COMPARATIVE ANALYSIS OF EFFICACY OF THE NEW LOCAL HEMOSTATIC AGENTS

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Various local hemostatics (based on collagen, gelatin, cellulose, etc.) are used to stop bleeding from parenchymal organs of the abdominal cavity. In the context of an acute *in vivo* experiment, this study aimed to comparatively assess the time and volume of bleeding from a trauma of abdominal cavity's parenchymal organs covered with a new collagen-based spongy hemostatics combined with Na-CMC. We used new multicomponent polymer sponge implants (MPSI) based on marine collagen and carboxymethyl cellulose sodium salt, Na-CMC; the components were mixed in the ratios of 15/85, 25/75, 50/50. Hemostatic activity of the samples was assessed by bleeding time and blood loss volume. For the experiments, rats underwent laparotomy and resection of the left lobe of liver (series 1) and lower pole of spleen (series 2). In both series of experiments, the controlled parameters (bleeding time and blood loss volume) were smallest in group 6, where the MPSI were 50/50 Na-CMC/collagen. The hypothesis of higher efficacy of composite local hemostatic agents (namely, made of Na-CMC and deep-sea squid collagen) in cases of trauma of the parenchymal organs was confirmed experimentally, and same experiment has also shown that collagen in the composition of MPSI boosts bleeding arrest (for liver injury, the smallest blood loss and hemorrhage control time was 41 s, for spleen injury — 57 s, respectively; $p \leq 0.05$).

Keywords: hemostasis, hemostatic sponges, polymers, *in vitro* experiment, bleeding, collagen

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Compliance with ethical standards: the study was approved by the Ethics Committee (Minutes #3 of November 16, 2020), conducted in compliance with international and national standards for care and use of laboratory animals.

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СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭФФЕКТИВНОСТИ НОВЫХ ОБРАЗЦОВ МЕСТНЫХ ГЕМОСТАТИЧЕСКИХ СРЕДСТВ

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Для остановки кровотечения из паренхиматозных органов брюшной полости применяют различные варианты местных гемостатических средств (на основе коллагена, желатина, целлюлозы и пр.). Целью работы было провести сравнительную оценку времени и объема кровотечения после травмы паренхиматозных органов брюшной полости с использованием новых образцов губчатых кровоостанавливающих средств на основе коллагена в сочетании с Na-КМЦ в остром эксперименте *in vivo*. Использовали новые образцы многокомпонентных полимерных губчатых имплантов (МПГИ) (на основе морского коллагена, в разных соотношениях по массе с натриевой солью карбоксиметиллцеллюлозы – Na-КМЦ (15/85, 25/75, 50/50). Оценивали гемостатическую активность (время кровотечения и объем кровопотери) указанных изделий в эксперименте: крысам выполняли лапаротомию и резекцию левой доли печени (серия 1) и нижнего полюса селезенки (серия 2) в коагулометрическом измерении времени свертывания крови доноров-добровольцев. Наименьшие значения оцениваемых показателей (время кровотечния и объем кровопотери) в обоих сериях эксперимента обнаружены в группе 6 с использованием новых образцов МПГИ (Na-КМЦ+коллаген, в соотношении 50/50). Гипотеза об увеличении эффективности использования местных кровоостанавливающих средств при травме паренхиматозных органов за счет разработки комбинированных изделий (а именно на основе Na-КМЦ и коллагена глубоководного кальмара) получила подтверждение в эксперименте, в котором также доказано позитивное влияние внесения коллагена в состав МПГИ на скорость остановки кровотечения (при травме печени наименьший объем кровопотери и время остановки кровотечения — 41 с, а при травме селезенки — 57 с соответственно; $p \leq 0,05$).

Ключевые слова: гемостаз, гемостатические губки, полимеры, эксперимент *in vitro*, кровотечение, коллаген

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Currently, there is a significant number of patients admitted to surgery departments with trauma of the abdominal cavity's parenchymal organs [1, 2]. This category of patients requires special attention, as their injuries can be complicated by massive intra-abdominal bleeding. Despite the advanced diagnostic equipment available at clinics today, including CT, thromboelastography in specialized hospitals, etc., the proportion of fatal liver and spleen trauma cases remains high, at 20 to 60% [3, 4]. Time is of crucial importance: the quicker the patient receives assistance (counting from the moment of injury), the better are his chances of recovery [5].

In such cases, the key goal of assistance is to stop bleeding, which is achievable not only in the context of a surgery but also with the help of a combination of hemostatics [6]. There are various hemorrhage arrest techniques, from the Pringle manoeuvre through atypical resections to suturing the wound [7]. However, currently, the preferred options are those allowing to preserve organs, enabled by the advancements in electrosurgery (coagulators and high-energy equipment forming the final clot), cryosurgery (non equilibrium plasma or cold plasma), multicomponent polymer sponge implants (MPSI), adhesive compositions (sulfacrylate adhesives), etc. [8]. The latter are gels, sponges, plates, powders; the choice of such product's shape depends on the degree of organ damage and its localization, and the possible pattern of surgery (laparotomy, as a rule, since laparoscopic access is used extremely rarely in urgent situations, with unstable hemodynamics a contraindication thereto) [9].

There are many polymers and organic compounds used as base for such products: gelatin, collagen, cellulose derivatives, etc. The respective MPSIs have proven to be effective, and they are common in clinical practice [10]. The relevance of research in this area is underpinned by a large number of publications by national and foreign authors that cover testing of MPSIs in *in vitro* and *in vivo* experiments, the goal of these studies being to find most effective hemostatic that would be highly adhesive and capable of arresting bleeding quickly [11].

This study aimed, in an acute *in vivo* experiment, to comparatively assess the time and volume of bleeding arrested with new collagen sponge hemostatics combined with Na-CMC.

METHODS

The materials used in this study are the new MPSI ("Composite hemostatic sponge," Russian Federation patent application #2023123284 of September 07, 2023; Table 1 below lists characteristics thereof), and hemostatics common in clinical practice.

The study was performed on mature male Wistar rats weighing 200–250 g, under general inhalation anesthesia, in two series (liver and spleen) of 60 animals each, divided into 6 groups as per the number of types of tested MPSIs (Table 1). All surgical interventions were carried out in sterile conditions of the operating unit of the Laboratory of Experimental Surgery and Oncology of the Research Institute of Experimental Medicine of KSMU.

We developed a technique to inflict damage to liver, which included a median laparotomy, liver's left lobe brought out through the wound for marginal resection (10 × 5 × 5 mm) [12]. The injury of the spleen was modeled similarly, with its posterior pole of appropriate dimensions cut off.

The tested sponge, measuring 1.0 × 1.0 cm with a known mass, was applied to the bleeding incision. We registered the volume of blood loss, i.e., how much blood the sponge absorbs, and the time of bleeding. The former (V) was established using the E.M. Levitae gravimetric method, which compares the weight of sterile material before surgery (m1, g) and after (m2, g), when it has siaked up blood. The latter (t, s) was controlled visually and timed with a stopwatch; we lifted the sponge up from the wound every 10 s, and the bleeding was considered arrested when there was no more blood absorbed by it. The animals were removed from the experiment by CO2-induced euthanasia immediately after surgery.

In the context of data processing, we determined the median, 25th and 75th percentiles — Me [25;75] (indicators of descriptive statistics). Due to the small size of the sample on the level of groups (n = 10), we established significance of differences with the help of the Mann-Whitney test, and normality of distribution using the Kolmogorov-Smirnov test, with $p \leq 0.05$, as acceptable for experimental biomedical research. The software used for the purpose was a licensed version of Statistica 13 Pro (Dell Software Company; Round Rock, USA).

RESULTS

According to the results of series 1 experiments (liver injury), hemorrhage was arrested fastest in group 6, where the new MPSI based on marine collagen and Na-CMC was used. In

Table 1. Characteristics of the examined materials and study groups

№	Name	Manufacturer	Composition	Product form
1	Tachocomb	Takeda Austria GmbH, 4020 Linz, Austria	Collagen from horse tendons; riboflavin; lyophilized human fibrinogen; thrombin; aprotinin	Absorbing hemostatic, sponge
2	Surgicel Fibrillar	Ethicon, Johnson & Johnson, USA	Fibers of oxidized and reduced cellulose	Absorbable fibrous hemostatic material
3	Na-CMC	Laboratory of Experimental Surgery and Oncology of the Research Institute of Experimental Medicine of KSMU, AS RS LLC, Kaliningrad, Russia	1% Na-CMC gel	Sponge produced through lyophilic drying of suspension
4	Na-CMC + collagen (85/15)		1% Na-CMC gel 3% suspension of deep-sea squid collagen; 1% Na-CMC gel collagen/Na-CMC ratio, % by weight 15/85	Sponge produced through lyophilic drying of suspension
5	Na-CMC + collagen (75/25)		3% suspension of deep-sea squid collagen; 1% Na-CMC gel collagen/Na-CMC ratio, % by weight 25/75	Sponge produced through lyophilic drying of suspension
6	Na-CMC + collagen (50/50)		3% suspension of deep-sea squid collagen, 1% Na-CMC gel collagen/Na-CMC ratio, % by weight 50/50	Sponge produced through lyophilic drying of suspension

Table 2. Controlled MPSI performance indicators, Me [25;75]

№	Group name	Series 1: liver injury		Series 2: spleen injury	
		Bleeding time, s	Blood loss volume, *m2–m1*, g	Bleeding time, s	Blood loss volume, *m2–m1*, g
1	Tachocomb	93.5 [89.5; 104.75]	0.04 [0.03; 0.05]	105 [101.75; 109.75]	0.024 [0.019; 0.035]
2	Surgicel Fibrillar	85 [83.25; 96.5]	0.02 [0.021; 0.029]	95 [85.5; 101.5]	0.019 [0.017; 0.023]
3	Na-CMC	96 [60.25; 135]	0.019 [0.007; 0.038]	97.5 [85; 126.75]	0.016 [0.01; 0.027]
4	Na-CMC + collagen (85/15)	65 [35.25; 80]	0.006 [0.005; 0.012]	130 [120; 156.75]	0.03 [0.027; 0.033]
5	Na-CMC + collagen (75/25)	97 [80; 122.75]	0.025 [0.017; 0.028]	97 [80; 113.25]	0.015 [0.01; 0.021]
6	Na-CMC + collagen (50/50)	41 [40; 50]	0.01 [0.007; 0.012]	57 [41.25; 70]	0.014 [0.007; 0.024]

that group, the bleeding was stopped 2.3 faster than in group 1, where a collagen plate (commonly used in clinical practice) was used (Table 2, 3). We registered significant differences (twofold and greater) between almost all control groups and group 6, in which the MPSI was 50% collagen, the highest proportion. Group 4, where the MPSI was 15% collagen, also exhibited significant differences with control groups 1 and 2 (sponge plates common in clinical practice).

The bleeding time comparison data given above are supported by the blood loss volume values in the respective study groups (Tables 2, 4). Minimum blood loss was registered in group 6, maximum — in group 3 (MPSI without collagen).

Series 2 (spleen injury) also confirmed efficacy of the sponges developed at KSMU (Table 2, 5, 6). In group 6, the time of bleeding and the volume of blood loss was at least 1.5 times less than in other test groups. The former was significantly different between groups 4 and 6 (Table 5), the latter — significantly different generally (Table 6).

A noteworthy fact is the lack of differences between new MPSI from group 5 and common hemorrhage arresting products used in control groups. However, the blood loss value registered for the group 5 sample differed from that recorded for group 1. It should also be noted that we have also established significant differences among between test groups (both controlled indicators, series 1 and series 2 experiments).

DISCUSSION

There are numerous published papers that present assessments of MPSI based on collagen and cellulose derivatives (usually, oxidized cellulose) that have already been adopted in clinical practice and currently are a standard for comparison, like Tachocomb and Surgicel Fibrillar. Nevertheless, new MPSI are being intensively developed, because the demand for such products is high, and their users are not satisfied with what is commercially available currently [13, 14]. There are solid philosophies dedicated to the design of such medical commodities, each with a certain opinion regarding their composition. In most cases, foreign manufacturers with established reputation on the market of medical products base their MPSIs on animal collagen or fibers of oxidized and reduced cellulose, medical gelatin, etc. [15, 16].

Table 3. Statistical significance of differences, bleeding time, liver injury, *p*

Group name Group №		2	3	4	5	6
		Surgicel Fibrillar	Na-CMC	Na-CMC + collagen (85/15)	Na-CMC + collagen (75/25)	Na-CMC + collagen (50/50)
1	Tachocomb	0.211	0.879	0.037*	0.622522	0.0004*
2	Surgicel Fibrillar		0.791	0.049*	0.363262	0.001*
3	Na-CMC			0.13	1	0.004*
4	Na-CMC + collagen (85/15)				0.129	0.271
5	Na-CMC + collagen (75/25)					0.003*

Note: * — statistically significant differences ($p \leq 0.05$).

Table 4. Statistical significance of differences, blood loss volume, liver injury, *p*

Group name Group №		2	3	4	5	6
		Surgicel Fibrillar	Na-CMC	Na-CMC + collagen (85/15)	Na-CMC + collagen (75/25)	Na-CMC + collagen (50/50)
1	Tachocomb	0.001*	0.053	0.001*	0.003*	0.0002*
2	Surgicel Fibrillar		0.623	0.004*	0.85	0.0002*
3	Na-CMC			0.104	0.677	0.212
4	Na-CMC + collagen (85/15)				0.006	0.623
5	Na-CMC + collagen (75/25)					0.001*

Note: * — statistically significant differences ($p \leq 0.05$).

Table 5. Statistical significance of differences, bleeding time, spleen injury, *p*

Group name Group №		2	3	4	5	6
		Surgicel Fibrillar	Na-CMC	Na-CMC + collagen (85/15)	Na-CMC + collagen (75/25)	Na-CMC + collagen (50/50)
1	Tachocomb	0.064	0.307	0.002*	0.472	0.0002*
2	Surgicel Fibrillar		0.791	0.0005*	0.791	0.0008*
3	Na-CMC			0.045*	0.733	0.003*
4	Na-CMC + collagen (85/15)				0.006*	0.0002*
5	Na-CMC + collagen (75/25)					0.012*

Note: * — statistically significant differences ($p \leq 0.05$).

Table 6. Statistical significance of differences, blood loss volume, spleen injury, *p*

Group name Group №		2	3	4	5	6
		Surgicel Fibrillar	Na-CMC	Na-CMC + collagen (85/15)	Na-CMC + collagen (75/25)	Na-CMC + collagen (50/50)
1	Tachocomb	0.14	0.162	0.623	0.026*	0.054
2	Surgicel Fibrillar		0.623	0.028*	0.344	0.427
3	Na-CMC			0.121	0.571	0.678
4	Na-CMC + collagen (85/15)				0.011*	0.017*
5	Na-CMC + collagen (75/25)					0.791

Note: * — statistically significant differences ($p \leq 0.05$).

Authors of this study accumulated data from the experiments designed to assess properties of MPSI based on marine collagen (publications describing it in this capacity are not freely available) and Na-CMC, which is known to prevent commissures, adhere well and have a pronounced hemostatic effect [17, 18].

Considering the acquired data, we can conclude that effectiveness of an MPSI grows together with concentration of collagen therein, which translates into shorter bleeding time and smaller blood loss. Collagen's hemostatic action has been studied sufficiently; it is assumed to trigger coagulation and blood clot formation. The results of our study confirm veracity of this statement for products based on collagen derived from deep-sea squid. Marine collagen has a number of advantages, including low immunogenicity, which reduces the risk of anaphylactic reactions (possible in case of products based on animal collagen), and high hemostatic efficacy that, in a respective MPSI, is boosted by the porous structure of Na-CMC, which adsorbs the liquid component of blood and thus increases concentration of shaped elements in the sponge-injury contact area.

Such products can be made by national manufacturers of medical commodities; they require no expensive imported raw materials. Subsequent studies of these products (reaction of macroorganism tissues, intraoperative and *in vitro* manipulative properties of MPSI) will allow an assessment of the possibility and prospects of their introduction into the clinical practice of surgical departments.

CONCLUSIONS

The hypothesis tested in this work has the efficacy of MPSI growing due to the addition of collagen (including that of marine origin) to its composition. Based on the resulting data, we can state that the hypothesis was justified: blood loss and bleeding time values were significantly different between control groups and test groups that employed MPSI (six groups, six collagen/Na-CMC ratios). The results of this work are a valid substantiation of further comprehensive testing of the developed MPSIs.

References

1. Abri B, Vahdati SS, Paknezhad S, et al. Blunt abdominal trauma and organ damage and its prognosis. Journal of Analytical Research in Clinical Medicine. 2016; 4 (4): 228–32. Available from: https://doi.org/10.15171/jarcm.2016.038.
2. Chiara O, Cimbanassi S, Bellanova G, et al. A systematic review on the use of topical hemostats in trauma and emergency surgery. BMC Surgery. 2018; 18 (1): 68. Available from: https://doi.org/10.1186/s12893–018–0398-z.
3. Hickman DA, Pawlowski CL, Sekhon UDS, et al. Biomaterials and advanced technologies for hemostatic management of bleeding. Advanced materials. 2017; 30 (4): 1–73. Available from: https://doi.org/10.1002/adma.201700859 4.
4. Li X, Li YC, Chen M, et al. Chitosan/rectorite nanocomposite with injectable functionality for skin hemostasis. J Mater Chem B. 2018; 6 (41): 1–6. Available from: https://doi.org/10.1039/c8tb01085d.
5. Huang H, Chen H, Wang X, et al. Degradable and bioadhesive alginate-based composites: an effective hemostatic agent. ACS Biomater Sci Eng. 2019; 5 (10): 5498–505.
6. Biranje SS, Madiwale PV, Patankar KC, et al. Hemostasis and anti-necrotic activity of wound-healing dressing containing chitosan nanoparticles. Int J Biol Macromol. 2019; 121: 936–46.
7. Lipatov VA, Fronchek JeV, Grigorjan AJu, Severinov DA, Naimzada M, Zakutaeva LJu. Ocenka jeffektivnosti novyh obrazcov mestnyh krovoostanavlivajushhih sredstv na osnove hitozana posle rezekcii pecheni v jeksperimente. Rossijskij mediko-biologicheskij vestnik im. akademika I. P. Pavlova. 2023; 1 (31): 89–96. Dostupno po ssylke: https://doi.org/10.17816/PAVLOVJ108094. Russian.
8. Burkova NV, Kirichuk OP, Kuznecov SI. Analiz aktivacionnyh vozmozhnostej i gemoliticheskoj aktivnosti plenok hitozana pri ih

kontakte s kletochnymi jelementami venoznoj krovi cheloveka in vitro. Smolenskij medicinskij al'manah. 2018; 4: 207–10. Russian.
9. Ismailov BA, Sadykov RA, Kim OV. Gemostaticheskij implantat iz proizvodnyh celljulozy. Jeksperimental'naja i klinicheskaja gastrojenterologija. 2019; 9: 56–61. Dostupno po ssylke: https://doi.org/10.31146/1682-8658-ecg-169-9-56-61. Russian.
10. Savickij DS, Tkachenko AN. Patomorfologicheskoe izuchenie gemostaza pri travmah pecheni v jeksperimente. Profilakticheskaja i klinicheskaja medicina. 2019; 2 (71): 46–51. Russian.
11. Chen K, Wang F, Liu S, et al. In situ reduction of silver nanoparticles by sodium alginate to obtain silver-loaded composite wound dressing with enhanced mechanical and antimicrobial property. International Journal of Biological Macromolecules. 2020; 148: 501–09.
12. Charyev JuO, Askerov JeM, Ryzhova TS, Muravljanceva MM. Gemostaticheskie preparaty mestnogo dejstvija v sovremennoj hirurgicheskoj praktike. Tverskoj medicinskij zhurnal. 2022; 1: 31–41. Russian.
13. Lipatov VA, Gavriljuk VP, Severinov DA, Grigorjan AJu. Ocenka jeffektivnosti gemostaticheskih materialov v ostrom jeksperimente in vivo. Annaly hirurgicheskoj gepatologii. 2021; 26 (2): 137–43. https://doi.org/10.16931/10.16931/1995-5464.2021-2-137-143. Russian.
14. Zhu X, Wang J, Wu S, et al. Biological application of novel biodegradable cellulose composite as a hemostatic material. Mediators of Inflammation. 2022: 1–8. Available from: https://doi.org/10.1155/2022/4083477.
15. Zemljanoj A. B. Sredstvo mestnogo gemostaza — tekuchaja aktivnaja gemostaticheskaja matrica.Hirurgija. Zhurnal im. N. I. Pirogova. 2019; 5: 104–15. Available from: https://doi.org/10.17116/hirurgia2019051104. Russian.
16. Huang L, Liu GL, Kaye AD, et al. Advances in topical hemostatic agent therapies: a comprehensive update. Adv Ther. 2020; 37(10). 4132–4148. https://doi.org/10.1007/s12325-020-01467-y.
17. Alisherovich UK, Ugli KNB, Ugli KY, et al. Evaluation of the effectiveness of multi-stage surgical tactics in severe liver damage. ReFocus. 2023; 1 (2): 312–18. Available from: https://doi.org/10.5281/zenodo.7592933.
18. Tompeck AJ, Gajdhar AUR, Dowling M, et al. A comprehensive review of topical hemostatic agents: The good, the bad, and the novel. J Trauma Acute Care Surg. 2020; 88 (1): 1–21. Available from: https://doi.org/10.1097/TA.0000000000002508.

Литература

1. Abri B, Vahdati SS, Paknezhad S, et al. Blunt abdominal trauma and organ damage and its prognosis. Journal of Analytical Research in Clinical Medicine. 2016; 4 (4): 228–32. Available from: https://doi.org/10.15171/jarcm.2016.038.
2. Chiara O, Cimbanassi S, Bellanova G, et al. A systematic review on the use of topical hemostats in trauma and emergency surgery. BMC Surgery. 2018; 18 (1): 68. Available from: https://doi.org/10.1186/s12893–018–0398-z.
3. Hickman DA, Pawlowski CL, Sekhon UDS, et al. Biomaterials and advanced technologies for hemostatic management of bleeding. Advanced materials. 2017; 30 (4): 1–73. Available from: https://doi.org/10.1002/adma.201700859 4.
4. Li X, Li YC, Chen M, et al. Chitosan/rectorite nanocomposite with injectable functionality for skin hemostasis. J Mater Chem B. 2018; 6 (41): 1–6. Available from: https://doi.org/10.1039/c8tb01085d.
5. Huang H, Chen H, Wang X, et al. Degradable and bioadhesive alginate-based composites: an effective hemostatic agent. ACS Biomater Sci Eng. 2019; 5 (10): 5498–505.
6. Biranje SS, Madiwale PV, Patankar KC, et al. Hemostasis and anti-necrotic activity of wound-healing dressing containing chitosan nanoparticles. Int J Biol Macromol. 2019; 121: 936–46.
7. Липатов В. А., Фрончек Э. В., Григорьян А. Ю., Северинов Д. А., Наимзада М., Закутаева Л. Ю. Оценка эффективности новых образцов местных кровоостанавливающих средств на основе хитозана после резекции печени в эксперименте. Российский медико-биологический вестник им. академика И.П. Павлова. 2023; 1 (31): 89–96. Доступно по ссылке: https://doi.org/10.17816/PAVLOVJ108094.
8. Буркова Н. В., Киричук О. П., Кузнецов С. И. Анализ активационных возможностей и гемолитической активности пленок хитозана при их контакте с клеточными элементами венозной крови человека *in vitro*. Смоленский медицинский альманах. 2018; 4: 207–10.
9. Исмаилов Б. А., Садыков Р. А., Ким О.В. Гемостатический имплантат из производных целлюлозы. Экспериментальная и клиническая гастроэнтерология. 2019; 9: 56–61. Доступно по ссылке: https://doi.org/10.31146/1682-8658-ecg-169-9-56-61.
10. Савицкий Д. С., Ткаченко А. Н. Патоморфологическое изучение гемостаза при травмах печени в эксперименте. Профилактическая и клиническая медицина. 2019; 2 (71): 46–51.
11. Chen K, Wang F, Liu S, et al. In situ reduction of silver nanoparticles by sodium alginate to obtain silver-loaded composite wound dressing with enhanced mechanical and antimicrobial property. International Journal of Biological Macromolecules. 2020; 148: 501–09.
12. Чарыев Ю. О., Аскеров Э. М., Рыжова Т. С., Муравлянцева М. М. Гемостатические препараты местного действия в современной хирургической практике. Тверской медицинский журнал. 2022; 1: 31–41.
13. Липатов В. А., Гаврилюк В. П., Северинов Д. А., Григорьян А. Ю. Оценка эффективности гемостатических материалов в остром эксперименте in vivo. Анналы хирургической гепатологии. 2021; 26 (2): 137–43. https://doi.org/10.16931/10.16931/1995-5464.2021-2-137-143.
14. Zhu X, Wang J, Wu S, et al. Biological application of novel biodegradable cellulose composite as a hemostatic material. Mediators of Inflammation. 2022: 1–8. Available from: https://doi.org/10.1155/2022/4083477.
15. Земляной А. Б. Средство местного гемостаза — текучая активная гемостатическая матрица. Хирургия. Журнал им. Н. И. Пирогова. 2019; 5: 104–15. Available from: https://doi.org/10.17116/hirurgia2019051104.
16. Huang L, Liu GL, Kaye AD, et al. Advances in topical hemostatic agent therapies: a comprehensive update. Adv Ther. 2020; 37(10). 4132–4148. https://doi.org/10.1007/s12325-020-01467-y.
17. Alisherovich UK, Ugli KNB, Ugli KY, et al. Evaluation of the effectiveness of multi-stage surgical tactics in severe liver damage. ReFocus. 2023; 1 (2): 312–18. Available from: https://doi.org/10.5281/zenodo.7592933.
18. Tompeck AJ, Gajdhar AUR, Dowling M, et al. A comprehensive review of topical hemostatic agents: The good, the bad, and the novel. J Trauma Acute Care Surg. 2020; 88 (1): 1–21. Available from: https://doi.org/10.1097/TA.0000000000002508.