. The mucous membrane is much thicker than in the previous group, and the folds have regained their crescent shape. In the submucousal layer along with microangiogenesis and fibrillogenesis, there are significantly reduce of edema, indicating improved tissue nutrition and complete absence of thrombosis.

Morphohistochemical examinations in the I subgroup of the main group led to the conclusion that intramuscular administration of human placental hydrolyzate in experimental animals stimulates both

the formation of a fibrous carcass, acceleration of collagen synthesis and also angiogenesis which results with higher density of microvessels in the anastomosis area. As a result, morpho-functional and vascular changes in the anastomosis zone of the intestinal wall accelerate the process of adaptation to new anatomical and physiological conditions. Correction of microcirculation improves the near and long-term results of the operation, prevents complications associated with postoperative microcirculatory changes, especially anastomotic leakage (Table 2).

Table 2.

Indications	3 day	5 day	7 day	15 day
Mucus secretion	4,0 (3,5-5,0)	3,5 (3,0-4,0)	2,5 (2,0-3,0)	2,0 (1,0-3,0)
Epithelial mitosis index (regeneration)	1,0 (0,5-1,5)	2,5 (2,0-3,0)	3,0 (2,0-4,0)	4,0 (3,0-5,0)
Fibroblastic activity	1,0 (0,5-1,5)	1,5 (1,0-2,0)	2,0 (1,0-3,0)	2,5 (2,0-3,0)
Muscle-cell response	3,0 (2.0-4.0)	4.0 (3.0-6,0)	2,0 (1,0-3,0)	1,0 (0,5-1,5)
De-novo fibers formation (collagen)	1,0 (0,5-1,5)	1,5 (1,0-2,0)	2,0 (1,0-3,0)	2,0 (1,0-3,0)
Density of microvessels (1mm^2) (angiogenesis)	30,0 (20,0-40,0)	30.0 (20,0-40,0)	35,0 (25,0-45,0)	40,0 (30,0-50,0)

Morphological parameters of I subgroup of main group experimental animals. The obtained results are expressed in conventional units. ($p<0,001$)

During the morphological examination of intestinal anastomoses taken from animals of the II subgroup of main group 3 days after operation, first of all, the thickening of the intestinal mucosa attracts attention. This is especially evident in the significant

elevation of the epithelial layer. It is composed of brush-edged enterocytes, goblet cells, enteroendocrine and cambial elements. The crypts, which are the main source of regeneration of the mucous membrane are compacted and deepened, in which the mitotic index of actively dividing yeast cells is fluctuated between 1.0 - 3.0 c.u. ($M = 2.0 \pm 0.12$; $p<0.001$). The epithelial layer is infiltrated by lymphocytes, but this infiltration is almost 2 - 3 times less than in other groups. Although symptoms of hyperemia generally persist, microangiogenesis is more intensive than in the control group. The special layer of the mucous membrane is slightly interstitial edematus and its collagen-elastic fibrous carcass retains the structural plan. The average intensity of fibrillogenesis is determined on a submucousal layer.

In the morphological examination of intestinal anastomoses taken on the 5th day of the experiment from animals of the II subgroup of the main group, the intensity of recovery in the epithelial layer of the mucous membrane was significantly increased compared to the control group, regeneration was more regular. Compared to other subgroup, there was no significant increase in these indicators, but a decreasing of lymphocyte migration to the epithelial layer was found. Mosaic-focal alternating fibrillogenesis and fibrillolysis are found in a special layer of the mucous membrane. The number of deformed and dystrophic vessels is less.

Examination of intestinal anastomoses taken 7 days after surgery in the II subgroup of the main group showed that the integrity of the epithelial layer of the intestinal mucosa was not damaged, the relief, folds and color of the mucous membrane of the anastomosis wall on the intestinal side did not differ significantly from neighboring intact areas. Density and depth measurements of mucous membrane crypts significantly increased, compared even I subgroup of the main group experimental animals. Active regenerative-mitotic processes were observed in crypts (3.0 - 5.0 c.u. $M = 4.0 \pm 0.12$; $p<0.001$). At this time, a special point caught our attention. So that, compared with the control group, a very high number of fibroblasts was recorded in the studied anastomosis area

of the main group of experimental animals. Especially fibroblastic activity was higher in the II subgroup of the main group (Figure 3). This is directly related to the effect of fibroblast growth factor (FGF) included in human placental hydrolyzate. The submucousal layer also retained the overall structural plan in full and was relatively thick. Unlike other observation groups, the formation of the fibrous carcass is more regular.

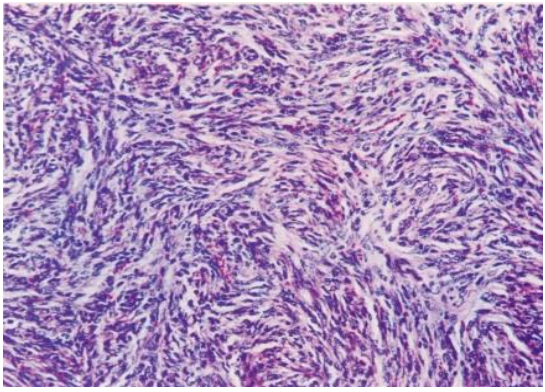

Figure 3. A large number of fibroblasts are noted in the anastomosis area.
Dye: hematoxylin-eosin
Magnification: ok.12.5, ob.10

Activation of angiogenesis mechanisms has accelerated the regeneration process. This indicator shows a direct correlation between vascularization and regeneration. This result indicates a close relationship between angiogenesis and the mitotic index of the epithelium, fibroblastic activity, de-novo formation of fibers, also give evidence of improved supply of oxygen and nutrients to cellular and non-cellular elements. Improved blood supply led to a decrease in the number of apoptotic and necrotic cells compared to the previous study day.

In experimental animals of the second subgroup of the main group, 15 days after the operation, the mucous membrane retained its macroscopic parameters almost completely. Microscopically, the folds of the mucous membrane are multi-numbered, crescent-shaped, deep enough, and regularly formed. Spiral-oblique vector collagen-reticular fiber bundles are formed on the submucousal layer, as well as in the muscle and serous membranes.

In the experimental animals of the II subgroup of the main group after the intestinal anastomosis was established, the application of human placental hydrolyzate to the root of the mesenter is characterized by a kind of "smoothing" of the morphological changes mentioned in the previous groups. So that, fibrillogenesis and fibrillolysis remain at a balanced level. Restoration of the function of the microcirculatory vessels indicates the complete provision of nutrition in the tissues. Lymphoid inhibition is not at a level that can block the immune defense system. The application of human placental hydrolyzate in this way allowed to bring the metabolic status of the wall structures of the anastomosis to an earlier optimal state than in the other subgroup. Histochemically, this is express itself comparing with statistical indicators and more with intact figures (Table 3).

Thus, after an experimental study, it was found that human placental hydrolyzate has a positive effect on the regeneration of intestinal anastomoses. So that, human placental hydrolyzate in the anastomosis zone increases the mitosis index, the activity of fibroblasts, collagen regeneration and also multiply the density of microvessels by stimulating angiogenesis. The above processes are observed during the use of human placental hydrolyzate both intramuscularly and intramesenteraly. But when applied to the root of the mesenter, the effects are express itself relatively more earlier. This suggests that in more severe cases, it is more appropriate to inject human placental hydrolyzate into the root of mesenter. In other cases, intramuscular use of the drug may be sufficient. By the obtained experimental studies it has been proved that human

placental hydrolyzate has a positive effect on the regeneration of intestinal anastomoses.

Table 3.

Indications	3 day	5 day	7 day	15 day
Mucus secretion	3,0 (2,0-4,0)	3,0 (2,0-4,0)	2,5 (2,0-3,0)	2,0 (1,0-3,0)
Epithelial mitosis index (regeneration)	2,0 (1,0-3,0)	3,0 (2,0-4,0)	4,0 (3,0-5,0)	4,0 (3,0-5,0)
Fibroblastic activity	1,5 (1,0-2,5)	2,0 (1,0-3,0)	5,0 (4,0-6,0)	3,0 (2,0-4,0)
Muscle-cell response	3,0 (2,0-4,0)	3,0 (2,0-4,0)	2,0 (1,0-3,0)	1,5 (1,0-2,0)
De-novo fibers formation (collagen)	1,5 (1,0-2,5)	2,0 (1,0-3,0)	4,0 (3,0-5,0)	3,0 (2,0-4,0)
Density of microvessels (1 mm^2) (angiogenesis)	30,0 (20,0-40,0)	40,0 (30,0-60,0)	60,0 (50,0-70,0)	50,0 (40,0-60,0)

Morphological parameters of II subgroup of main group experimental animals. The obtained results are expressed in conventional units. ($p<0,001$)

Clinical studies have shown that intestinal anastomotic leakage in patients in the comparison group is due to late visit to the doctor, inadequate preoperative preparation without taking into account risk factors, tactical and technical mistakes during operation, incorrect assessment of intestinal viability, lack of complex postoperative prophylaxis methods.

In the comparison group, 7 out of 8 patients with intestinal anastomotic leakage reported an acute decrease in parthial blood oxygen pressure on the 1st or 2nd day of operation. Decreased parthial pressure of oxygen in the blood leads to increased tissue

hypoxia in the intstinal wall and in the area of the anastomosis in patients with already impaired intramural blood supply. This leads to an increase in inflammatory destruction processes at the anastomosis junction and a delay in regeneration and collagenesis. As a result, the process of primary healing of anastomoses does not proceed in its own physiological rhythm, which leads to inconsistency of the anastomosis.

One of the reasons for the anastomotic leakage is due to the incorrect choice of the type of anastomosis. In the comparison group, suture inconsistencies occurred in 5 (21.7%) of the 23 patients with end-to-end anastomosis and in 3 (8.1%) of 37 patients with side-by-side anastomosis. This suggests that especially during emergency surgical operations side-by-side anastomoses are safer.

In the patients of the main group before the operation general blood tests, coagulogram, blood gases, albumin, total protein, CRP in the blood were checked, heart rate fraction was measured by echocardiography, double contrast computer tomography of the abdomen, colonoscopy, irrigography were performed. Before the operation for antibiotic prophylaxis a combination of ceftriaxone and metronidazole affecting aerobic and anaerobic microflora was used, and isoperistaltic intestinal lavage was performed. We have paid special attention to the technique of intestinal anastomosis in patients in the main group. In most cases, double-stitch sutures and absorbable polyglycolic acid-containing threads were used. In addition, especially during laparoscopic operations we fixed the intestinal anastomosis to the parietal peritoneum with 2-3 supporting sutures. This relieves tension directly on the anastomosis line. To do this, at a distance of ~ 3 - 4 cm from the anastomosis, the serous membrane of the intestinal wall is fixed to the parietal peritoneum and the Sigma or descending colon lowered into the pelvis is attached to the uterine cruciate ligaments in female patients to prevent tension in the intestinal anastomosis.

In the patients of the main group complex prophylaxis measures for intestinal anastomotic leakage was performed in the postoperative period. In this case, hypoproteinemia was corrected by

transfusion of 20% albumin, plasma of the same group, and patients with hypotension were prevented by intravenous infusions. To improve the blood circulation of the segments to be anastomosed, fractionated heparin molecules were used, taking into account the rheological properties of the blood and INR. Efforts have been made to keep the INR as close to maximum as possible. In some group of patients, these measures were started before the operation.

Another important point was the control of the parthial pressure of oxygen in the blood. Because in the comparison group, the majority of patients with intestinal anastomotic leakage reported a decrease in parthial oxygen pressure in the blood on days 1st – 2nd of operation. Taking this into account, we determined nasal oxygen support in patients in the postoperative period, depending on the degree of saturation. In addition, patients received high doses of vitamin C (500 - 1000 mg / day).

One of the points we paid special attention was the avoidance of drugs that have a negative effect on the regeneration of anastomoses. Considering the fact that in the literature of recent years there are reports that non-steroidal anti-inflammatory drugs impair the regeneration of the intestinal anastomosis, we often prefer to use narcotic analgesics for analgesia. It should also be noted that analgesics were used only on the first day of surgery after laparoscopic bowel resections.

In all patients in the main group for the first time, we used human placental hydrolyzate to prevent intestinal anastomotic leakage. In 65 patients 2 - 4 ml of human placental hydrolyzate was injected intramuscularly 1 - 2 times a day for 7 - 10 days. In 3 patients who underwent laparoscopic surgery, 8 French microirrigators were placed at the root of the mesenter during the operation and in the postoperative period, 4 - 6 ml of human placental hydrolyzate diluted in 0.9% - 50 ml of saline was applied once a day for 5 - 7 days, then it was continued as intramuscular use in a dose of 2 - 4 ml of human placental hydrolyzate.

As a result of the use of human placental hydrolyzate as part of complex surgical and consevative treatments to prevent intestinal

anastomotic leakage, in patients of the main group intestinal anastomotic leakage was observed in only 1 (1.5%) of 68 patients. Accelerated regeneration in placed primary intestinal anastomoses has led to earlier recovery, activation, nutrition, and earlier restoration of defecation in patients in this group. So that, out of 68 patients included in this group, 18 were activated on the 1st day of operation, 34 on the 2nd day of operation, 13 on the 3rd day of operation and 3 on the 4th day of operation. Also, defecation was restored on the 1st day of surgical operation in 16 patients, on the 2nd day of surgical operation in 42 patients, and on the 3rd day of surgical operation in 10 patients, and that's why patients could fed early. In this regard, the initiation of early feeding led to an earlier stop of parenteral nutrition, created conditions for faster recovery of microelement and protein balance in the blood. All this has led to a reduction in medical consumption of patients, shortening the duration of inpatient treatment, earlier recovery of working capacity.

Thus, as the successful results of the experiment have proven themselves in clinical practice the inclusion of human placental hydrolyzate in a complex treatment regimen to prevent intestinal anastomotic leakage has been important in preventing this complication. This demonstrates the effectiveness and practicality of the conducted research. As a result, we recommend that the drug should widely used in clinical practice for the prevention of intestinal anastomotic leakage. We consider that the widespread use of the drug for this purpose will reduce the incidence of appropriate complications.

.

RESULTS

1. Morphological examination of structural changes in primary intestinal anastomoses against the background of the model of acute intestinal obstruction in the experiment showed low levels of mitosis index, fibrillogenesis and angiogenesis in cells [6, 9, 12].

2. In the experimental studies in order to research the effect of intramuscular application of human placental hydrolyzate on the

structural changes in primary intestinal anastomoses in the background of the acute small bowel obstruction model, it has been found out that in the anastomosis area by increasing the mitosis index 20 - 75% ($p<0.001$), fibrillogenesis 25 - 50% ($p<0.001$), and angiogenesis 0 -50% ($p<0.001$) it had a positive effect on the regeneration of intestinal anastomoses [6, 9, 12].

3. In the experimental studies it has been determined that injection of human placental hydrolyzate into the root of mesenter increases mitosis index 30 - 75% ($p<0.001$), fibrillogenesis 50 - 70% ($p<0.001$) and angiogenesis 16 - 60% ($p<0.001$) in the anastomosis area, which means higher and earlier results in regenerative processes than intramuscular injection of the same drug. From this point of view, in order to prevent intestinal anastomotic leakage in patients inclouding at risk group, it is more expedient to inject human placental hydrolyzate into the root of the mesenter [6, 9, 12].

4. In clinical practice the use of human placental hydrolyzate in combination with other complex treatment measures has reduced the incidence of intestinal anastomotic leakage incidence from 13.3% to 1.5%. These percentages are the result of a "randomization" study in a comparison group of patients [4, 6, 7, 8, 10, 11, 14, 16].

PRACTICAL RECOMMENDATIONS

1. In clinical practice, in order to minimize the incidence of intestinal anastomotic leakage, operations should be performed by experienced surgeons in this field and the principles of minimally invasive, atraumatic should be observed.

2. The use of human placental hydrolyzate as part of a complex preventive measures to prevent intestinal anastomotic leakage allows to achieve positive results. Although 2 - 4 ml of the drug 1 - 2 times a day for 7 - 10 days is usually enough, but in the patients in the risk group 4 - 6 ml of the drug diluted in 0.9% - 50 ml of saline to inject through a microirrigator installed into the root of mesenter once a day is more expedient.

3. As part of the complex prevention of intestinal anastomotic leakage treatment measures should be taken against hypotension, hypercoagulation, hypoproteinemia, and give nasal oxygen support and blood gas and also CRP, rheological properties of the blood should be dynamically controlled.

4. The reduction of intestinal anastomotic leakage due to prophylactic measures has led to a smoother postoperative period, earlier activation, feeding, restoration of defecation and rehabilitation of patients, also shortening of inpatient treatment period, a significant reduction in medical consumption, that provides a basis for the widespread application of this method of treatment in clinical practice.

List of published scientific works on the topic of the dissertation

1. Ağayev E.K., Məmmədov T.E. İsmayılova Z.E. Bağırsaq anastomozu tikişləri tutmazlığının profilaktikası üsullarının müştərək tətbiqi // Cərrahiyyə jurnalı, - 2015. N2(42), - s.46-50.
2. Ağayev E.K., Məmmədov T.E. İsmayilova Z.E. Təcili və təxirəsalınmaz müdaxilələr zamanı müxtəlif bağırsaq anastomozu növlərinin müqayisəli təhlili // Cərrahiyyə jurnalı, - 2017. N2, - s.17-20.
3. Ağayev E.K., Məmmədov T.E. İsmayılova Z.E Bağırsaq yaralanmalarının ağırlaşmalarının inkişaf səbəbləri və profilaktikasının səciyyəvi xüsusiyyətləri // IV beynəlxalq tibb konqresi materialları, - 2017. s.66-69.
4. Məmmədov T.E. Bağırsaq anastomozu tutarsızlığının profilaktikasında plasentar hidrolizatın tətbiqi // Doktorantların və gənc tədqiqatçıların XXII respublika elmi konfransının materialları, - 2018. Noyabr, s.128-130.
5. Ağayev E.K., İsmayılova Z.E., Məmmədov T.E. Təcili və təxirəsalınmaz müdaxilələr zamanı müxtəlif bağırsaq anastomozu növlərinin müqayisəli təhlili // Azərbaycan respublikasının silahlı qüvvələrinin yaranmasının 100 illiyinə həsr olunmuş hərbi təbabətin aktual problemləri elmi praktik konfransının materialları, - 2018. may, - səh.70-74.
6. Agayev E.K., Mammadov T.E., Qasımov E.M. Эффективность применения человеческове плацентарново гидролизата в профилактике несостоятельности швов кишечных анастомозов // Klinichna khirurhiia, - 2019. July 86(7), - p.9-12.
7. Agayev E.K., Mammadov T.E., Ismayilova Z.E. Оценка эффективности комбинированного применения способов профилактики несостоятельности швов кишечных анастомозов // Klinichna khirurhiia, - 2019. Aug; 86(8), - p.9-12.
8. Məmmədov T.E. Bağırsaq anastomozu tutarsızlığının profilaktikasında yeni medikamentoz üsul // Sağlamlıq jurnalı, - 2019. N5,(24) - s.54-59.

9. Məmmədov T.E. Bağırsaq anastomozlarının regenerasiyasına insan plasentar hidrolizatının təsirinin morfohistokimyəvi xüsusiyyətləri // Sağlamlıq jurnalı, - 2019. N6, (24) - s.140-146.
10. Ağayev E.K., Məmmədov T.E., Hüseynov L.M. Klinik praktikada plasentar hidrolizatın tətbiqinə dair // Azərbaycan Tibb Jurnalı, - 2019. səh 96.
11. Ağayev E.K., Məmmədov T.E., Qasımov E.M. Bağırsaq anastomozu tutarsızlığının profilaktikasında insan plasentar hidrolizatının tətbiqi // Tibb fakültəsinin yaradılmasının 100 illik yubileyinə həsr olunmuş beynəlxalq konfrans materialları, - 2019 səh.8.
12. Mammadov T.E. İnfluence of human plasentar hydrolyzate on regeneration of intestinal anastomoses // Abstrac of the XVIII international euroasian congress of surgery and hepatagastroenterology, - 2019. səh. 108-109.
13. Agayev E.K., İsmayılova Z.E., Mammadov T.E. The gunshot injures of the intestines // Abstrac of the XVIII international euroasian congress of surgery and hepatagastroenterology, - 2019. - səh.69.
14. Agayev E.K., Ismayılova Z.E., Mammadov T.E. Application of human placental hydrolyzate in the prevention of early complications after intestinal resection operations // Abstrac of the XVIII international euroasian congress of surgery and hepatagastroenterology, - 2019. - səh.69-70.
15. Агаев Э.К., Юсубов М.О., Мамедов Т.Э. Наш многолетний клинический опыт по профилактике несостоятельности швов кишечных анастомозов // Хирургия Восточная Европа, - 2019. - С.13.
16. Ağayev E.K., Məmmədov T.E., İsmayılova Z.E. Bağırsaq anastomozu tikişləri tutmazlığının profilaktikasına dair 31 illik təcrübəmiz – ixtiralarımız, yeniliklərimiz və təkliflərimiz // Azərbaycan Tibb Universitetinin 90 illik yubileyinə həsr olunmuş Təbabətin aktual problemləri - 2020 mövzusunda beynəlxalq elmi praktiki konqresin materialları, - 2020. - səh. 31-32.

The defense will held on the 24 november 2021 at 14^{00} at the meeting of the Dissertation council ED 2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University

Address: Baku, A.Gasimzadeh str. 14, Conference Hall of AMU, postal index: AZ1022

Dissertation is accessible at the library of the Azerbaijan Medical University

Electronic versions of dissertation and its abstract are available on the official website of the Azerbaijan Medical University.

Abstract was sent to the required addresses on «19» october 2021 year

Signed for print: 30.09.2021
Paper format: 60 x 84 1/16
Volume: 37037 characters
Number of hard copies: 30