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Original Scientific Paper

MORPHOLOGICAL TRAITS OF HEPATIC PARENCHYMAL TISSUE REPAIR FOLLOWING EXPERIMENTAL INJURY

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SUMMARY – The aim of the study was to investigate morphological traits of hepatic parenchymal tissue repair in response to injury using the conventional technique (closure) and an innovation method (such as hemostatic medication swab packing and modified batching). The experimental study was carried out on laboratory rats of the Winzar breed using light microscopy, standard stains for micropreparations, and morphometry. Histopathologic examination of micropreparations stained by standard methods revealed pronounced dystrophic processes in hepatocytes located near the necrotic zone (albuminous and hydropic degeneration and chromatin fragmentation in the nuclei). Morphometric studies showed a significant decrease ($p<0.001$) in almost all indicators of the size of cells and nuclei both near necrosis and distant from it on day 28 of the experiment in the experimental group in comparison to the control group. The results obtained pointed to more intense repair processes when applying the innovation method.

Key words: *Hepatic damage; Repair; Morphometry; Parenchymal tissue; Proliferation*

Introduction

Liver is one of the organs most commonly injured in trauma due to its size, anatomic structure, and location. Over the past decades, recommendations for the treatment of hepatic injury have changed significantly, and the global tactics of treating hepatic damage have led to significant improvements in results[1-3]. At the present stage of development in the treatment of traumatic injuries of parenchymal organs, most specialists prefer non-operative methods of treatment. However, despite technologic advances in diagnosis and treatment, mortality rates for hepatic injuries remain high, especially in patients with open abdominal trauma. Therefore, it should be borne in mind that patients with serious hepatic injury and unstable hemodynamics should be operated on urgently, and therefore, surgical treatment of severe hepatic injuries is currently still relevant[1,3-12].

Technical support of the operating rooms, highly qualified surgeon and modern anesthesiologic and resuscitation aids allow the use of resection methods with a high frequency of favorable outcomes. Since uncontrolled bleeding remains the main cause of death in patients with hepatic damage, in practice of operative surgery various hemostasis methods are used, from standard closure and application of biologic and synthetic films and adhesive compositions to non-contact methods (laser, plasma), argon coagulator, and spray coagulation[1-3,5,13-22]. At the same time, in patients with severe hepatic damage against the background of unstable hemodynamics and increasing hypovolemia,

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primary surgical intervention should be performed in the minimum volume to save life. In this regard, the possibility of using many modern and high-tech methods of hemostasis in such patients is sharply limited. The few methods with minimal surgical intervention include the use of hepatic tamponade[7,11,23,24] applying various hemostatic materials[14-17,20,21,25]. At the moment, there are several studies in the literature that assessed hemostatic efficacy of various groups of medications; results of the studies on the rate of their biodegradation and participation in tissue regeneration are presented[14-17,20,21,25]. From this point of view, the rate of the hepatic parenchyma repair process with various hemostasis approaches is of no small interest. This is part of the task of developing organ-preserving operations aimed at faster recovery of damaged organ tissues and reduction of the postoperative rehabilitation period. The aim of the research presented was to investigate morphological features of hepatic parenchymal tissue repair using the standard 'closure' technique and hemostatic medication swab packing and modified batching.

Materials and Methods

Assessing the efficacy of various hemostatic medications in bleeding control in vitro

The medications that have been widely used in medical surgical practice of native healthcare were selected as test sorbents[12,26,27]: Tachokomb (Takeda Austria GmbH, Linz, Austria) and hemostatic sponge (LLC Luga Plant BELKOZIN, City of Luga, Leningrad Region, Russia). During the experiment, test materials of approximately the same volume (10-15 cm^2) were placed in tubes with the same amount (30 mL) of blood from a healthy donor. The results of general blood test, biochemical analysis and coagulogram measured at the laboratory of the Department of Clinical Diagnostics, Autonomous Public Health Care Institution Bryansk City Hospital No. 1 in Bryansk were within the normal limits. The time of complete saturation of materials with blood was determined by the method of direct assessment (the level of absorbed blood in the test tube remained at the same level for 5 min). Subsequently, control measurement of the blood level in the laboratory test tube with a scale from 0 to 50 mL was performed by the method of direct assessment of the absorbed volume by each material.

To assess the efficiency of using materials of arbitrary shape, mathematical description of dependence of the volume of absorbed blood on the volume of the substance used was performed. The experimental data obtained were approximated by fifth-degree polynomial by the least-squares method:

$$V_k(V_r)=a_0+a_1V_r+a_2V_r^2+a_3V_r^3+a_4V_r^4+a_5V_r^5\ , \qquad (1)$$

where V_r is the volume of material;
V_k is the volume of absorbed blood;
a_0, a_1, a_2, a_3, a_4, a_5 are the parameters to be identified.

To calculate the parameters identified, the objective function was used, which determined the degree of discrepancy between the experiment and the calculated model. The criterion of standard deviations of the absorbed blood volume from the experimental data was used as an objective function:

$$Q=\int_0^{t\max}(Vk(t)\ э-Vk(t)M)^2\,dt\ , \qquad (2)$$

where $Vk(t)_э$ is the experimental value of the absorbable blood volume;
$Vk(t)_M$ is the calculated value of the absorbed blood volume.

Minimization of the objective function was carried out according to Hook-Jeeves criterion. Fisher F-test was used to verify the adequacy of the mathematical model developed, taking into account experimental data.

Simulation of injury and conducting hemostasis in laboratory animals

The experimental work was carried out following the requirements of the European Convention for the Protection of Experimental Animals 86/609 EEC; euthanasia of animals was carried out by decapitation under ether anesthesia. The keeping of animals, the implementation of various procedures, and the conclusion from experience were carried out following the requirements of the European Convention for the Protection of Vertebrate Animals used for experiments or other scientific purposes (Strasbourg, March 18, 1986, ETS No. 123).

The experimental study was carried out at the Research Institute of Biological Problems, Voronezh State Medical University. For experimental studies, 60 laboratory Winzar rats (weighing 150-200 g) were se-

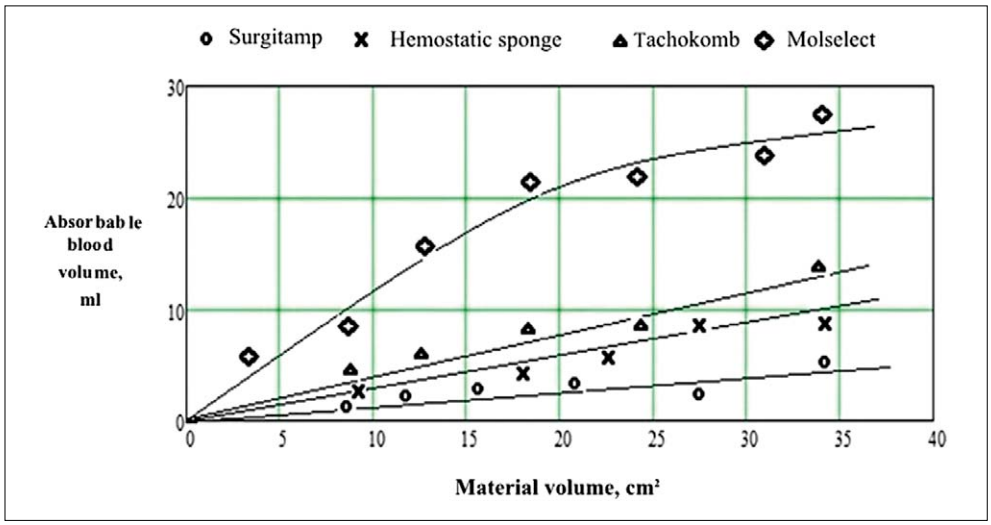

Fig. 1. Dependence of the absorbable blood volume on the material volume.

lected and divided into 2 groups of 30 rats, control and experimental group. The animals were kept in standard vivarium conditions, each rat separately. Bringing out from the experiment in each group of rats was carried out on days 4, 14 and 28 from the time of injury (the selected time periods correspond to stages of hepatic tissue repair). Then the animal's liver was removed under anesthesia for histologic examination.

The experiment was carried out under aseptic conditions. The animals were fixed in supine position to a special bench. Laparotomy was performed under ether anesthesia for 10-15 minutes after treatment with 0.5% alcoholic solution of chlorhexidine and lining of the operating field with sterile wipes (Fig. 1). The hepatic lobe was removed and placed on a special stand, after which trauma was inflicted with a hollow metal cylinder of 1 cm in diameter with extraction of a part of hepatic parenchyma to obtain active parenchymal bleeding.

In the control group, a standard suture material used in surgical practice was applied, i.e. monofilament PGA 3.0 (manufactured by Volot LLC, City of Tula, Russia) for hemostasis of the wound surface[28,29]. In the experimental group, the technique we developed was applied, the essence of which was in swab packing of the hepatic wound with hemostatic material and wrapping it with strips of polypropylene cellular implant. The operation ended with drainage of the abdominal cavity and an antibiotic (cefotaxime 0.25 g) was administered intramuscularly to prevent purulent complications, after which laparotomy wound was closed tightly.

Histologic analysis of hepatic tissue

Histologic studies of the liver tissue in experimental animals were carried out on days 4, 14 and 28 of the experiment[12]. The liver removed was weighed, measured, and photographed. Pieces of hepatic tissue measuring 1.0x1.0x0.5 cm were subjected to standard histologic processing (hepatic tissue 0.5 cm thick was placed in standard cassettes, fixed in 10% neutral, buffered formalin, dehydrated through alcohols of ascending density, and embedded in paraffin). Microtome was carried out on a rotary microtome (Orion Medic, St. Petersburg, Russia)[18,30]. Sections 3-5 micron thick were stained with hematoxylin-eosin survey stain. Histologic preparations with a standard stain were examined using light microscopy followed by morphometry. Morphometric study of the size of hepatocytes, nuclei, and their volume near necrosis and at a distance of two fields of vision with microscope magnification x100 was carried out. Thirty fields of vision were examined in each preparation.

Statistical data processing

The data obtained were processed using standard methods of statistical analysis, i.e. mean values (M), standard errors (SE) of the mean values (m) were calculated, and Student's t-test was used to check statisti-

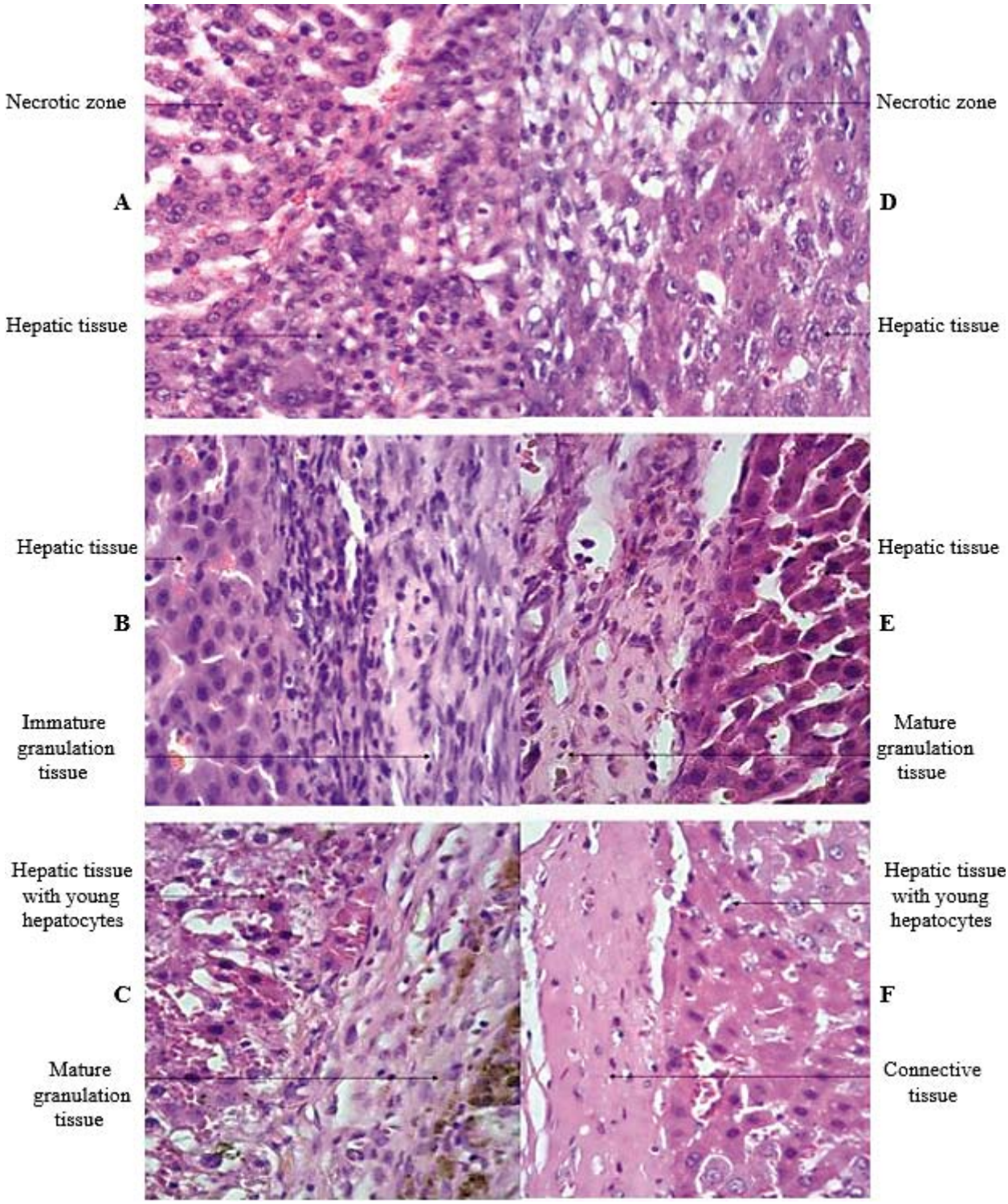

Fig. 2. Rat hepatic histologic specimen: A, B, C – control group on days 4, 14 and 28 of experiment, respectively; D, E, F – experimental group on days 4, 14 and 28 of experiment, respectively (hematoxylin–eosin staining; magnification ×40).

cal significance of deviations. The normality of distribution was also checked by Pearson χ^2-test, which turned out to be sufficient (p=0.05). Statistical analysis of the morphometric data obtained was carried out using the tools of the StataSE 14.2 package.

Results

Evaluation of the efficiency of bleeding control with various hemostatic medications in vitro

During the research, it was noted that the absorption process directly depended on the total surface area of the sorbent. To assess the efficiency of using materials of arbitrary shape, mathematical description of the dependence of the volume of absorbable blood on the volume of the substance used was implemented (Fig. 2).

After approximating the experimental data, it was found that dependence of the volume of absorbable blood on the volume of the substance used was close to linear for the hemostatic sponge, Tachocomb (Takeda Austria GmbH, Linz, Austria), and Surgitamp (Molodechno, Minsk Region, Republic of Belarus) materials, whereas it was nonlinear in the case of the Molselect material (Miass, Office 202). In general, study results showed the largest volume of blood to have been absorbed by the Molselect material (up to 30% of the initial volume), which confirmed the prospects of its use. It was also found that this material had the shortest period of swelling in the blood since this sorbent absorbed more blood within a shorter period of time. Based on the results of the experiment, the most promising Molselect material was selected for further research.

Assessment of repair processes in hepatic tissue

On day 4 of the experiment, the slides of both control and experimental groups revealed structural changes characterized by microscopic view in the hepatic parenchymal tissue near the necrotic zone and in two microscopic fields of view (magnification x100) (Fig. 2a,d). Around the focus of traumatic injury, hemorrhages, desolation of hepatic parenchyma, lymphedema, and infiltration of hepatic tissue by inflammatory cells were detected. Focal and massive necrosis of hepatocytes and vacuolar hydropic dystrophy were seen. These changes, but to a lesser extent, were noted in hepatic parenchyma remote from the necrotic zone. There were no significant visual differences between the two groups compared.

On day 14 of the experiment, marked changes of inflammatory nature with formation of demarcation inflammation around the injury zone were noted on the slides of the control group (Fig. 2b). There was formation of a chronic inflammatory response with the presence of giant cells of 'foreign bodies' around the suture with hypoxic reactions of hepatocytes in the damage zone and peripherally. Cells of various size, with a fuzzy cell membrane, nuclei of different intensities of staining, cytoplasm containing granular inclusions, and vacuolar hydropic dystrophy were observed. Mild infiltration with lymphohistiocytic cells surrounding the tissue damage zone was noted. Far from damage area, local infiltrates took place in the hepatic parenchymal tissue, with severe hepatocyte karyopyknosis and expansion of Disse space. In the control group, hepatic compensatory reactions to damage were weakly expressed.

On day 14 of the study, the microscopic picture on the slides of the experimental group was characterized by the formation of an inflammatory bank around the spongy mass (gel) (Fig. 2e). The processes of hepatocyte dystrophy (granular, vacuolar, hydropic) and focal lymphohistiocytic infiltration in the injury zone and away from it were less pronounced than in the control group.

On day 28 of the experiment, an increase in the repair processes was noted in the preparations of the control group (Fig. 2c). Young, smaller hepatocytes with hyperchromic nuclei and a greater number of binuclear hepatocytes appeared. In turn, the infiltrates of inflammatory cells disappeared at a distance from the focus of hepatic damage. There was pronounced neoangiogenesis around the zone of the fibrous capsule surrounding the zone of hepatic damage (Fig. 2). The morphological picture on day 28 of the experiment in the experimental group indicated diffuse proliferation of young hepatocytes near the lesion focus, with a large number of binucleated hepatic cells (Fig. 2f).

As Table 1 shows, there were no statistically significant differences in the size of cells and nuclei close to the necrotic zone and away from it in the control group. An exception were the indicators between the minimum cell size in the necrotic zone and away from it in the K4 group.

As a result of morphometric studies in the experimental group, statistically significant differences ($p<0.05$)

Table 1. Results of morphometric studies in control group

Group	Close to necrotic zone				Away from necrotic zone			
	Cell size (μm)		Nucleus size (μm)		Cell size (μm)		Nucleus size (μm)	
	Min	Max	Min	Max	Min	Max	Min	Max
C4*[a]	12.7±0.43	19.2±0.37	5.8±0.35	6.8±0.32	12.2±0.39	19.1±0.66	5.6±0.33	6.8±0.26
C14	12.9±0.45	20.2±0.90	5.8±0.47	7.6±0.26	12.2±1.11	19.7±1.04	5.7±0.51	7.4±0.16
C28	13.3±0.50	20.3±1.00	6.5±0.22	7.7±0.18	13.8±0.50	20.5±0.78	6.5±0.30	7.6±0.33

*p<0.05; [a]differences between minimum cell size near necrosis and away from necrosis in C4 group; C = control group, day of experiment

Table 2. Results of morphometric studies in experimental group

Group	Close to necrotic zone				Away from necrotic zone			
	Cell size (μm)		Nucleus size (μm)		Cell size (μm)		Nucleus size (μm)	
	Min	Max	Min	Max	Min	Max	Min	Max
E4*[a,b,c]	12.6±0.18	19.2±0.29	6.2±0.43	7.6±0.33	12.2±0.22	18.6±0.30	6.1±0.04	7.3±0.10
E14	12.3±0.46	18.1±0.97	6.1±0.50	7.4±0.62	12.9±0.31	18.3±0.44	5.9±0.33	7.1±0.38
E28	12.2±0.39	17.4±0.86	5.8±0.30	7.0±0.32	12.5±0.48	17.8±1.02	6.0±0.37	7.4±0.35

*p<0.05; [a]differences between minimum cell size near necrosis and away from necrosis in groups E4 and E14; [b]differences between maximum cell size near necrosis and away from necrosis in group E4; [c]differences between maximum nucleus size near necrosis and away from necrosis in groups E4 and E28; E = experimental group, day of experiment

were recorded between minimum cell size, maximum cell size and maximum nucleus measured near necrosis and away from it in the E4 group (Table 2).

It should be noted that comparative assessment of the size of cells and nuclei between the control and experimental group is more important than morphometric analysis within either group, as shown in Tables 1 and 2. As a result of morphometric studies in the control and experimental group on day 28 of the experiment, significant differences were established between almost all indicators of the size of cells and nuclei, both near necrosis and away from necrosis, at a significance level of $p<0.001$ (except for the maximum nucleus size away from necrosis). In the experimental group, there was a decrease in both minimum and maximum cell size near and away from necrosis ($p<0.001$). There was also a significant decrease in the minimum and maximum size of the nucleus near necrosis and in the minimum size of the nucleus away from necrosis ($p<0.001$).

Discussion

Severe intra-abdominal bleeding is the main reason for adverse outcome of hepatic injuries; therefore, the timeliness of surgical intervention and the choice of an appropriate method of hemostasis acquire special significance[8]. According to published data, today there is no universal hemostatic medication that would satisfy all the requirements of an operating surgeon in the process of bleeding control on parenchymal organs, liver in particular[14-17,20,21,25]. Search for new methods and development of modern hemostasis agents with high efficiency and ease of application is an urgent problem of surgery[14-17,20,21,25]. In the course of this study, it was noted that the process of blood absorption by the hemostatic medications described directly depends on the maximum surface area. After approximating the experimental data, it was found that among the studied materials, Molselect was characterized by the greatest amount of absorbed blood for the shortest swelling period, which confirms the prospects of its use in clinical practice. In addition, the widespread introduction of modern local hemostatic agents into surgery (including the studied materials Surgiplast and Tachocomb) is hindered by their high cost[14,16,17], while the use of Molselect is economically justified.

Experimental evaluation of the efficacy of hemostatic medications is decisive at the next stage in the development of technologies for the operation of he-

patic injuries. Of interest is the rate of hepatic parenchyma repair with various approaches of hemostasis, which is part of the development of organ-preserving surgeries aimed at faster restoration of damaged organ tissues and reduction of the postoperative rehabilitation period. Comparative assessment of the rate of parenchyma regeneration with different methods of hemostasis depends, first of all, on the stage of the experiment. Several studies have established that hepatic regeneration in rats completes in 7-14 days, therefore most authors recommend removing animals on day 14 after modeling organ injury. However, some authors insist on the presence of significant changes in the structure of the studied organs in dynamics, up to 30 days after surgery[31], for the possibility of a comparative study in various groups of macro- and micromorphological parameters[7,24].

According to the data obtained in our study, at the initial stage of the experiment (day 4), the morphological picture of changes in hepatic parenchyma in both groups did not show significant differences in the repair process. In this case, the reaction of hepatic parenchyma was a consequence of recent damage to the integrity of its structure, which manifests itself in the form of expansion and blood filling of the vascular bed, the phenomena of incipient interstitial edema, and the growing processes of hepatocyte dystrophy. From the middle of the experiment (day 14) in both groups, as inflammation developed, degenerative and necrotic changes developed, which were more pronounced in the control group. In the case of hepatic damage, a complex mechanism of regeneration was initiated, microscopically manifested as proliferation, differentiation, and angiogenesis[31]. By the end of the experiment (day 21), the microscopic view of repair changes in both groups was characterized by pronounced proliferation of young hepatocytes near the injury site and neoangiogenesis around the fibrous capsule zone surrounding the zone of hepatic damage. Thus, demonstrative indicators of successful hepatic regeneration in both groups was the predominance of the number of binuclear cells over degenerating cells, indicating an increase in the protein synthesis function of hepatocytes.

As a result of morphometric research, statistically significant differences were established in metric indices between the experimental and control groups, which may indicate different mechanisms of the reparative process in the studied groups. Thus, throughout the experiment, a moderately increasing hepatocyte hypertrophy, which was characterized by an increase in the size of cells and their nuclei, was observed in the control group. As a rule, in pathologic processes, hepatocyte hypertrophy is a type of reparative regeneration, which is accompanied by enhanced DNA synthesis and accumulation of all intracellular components[31,32]. In the experimental group, changes in morphometric parameters were nonsignificant in time, and regeneration of rat liver most likely occurred due to increased proliferation of hepatocytes. There is an opinion that hepatocyte hypertrophy of the liver is a mechanism for protecting hereditary material from oxidative damage that occurs when the liver is injured and its functional load changes[33-35]. It is likely that the use of an innovative approach (using swab packing with Molselect medication) is a gentler method of hemostasis and does not cause a sharp working stress to the organ, and accordingly, hepatic regeneration takes place in the normal metabolism mode.

Conclusions

1. The results obtained show that the selected Molselect medication had the highest absorbing properties in comparison to others, making its use most promising in clinical practice.
2. The morphological picture of hepatic parenchyma in the control and experimental groups on day 4 of the experiment demonstrated no significant differences. Dystrophic changes in hepatic parenchyma near the lesion focus on day 14 of the experiment were more pronounced in the control group of animals than in the experimental group.
3. As a result of morphometric studies on day 28 of the experiment, a significant ($p<0.001$) decrease in almost all indicators of the size of cells and nuclei, both near necrosis and away from necrosis, was found in the experimental group in comparison to the control group.

In surgical treatment of traumatic injuries of the liver, the nature, speed and volume of blood loss play a major role; therefore, search for an optimal hemostatic medication is the cornerstone of successful elimination (minimization) of this serious complication for the patient. This experiment has become part of the evidence base for development and introduction in clinical

practice of a new technology for surgical treatment of traumatic hepatic injuries. In the course of the study, it was found that the process of blood absorption by the hemostatic medications selected directly depended on the maximum surface area. Molselect showed most efficient absorbent properties in comparison with other medications, which makes its use most promising in clinical practice. Assessment of the difference in reparative processes and the innovative approach (using swab packing and Molselect medication) in the treatment of traumatic hepatic injuries revealed similar morphological patterns in the early stages of the experiment; differences in reparative processes increased starting from the middle of the experiment. The most statistically significant differences were found on day 28 of the experiment, recorded in almost all indicators of the size of cells and nuclei, both near necrotic zone and away from it. When extrapolating the morphological and morphometric data obtained to clinical material, it can be assumed that this approach to the treatment of traumatic injuries of the liver, in our opinion, will contribute to its faster recovery.

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Sažetak

MORFOLOŠKE ZNAČAJKE OPORAVKA JETRENOG PARENHIMA NAKON EKSPERIMENTALNO IZAZVANOG OŠTEĆENJA

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Cilj istraživanja bio je ispitati morfološke značajke oporavka parenhimnog tkiva jetre u odgovoru na oštećenje primjenom konvencionalne tehnike (zatvaranje) i inovacijske metode (kao što je oblaganje gazom natopljenom hemostatskim lijekom i modificiran *batching*). Ovo eksperimentalno istraživanje provedeno je na laboratorijskim Winzar štakorima primjenom svjetlosne mikroskopije, standardnih boja za mikropreparate i morfometrije. Histopatološka analiza mikropreparata obojenih standardnim metodama pokazala je znatne distrofične procese u hepatocitima blizu nekrotične zone (albuminozna i hidropična degeneracija, fragmentacija kromatina u jezgrama). Morformetrijska ispitivanja pokazala su značajno smanjenje ($p<0,001$) svih pokazatelja veličine stanica i jezgara kako blizu nekroze tako i dalje od nje 28. dana eksperimenta u eksperimentalnoj skupini u usporedbi s kontrolnom skupinom. Dobiveni rezultati ukazuju na intenzivnije procese oporavka kad je primijenjena inovacijska metoda.

Ključne riječi: *Oštećenje jetre; Oporavak; Morfometrija; Parenhimno tkivo; Proliferacija*