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RESEARCH ARTICLE



# Platelet-rich plasma role in the local protection of the colon anastomosis

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## ABSTRACT

**Introduction.** Intestinal anastomosis dehiscence has been and remains a critical problem in modern colorectal surgery, associated with significant morbidity and mortality. Currently, there are various studies focused on the development of a method to protect the intestinal anastomosis. The new method with the use of biological substances is the local application of platelet-rich plasma.

**Material and methods.** The experimental study included 42 rats, which were divided into two groups. Group 1 – application of unprotected colon anastomosis (n = 21); group 2 – local application of platelet-rich plasma on the colon anastomosis (n = 21). 37 patients were included in the clinical study, who underwent colon anastomosis. The patients were divided into 2 groups: group I (n = 16) had unprotected colon anastomosis and group II (n = 21) - protected anastomosis with platelet-rich plasma.

**Results.** It was experimentally proven that platelet-rich plasma does not aggravate the adhesion process and actually increases significantly the mechanical resistance of colon anastomosis. Microscopical examination demonstrated the acceleration of regenerative processes, in particular, angiogenesis and fibrillogenesis. The clinical study showed significant improvement of the postsurgical results – absence of colon anastomosis dehiscence in cases where local application of platelet-rich plasma was used.

**Conclusions.** A statistically significant increase in dehiscence pressure of the anastomosis at 3<sup>rd</sup>, 7<sup>th</sup> and 8<sup>th</sup> day after surgery was noticed in group 2 vs. group 1. Using platelet-rich plasma does not influence significantly the process of abdominal adhesion, leads to increased regeneration process in the anastomosis area, especially neogenesis and fibrillogenesis (p < 0.5). Using platelet-rich plasma significantly improves the post-surgical results.

**Keywords:** colon anastomosis dehiscence, platelet-rich plasma.

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## Key messages

### What is not yet known on the issue addressed in the submitted manuscript?

Currently, the effects of platelet-rich plasma on the healing process of the colon anastomosis are not fully known.

### The research hypothesis

Clinical and experimental evaluation of platelet-rich plasma effectiveness for local protection of the colonic anastomosis: benefits and disadvantages.

### The novelty added by manuscript to the already published scientific literature

A complex clinical and experimental evaluation of platelet-rich plasma effect on healing of colon anastomosis was performed. Postoperative results were studied, in particular the development

of complications, such as dehiscence of colon anastomosis or postoperative peritonitis. In medical literature, this subject is presented vaguely, while the scientific data is insufficient. Further studies are required.

## Introduction

Intestinal anastomosis dehiscence is a surgical complication that remains an important issue in modern public health and has a major medical, social and economic impact. Anastomosis dehiscence can be considered one of the quality indices of medical care in surgical departments [1-3]. According to medical literature, the incidence of the development of colon anastomosis dehiscence ranges widely, from 3.3% to 25.1% [4, 5]. The occurrence of this complication is associated with a significant increase in postoperative morbidity and mortality [6], and, respectively, reflects the quality of the surgical service [7].

Currently, in order to protect the intestinal anastomosis and prevent the occurrence of anastomosis dehiscence, various studies are carried out based on studying the role of human blood elements and the use of various synthetic substances. A new proposed method is the use of platelet-rich plasma. This term was first proposed in 1998 by Marx [8]. Platelet-rich plasma ensures the penetration of platelets in excessive quantity, accelerating the wound healing process. The regenerative effect can be explained by modulating growth factors such as platelet-derived growth factor, insulin-like growth factor, transforming growth factors  $\beta 1$  and  $\beta 2$  [9]. The active secretion of these factors is initiated due to the blood coagulation process and begins within 10 minutes of coagulation. More than 95% of growth factors are synthesized during the first hour [10]. Clinical and experimental studies are necessary for the correct assessment of the effectiveness of the use of platelet-rich plasma in the local protection of the anastomotic area.

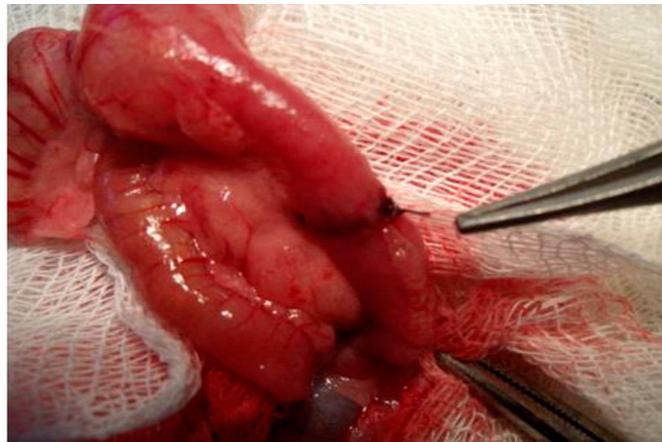
**The study objective** was to assess the efficacy of platelet-rich plasma in local protection of colon anastomosis.

## Material and methods

**Experimental part.** Forty-two rats were divided into two groups: group I – unprotected colon anastomosis (n = 21); group II – protected colon anastomosis with local application of platelet-rich plasma (n = 21). Anesthesia was performed by intraperitoneal administration of ketamine hydrochloride solution (Kalypsol<sup>®</sup>, Gedeon Richter, Hungary). The experimental study was carried out in accordance with the „Directive 2010/63/EU of the European Parliament and of the Council” regarding the protection of animals used for scientific purposes [11]. The research project was examined at the meeting of the *Nicolae Testemițanu* State University of Medicine and Pharmacy Research Ethics Committee, which took place on September 15, 2014.

Colon anastomosis was performed according to the standardized method, which included the following steps: opening the abdominal cavity through mid-median laparotomy; transection of the transverse colon at a distance of 1

cm from the cecum with the application of end-to-end unprotected colon anastomosis with continuous suture, using Polypropylene monofilament thread 5/0 in rats from group I (Fig. 1). In rats from group II, platelet-rich plasma was applied on the line of anastomosis. Layered closure of the abdominal wall was performed.



**Fig. 1.** Colon anastomosis, intraoperative photograph.

Animals were euthanized in CO<sub>2</sub> chamber. The autopsy of the rats was performed at 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> postoperative day, 7 rats for each group. The anastomoses were examined macro- and microscopically to assess for abscesses, dehiscence, signs of peritonitis, adhesences and to evaluate mechanical resistance. During autopsy, a 4 cm portion of the colon was taken, with the suture in the center and 2 cm on both sides of the anastomosis (fig. 2 a, b, c; fig. 3 a, b, c). The fragments were prepared for histological examination and to evaluate the anastomosis burst pressure.

**Clinical part.** 37 patients were included in the clinical study, who underwent colon anastomosis. The patients were divided into 2 groups: group I (n = 16) had unprotected colon anastomosis and group II (n = 21) - protected anastomosis with platelet-rich plasma. The anastomosis was applied in 2 steps: internal with suture polydioxanone 3/0 - 4/0 and external - polypropylene 3/0 (fig. 4 A, B).

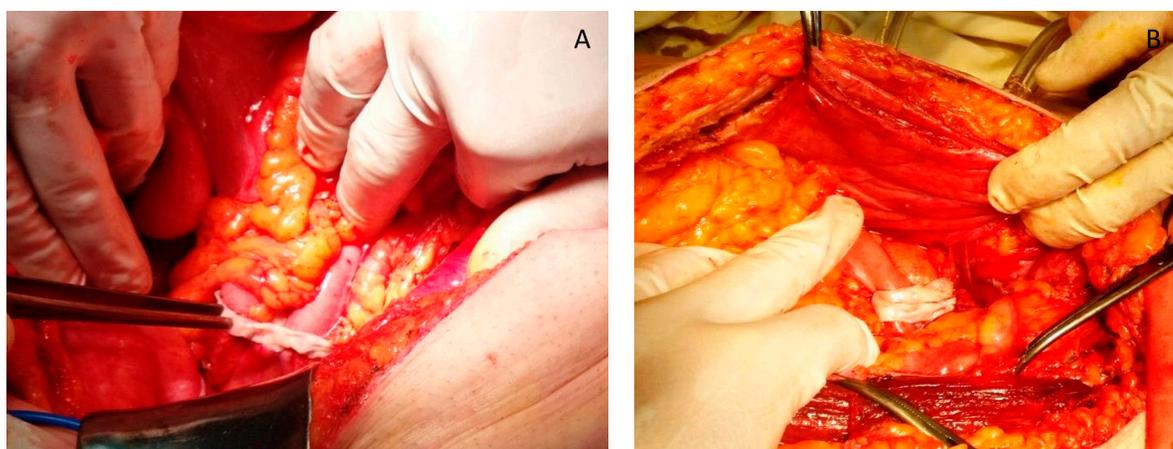
The patients were carefully monitored in the postoperative period. Procalcitonin was used for the laboratory diagnosis of colon anastomosis dehiscence. Postoperatively, the changes in the level of serum procalcitonin on the 3<sup>rd</sup>, 5<sup>th</sup> and 7<sup>th</sup> day were studied. For the assessment of procalcitonin, an immunoenzymatic analysis kit (Бектор Б, Novosibirsk, Russia) was used performed on the automated immunological ELISA analyzer Uno (Human), Germany. The normal value of procalcitonin is < 0.1 ng/ml.



**Fig. 2.** Group I: a) 3<sup>rd</sup> day after anastomosis, b) 7<sup>th</sup> day after anastomosis, c) 14<sup>th</sup> day after anastomosis



**Fig. 3.** Group V: a) 3<sup>rd</sup> day after anastomosis, b) 7<sup>th</sup> day after anastomosis, c) 14<sup>th</sup> day after anastomosis



**Fig. 4.** End-to-end sigmocolic anastomosis protected by local application of platelet-rich plasma.

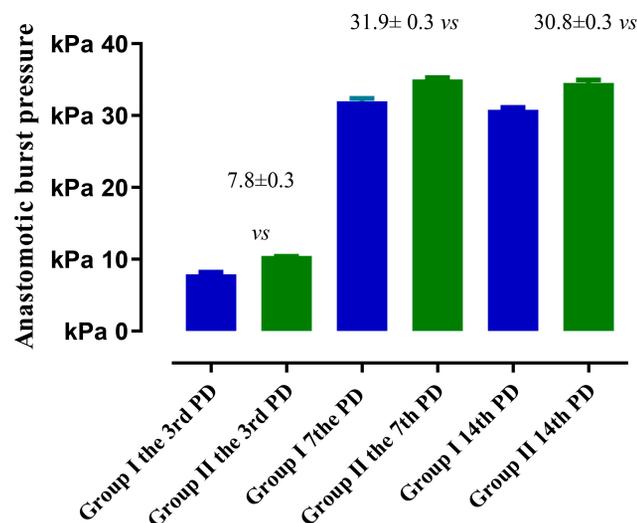
## Results

**Experimental study.** Analyzing the degree of adhesion formation according to van der Hamm's score [12], we can conclude that there is a statistically insignificant increase in the degree of intra-abdominal adhesion formation from the 3<sup>rd</sup> to the 7<sup>th</sup> day, with a statistically insignificant decrease from 7<sup>th</sup> to 14<sup>th</sup> day.

According to the data obtained in the current study, a statistically insignificant increase in the degree of adhesion formation was demonstrated in group II vs. group I (NS).

The burst pressure of the anastomosis was also studied. According to the obtained data, there is a statistically significant increase in the burst pressure of the anastomosis from the 3<sup>rd</sup> to the 7<sup>th</sup> postoperative day and a statistically insignificant decrease of this parameter from the 7<sup>th</sup> to the 14<sup>th</sup> postoperative day (Fig. 5).

Analyzing the obtained data, a statistically significant increase ( $p < 0.05$ ) of the anastomosis burst pressure was demonstrated on the 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> postoperative day in group II vs group I.



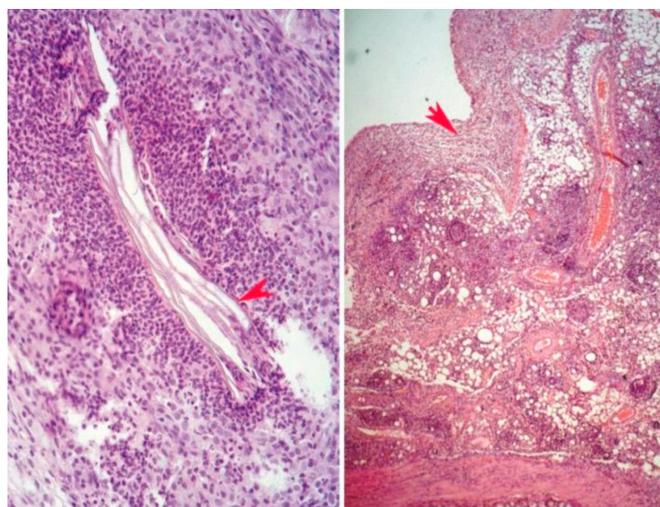
**Fig. 5** Assessment of anastomosis burst pressure.

**Note:** Group I – unprotected colon anastomosis ( $n = 21$ ); Group II – protected colon anastomosis with local application of platelet-rich plasma ( $n = 21$ ).

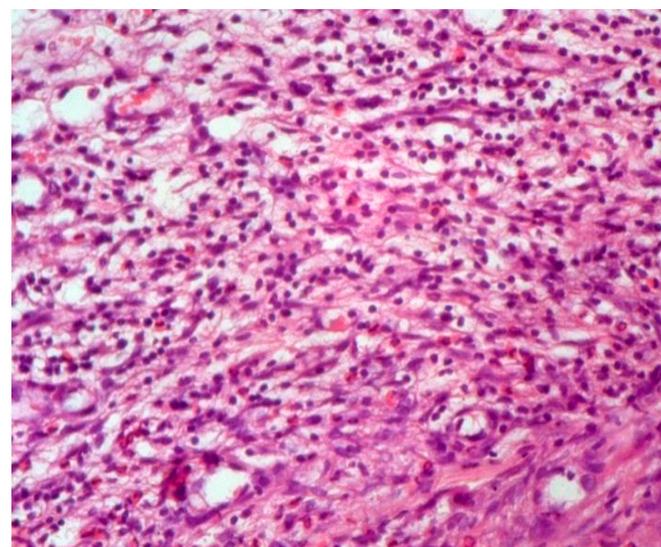
**Histological examination.** Microscopic examination of the samples from group I revealed deformations and volume changes, reactive edema, adhesions and slowing of the regenerative processes. An important key in this group was the activation of the local bacterial microflora, which on the 3<sup>rd</sup> and 7<sup>th</sup> day, due to its proteolytic features, manifested itself through excessive activity, forming the bacterio-necrotic-purulent demarcation line. In the anastomoses with a predominance of bacterial flora, the necrolytic and inflammatory processes in some places were significantly more aggressive, sometimes with penetration into the depth of the anastomosis, thus contributing to the appearance of anastomotic leakages, abscesses, deformations of the anastomosis, as well as the appearance of diverticula (fig. 6). The formation of granulation tissue was manifested by increased proliferation of fibroblasts and the presence of collagen deposits (fig. 7). Persistence of dystrophy of the ganglioneuronal structures of the Auerbach plexus was frequently detected, at a distance of up to 2.5 cm from the anastomosis.

The microscopic examination of the samples from group II demonstrated that in most cases the anastomoses had a tubular appearance, with preserved permeability. The histological examinations in this group were demonstrated by the significant regenerative processes.

In group II, in the internal area of the anastomosis was noticed a decrease in the activity of thrombo-vascular and exudative processes, while in the external area these processes were absent, unlike group I (fig. 8). From the external examination, a mantle of newly formed tissue with an insignificant tissue-tuberous appearance was observed, prominent outside the anastomotic area with the activity of sub-total/total epithelization attested on the 14<sup>th</sup> day. In group II, it was attested a numerical increase of mast cells from



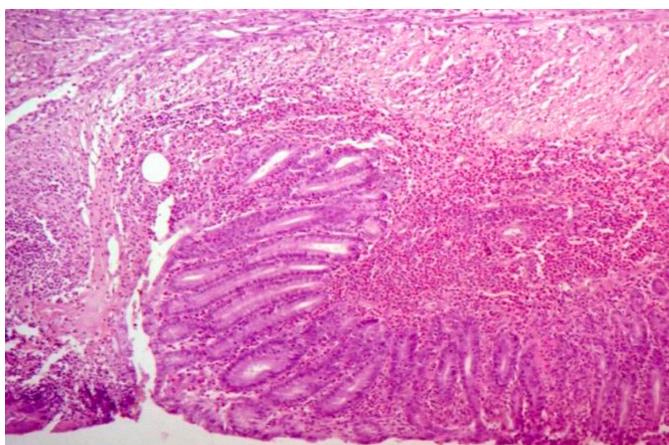
**Fig. 6** Anastomotic leakage: fecaloid elements in the cellular mass (red arrow). Coloration H&E.



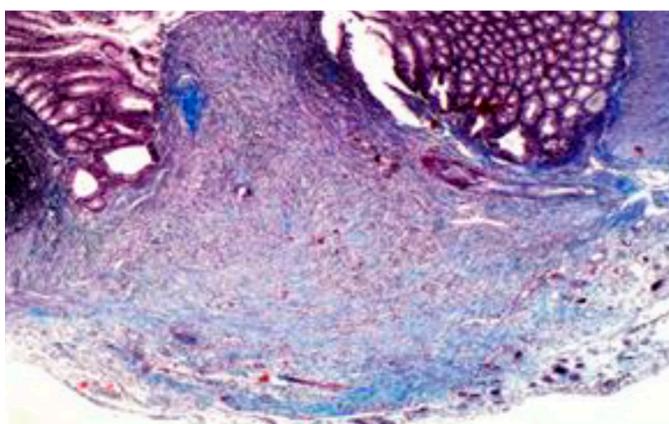
**Fig. 7** Vascular granulation tissue with collagen arrangement in fibers x200. Coloration H&E.

2-3 to 8-9 at x20 high-power field, mainly in the external area of the anastomosis. In parallel, the emphasis of the proliferative-fibroblastic process was observed at the level of the cellular-adipose tissue, directed towards the anastomosis, with voluminous hyper granulated mast cells present or with the spread of granules in the extracellular matrix. Compared to the anastomoses in group I, the dystrophy of the nerve plexuses was insignificant, with the exception of 2 cases. It is necessary to mention that no anastomotic leakages were detected in this group. On the 14<sup>th</sup> day, the line of anastomosis in some places was completely diminished macroscopically (Fig. 9).

According to this study, the mast cells were actively involved in the initial stages of triggering the acute inflammatory process. The attested cellular morphological manifestations were characterized by hypergranulation, which reflects the activation of mast and degranulation cells, the



**Fig. 8** Necrotic process at the level of the fold and leukocyte reaction with the predominance of eosinophils in the adjacent areas x25. Coloration H&E.



**Fig. 9** Cicatricial remodeling of the anastomosis on the 14<sup>th</sup> day x25. Masson's staining.

phenomenon of release in the extracellular matrix of mediators and chemotactic substances [13, 14], which contribute to the initiation and migration of leukocytes towards the anastomosis areas. It is also necessary to mention that the degranulation phenomenon reflects the activation of the neovascularization process through the release of endothelial-vascular growth factors and platelet activation. Based on the experimental data, we can conclude that the application of platelet-rich plasma on the anastomosis line does not worsen the adhesion process and increases statistically significant the burst pressure of the colonic anastomosis. The microscopical examination showed the acceleration of regenerative processes, in particular, angiogenesis and fibrillogenesis, in group II vs. group I ( $p < 0.05$ ).

**Clinical study.** Thirty-seven patients were included in the clinical study, who were hospitalized urgently or electively in the Institute of Emergency Medicine. The average age was  $59.49 \pm 2.16$  (23-78) years. There were 21 males (56.75%), and 16 females (43.24%), the ratio M:F = 1.3:1. 16 patients were included in group I, of which 10 – males and 6 – females; in group II – 11 males and 10 females. The distribution of patients by sex and age is shown in table 1.

**Table 1.** Distribution of patients according to age

Age (years)	20-30	31-40	41-50	51-60	61-70	71-80	Total
<b>Males</b>	1 (%)	4 (%)	-	7 (%)	7 (%)	2 (%)	21 (%)
<b>Females</b>	-	-	1 (%)	2 (%)	9 (%)	4 (%)	16 (%)
<b>Total</b>	1 (%)	4 (%)	1 (%)	9 (%)	16 (%)	6 (%)	37 (%)

According to the etiology of the pathological process, the most predominant cause was neoplasia. Colon cancer was diagnosed in 17 cases (45.94%), other localized cancer - 2 (5.4%) cases, terminal colostomy – 7 (18.9%) cases, terminal ileostomy – 4 (10.8%) cases, colonic fistula – 2 (5.4%) cases, adhesion disease - 1 (2.7%) case, appendicular plastron - 1 (2.7%) case, appendicular mucocele - 1 (2.7%) case, sigmoid diverticulum - 1 (2.7%) case, colonic endometriosis - 1 (2.7%) case.

There were miscellaneous types and indications of surgeries. In 10 cases - the surgical procedures were performed urgently, while in 27 cases – planned. In group I, right hemicolectomy was performed - 7 cases, colostomy reversal - 4 cases, ileostomy reversal - 3 cases, ileum resection with ileocolic anastomosis - 1 case, ileosigmoid bypass - 1 case. In group II, right hemicolectomy was performed - 6 cases, segmental colectomy - 4 cases, left hemicolectomy - 4 cases, colostomy reversal - 4 cases, subtotal colectomy - 2 cases, previous rectal resection - 1 case.

Currently, there are numerous definitions and classifications of intestinal anastomosis dehiscence. This study used the classification of anastomotic dehiscence proposed by the International Rectal Cancer Study Group in 2013 [15]. In group I, grade B anastomosis dehiscence was diagnosed in 2 cases after planned right hemicolectomy, in one case after colostomy and one after ileostomy reversal. Grade C anastomotic dehiscence was detected in one case after emergency right hemicolectomy. This patient required repeated surgery – relaparotomy with anastomosis resection and ileostomy. In group II, there were no cases of anastomosis dehiscence. Thus, from the results of the clinical study data, the incidence of anastomotic dehiscence was in group I – 4 (25%) cases of grade B and 1 (6.25%) of grade C vs. group II – 0 cases ( $p = 0.01$ ).

In the postoperative period, procalcitonin level was evaluated. Based on the obtained data, in uncomplicated cases with the development of anastomotic dehiscence, there is an increase in the serum level of procalcitonin on the 3<sup>rd</sup> postoperative day with a subsequent decrease on the 5<sup>th</sup> and 7<sup>th</sup> postoperative day. During the progressing of the colon anastomotic dehiscence a statistically significant increase in the procalcitonin serum level is determined, in particular - in grade C anastomotic dehiscence, on the 3<sup>rd</sup>, 5<sup>th</sup> and 7<sup>th</sup> postoperative day ( $p < 0.0001$ ).

## Discussions

Colorectal surgery represents an important field of contemporary surgery, due to the increasing incidence of surgical pathology of the colon. Despite the breakthroughs of modern medicine in general, and surgery in particular, dehiscence of intestinal anastomosis was and remains one of

the most dangerous postoperative complications [16], without significant improvements [5].

Currently there are different definitions of intestinal anastomosis dehiscence. The Surgical Infection Study Group in 1991 defined anastomosis dehiscence as the leakage of intestinal contents through the surgical connection between two cavity organs [17]. According to the results from Komen N. *et al.*, anastomosis dehiscence represents the leakage of intestinal content into the peritoneal cavity through the defect of anastomosis [18]. According to other authors, anastomosis dehiscence can be defined as the defect of the intestinal wall, which leads to the communication between the intra- and extraluminal compartment [19]. The International Study Group of Rectal Cancer defines dehiscence of the intestinal anastomosis as a communication between the intra- and extraluminal compartment through an anastomosis defect in the intestinal wall between the colon and the rectum or between the colon and anus. According to the data of this group, the abscess near the anastomosis, even without an obvious fistula, is to be interpreted as anastomotic dehiscence [15].

Early diagnosis and timely surgical intervention have a considerable influence on the final result. The diagnosis is primarily based on clinical data; however, epidural block [20], administration of analgesic drugs, including opioids, antibacterial therapy, and infusion therapy can reduce the clinical signs and symptoms. The increase in the concentration of serum inflammatory markers can be suggestive for anastomosis dehiscence, but the accuracy and specificity of the method is low, and the respective changes appear with a significant delay. The role of procalcitonin as a serological marker of intestinal anastomosis dehiscence is currently being researched. According to literature data, the increase in the serum concentration of procalcitonin was detected in all patients undergoing colorectal interventions, without complications, on the first postoperative day, with subsequent normalization on the 4<sup>th</sup> postoperative day in patients without complications and with a statistically significant increase on the 3<sup>rd</sup> to 5<sup>th</sup> postoperative day in patients with major anastomotic dehiscence [21]. Mokart *et al.* demonstrated the increased sensitivity and specificity of procalcitonin regarding the early diagnosis of septic complications after oncological surgery [22]. Thus, procalcitonin can be used as an early serological marker of major anastomotic dehiscence.

Protecting intestinal anastomosis remains an important problem in colorectal surgery. Various research is currently being carried out focusing on studying the natural factors that influence the regenerative processes. A new method in this field is the local application of platelet-rich plasma. Currently, platelet-rich plasma is used in various fields of contemporary medicine, such as: periodontology [23], maxillofacial surgery [24], dental implantology [25], orthopedics and sports medicine [26], chronic skin ulcers [27]. In the specialized literature, there are case reports about the use of platelet-rich plasma in colorectal surgery. Yol S. *et al.* (2008) experimentally proved that the application of plate-

let-rich plasma on colonic anastomosis suture is associated with an increase in the burst pressure of the anastomosis, by increasing the tissue hydroxyproline concentration [28]. Microscopical examinations of the anastomoses protected with platelet-rich plasma demonstrated the improvement of regenerative processes, in particular, neoangiogenesis and fibrillogenesis. Therefore, the local application of platelet-rich plasma on the anastomosis suture does not significantly worsen the abdominal adhesion process, statistically increases the burst pressure of the anastomosis and increases the regenerative processes.

Thus, the use of platelet-rich plasma has a beneficial influence on the healing process of the colon anastomosis and improves postoperative results.

### Conclusions

- A statistically significant increase ( $p < 0.05$ ) in anastomotic burst pressure was demonstrated on the 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> postoperative day in group II vs. group I. Also, the use of platelet-rich plasma does not significantly influence the abdominal adhesion process.
- The microscopical examination demonstrated that the local use of platelet-rich plasma leads to the improvement of regeneration processes in the anastomosis area, in particular, neoangiogenesis and fibrillogenesis ( $p < 0.05$ ).
- The use of platelet-rich plasma for local protection of colonic anastomosis improves postoperative outcomes.

### Competing interests

None declared.

### Patient consent

Obtained.

### Ethical Statement

This study was carried out in accordance with the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* („Directive 2010/63/EU of the European Parliament and of the Council”) and approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy, Minutes No. 5 from 15.09.2014.

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