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Evaluation of the Safety and Efficacy of Chitosan-Based Hemostatic Sponges in a Chronic Large-Animal Model

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ABSTRACT

BACKGROUND: The development of agents aimed at achieving hemostasis in parenchymal organ bleeding remains one of the current challenges in medicine. Chitosan-based sponges are considered a promising approach to achieving effective hemostasis. The safety of these products was previously demonstrated in a 60-day experiment in rats.

AIM: To evaluate the efficacy and safety of chitosan-based hemostatic sponge samples in a standardized liver trauma model in pigs during a long-term experiment.

MATERIALS AND METHODS: The study was conducted in three same-sex pigs. A standardized model of intraperitoneal bleeding was created using laparoscopic access, followed by the application of a chitosan-based hemostatic sponge, which was left in the abdominal cavity for the entire duration of the experiment. The animals were observed for 60 days, during which general condition, body weight, and complete blood count were monitored. On day 30, repeat laparoscopy was performed to visually inspect the trauma site. At the end of the observation period, the animals were euthanized.

RESULTS: The hemostatic sponge provided complete hemostasis of parenchymal bleeding, with no recurrence of bleeding. No behavioral abnormalities were observed in animals throughout the entire experiment. Blood parameters remained within reference ranges. On day 30, repeat laparoscopy revealed adhesion formation and encapsulation of the hemostatic sponge in the peritoneal cavity. Histological examination of liver tissue on day 60 revealed an increased number of inflammatory cells at the site of contact with the hemostatic sponge. Maturation of granulomatous connective tissue in the liver was also observed, suggesting active wound healing.

CONCLUSION: The developed chitosan-based hemostatic sponge demonstrated both efficacy and biocompatibility, which allow it to remain in the abdominal cavity throughout medical evacuation. However, subsequent removal is recommended to prevent adhesion formation and potential peritoneal inflammation.

Keywords: biocompatibility; intraperitoneal bleeding; inflammatory response; hemostasis; chitosan lactate; topical hemostatic agent; liver trauma.

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Оценка безопасности и эффективности гемостатических губок на основе хитозана в хроническом эксперименте на крупных животных

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АННОТАЦИЯ

Актуальность. Одной из актуальных задач медицины остается разработка средств для остановки кровотечений из паренхиматозных органов. Для достижения эффективного гемостаза могут быть использованы губки на основе хитозана. Ранее безопасность данных изделий была подтверждена в 60-дневном эксперименте на крысах.

Цель исследования — определить эффективность и безопасность использования образцов гемостатических губок при стандартизированной травме печени у свиней в длительном эксперименте.

Материалы и методы. Исследование проводилось на трех однополых свиньях. Моделирование внутрибрюшного кровотечения с последующим применением гемостатического средства осуществлялось с помощью лапароскопического доступа. После применения губку оставляли в брюшной полости на все время эксперимента. Животные оставались под наблюдением в течение 60 сут. В этот период осуществлялся мониторинг общего состояния, массы тела, показателей общего анализа крови. Через 30 сут проводилась визуальная оценка места травмы путем выполнения повторной лапароскопии. По окончании периода наблюдения животных выводили из эксперимента.

Результаты. Гемостатическая губка обеспечила полную остановку паренхиматозного кровотечения, рецидива не установлено. Отклонений в поведении во время всего эксперимента у животных не выявлено. Отклонений в показателях крови животных не выявлено. Через 30 сут наблюдения при повторной лапароскопии выявлено образование спаек и инкапсулирование гемостатического материала в брюшной полости. По результатам микроскопического анализа гистологических срезов через 60 сут установлено повышенное количество воспалительных клеток в месте контакта губки с тканями печени. Также наблюдалось созревание гранулематозной соединительной ткани печени, что свидетельствует об активном заживлении раны.

Заключение. Разработанная гемостатическая губка обладает эффективностью и биосовместимостью, что позволяет оставлять ее в брюшной полости на все время медицинской эвакуации, однако в дальнейшем губка требует удаления из брюшной полости с целью предотвращения образования спаечного процесса и вероятного развития воспалительной реакции брюшины.

Ключевые слова: биосовместимость; внутрибрюшное кровотечение; воспалительная реакция; гемостаз; лактат хитозана; местное гемостатическое средство; травма печени.

Как цитировать
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BACKGROUND

The development of hemostatic agents for controlling bleeding during trauma and surgical interventions on parenchymal organs remains a relevant medical challenge. The liver is the most common source of intra-abdominal bleeding: its injury rate reaches 47% in blunt abdominal trauma and 86% in penetrating injuries. In such cases, mortality may reach 35% [1, 2]. Currently, the primary method for achieving hemostasis is liver wound suturing. Topical hemostatic agents (THAs) are used in <10% of cases, including in combination with suturing [3].

The limited use of THAs is associated with potential adverse reactions caused by biodegradation of medical product over time and with their relatively low efficacy [4]. At present, the market is dominated by hemostatic sponges based on collagen or gelatin, such as TachoComb (Takeda, Austria), and the collagen-based hemostatic sponge (Zelenaya Dubrava LLC, Russia). This is due to the complete biodegradability of these polymers in the body within approximately 1 month. Nevertheless, the hemostatic efficacy of such sponges is inferior to that of other biopolymers, particularly chitosan, which is a biocompatible and biodegradable compound with mucoadhesive properties [5].

Chitosan is a naturally occurring cationic polysaccharide derived from chitin through acetylation. It contains a positively charged amino group that electrostatically interacts with anions on the surface of erythrocytes, resulting in their aggregation on the surface of the biopolymer and formation of "pseudothrombi," which contribute to rapid hemostasis [6]. Chitosan exhibits four mechanisms that ensure rapid bleeding control: erythrocyte aggregation, platelet stimulation, contact activation of the coagulation cascade, and high sorption capacity [7–9]. The synergistic action of these mechanisms enables external bleeding arrest using chitosan, even during hypocoagulable conditions—a common complication of massive blood loss in extreme situations. Based on this biopolymer and its derivatives, various THAs for external arterial bleeding control have been developed and successfully applied, including GemoHit, Hemoflex, Hepoglos, Ellarga, HemoSpas Bio, and Absorba (Russia); Celox Gauze and Celox Rapid (UK); and ChitoGauze and ChitoSAM 100 (USA).

Thus, chitosan-based hemostatic sponges can be effectively used to control intensive (>10 mL/min) parenchymal bleeding, and THAs can be left in the abdominal cavity throughout medical evacuation (from the moment of urgent qualified care to definitive surgical treatment) within the framework of multistage surgical care [10, 11].

In a previous study on the safety of these hemostatic sponges in rats, a dry fragment of the material was intraperitoneally introduced in an amount significantly exceeding the recommended clinical dosage [12]. The observation period lasted 60 days, with a subset of animals euthanized at 30 days. Throughout the experiment, the hemostatic agent demonstrated partial biodegradation in approximately 30% of animals. No complications and animal deaths were noted, indicating the biocompatibility of the medical product.

This study aimed to evaluate the efficacy and safety of experimental chitosan-based hemostatic sponges in a standardized liver trauma model of large animals during a long-term experiment.

METHODS

A method for producing a chitosan derivative with high sorption capacity for water and whole blood had been developed [13]. Using this material, highly porous hemostatic sponges were fabricated by freeze-drying. The resulting medical products were sterilized by radiation and used in this large-animal experiment.

The study was conducted on three Landrace pigs (male) with a mean body weight of 27.6 [27.5; 28.9] kg. During preparation, the animals were fasted for 24 h while maintaining free access to water. On the day of surgery, prior to transportation from the animal facility to the experimental operating room, pharmacological immobilization was achieved by intramuscular injection of 10 mg/kg of tiletamine and zolazepam (Zoletil® 100).

The animal was fixed supine on the surgical table with limbs extended, and endotracheal intubation was performed to facilitate mechanical ventilation. Throughout the experiment, intermittent positive pressure ventilation was maintained using a veterinary anesthesia ventilator TH1 (A) (China) at 12–15 breaths per minute, with inhalation of an oxygen-enriched air mixture (minimum: 30 vol% oxygen) provided by an Armed 7F5L oxygen concentrator. Initially, 5% of the total dose of isoflurane was used, followed by 2%–4% for maintenance, delivered using an Eagle 2000 veterinary anesthesia vaporizer.

The internal bleeding model was created as follows. Under ultrasound guidance (digital diagnostic ultrasound system S6Pro), the right femoral vein was catheterized using a 5 Fr introducer. Controlled blood withdrawal was conducted using a Hema plasmapheresis device in an amount equivalent to 30% of the estimated circulating blood volume (CBV) (6.5% of the animal's body weight). Volume replacement was carried out using 0.9% sodium chloride solution at a 1:1 ratio to the volume of blood withdrawn.

Using the KST-EH 01 endosurgical field kit, laparoscopic access to the diaphragmatic surface of the right hepatic lobe was obtained. Furthermore, a round liver

defect 30 mm in diameter and 10 mm deep was created using surgical scissors to simulate ongoing parenchymal bleeding. The midline incision was extended to 20 mm. Under video assistance, spilled blood and clots were aspirated, and the experimental THA sample was applied to the liver wound using forceps, fully covering the defect, followed by instrumental compression. Visual assessment was employed to confirm achievement of hemostasis. The abdominal cavity was closed in layers. After recovery from anesthesia, the animal was observed according to the study protocol. During postoperative days 1–5, ceftriaxone was administered intramuscularly at 1.0 g once daily to prevent surgical infection.

The animals were monitored for 60 days after modeling of internal bleeding and application of THAs. Observations included the general condition, body weight gain, and changes in complete blood count, biochemical profile, and coagulation panel. Laboratory tests were performed using the Mindray BC30 Vet hematology analyzer, Skyla VB1 veterinary biochemical analyzer, and two-channel hemostasis analyzer APG 2-02-P. Blood samples for laboratory monitoring were collected by puncture of the superficial jugular vein before surgery and on days 1, 4, 10, 20, 30, 40, 50, and 60. Complete blood count included blood cell content, hemoglobin concentration, hematocrit, granulocyte, and lymphocyte levels. The concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, urea, glucose, and total protein in the blood of the experimental animals were monitored. Coagulation parameters (i.e., activated partial thromboplastin time [aPTT], prothrombin time [PT], and prothrombin index [PTI]) were assessed before surgery and on postoperative days 1 and 4.

On postoperative day 30, all experimental animals underwent diagnostic laparoscopy of the abdomen to assess changes in the experimental liver wound region.

On postoperative day 60, the animals were euthanized by intracardiac injection of 10% potassium chloride under prior general anesthesia. Then, necropsy was performed, during which the local condition was evaluated macroscopically, and tissue samples were collected for subsequent morphological examination.

Observation data were recorded in individual animal monitoring sheets.

For histological analysis, tissue samples were incubated in 10% buffered neutral formalin, embedded in paraffin, and sectioned into 5 μm slices, followed by hematoxylin and eosin staining using standard protocol. Microscopic images of the slides were captured using a CX41 microscope.

RESULTS AND DISCUSSION

A shock-inducing model of intraperitoneal bleeding from a traumatic liver wound with acute blood loss up to 30% of CBV was used. The simulated grade II traumatic shock was managed in all experimental animals by intravenous infusion of normal saline, and stable hemostasis was achieved by applying the experimental chitosan-based hemostatic sponge to the liver wound. No animal deaths occurred during surgery and throughout the postoperative observation period. No recurrent bleeding was observed after recovery from anesthesia or during postoperative day 1.

The general condition of the animals was assessed as moderate on postoperative day 1, based on signs of lethargy, low mobility, and refusal to eat. On subsequent days and throughout the follow-up period, the animals were active, willingly consumed food and water, and showed no signs of disrupted physiological functions. Body weight increased by 44% over the 60-day period, from 27.6 [27.5; 28.9] kg to 39.8 [38.3; 41.9] kg.

Before surgery (day 0), all the animals demonstrated normal blood parameters. On the day after laparoscopy, decreased hemoglobin and hematocrit concentrations as a result of blood loss were observed (Fig. 1). On day 10 and thereafter, all parameters returned to normal values. Increased leukocyte count was observed in only one animal during the first 20 days post-experiment.

The biochemical parameters of the peripheral blood were monitored throughout the experiment. Total bilirubin, creatinine, urea, glucose, and total protein levels remained within normal ranges in all animals during the 60-day observation period. On day 1 after the start of the experiment, increased levels of ALT and AST were noted in all animals, ranging from 58–68 U/L and 80–97 U/L, respectively (normal reference values: 31–58 U/L and 32–84 U/L, respectively). On observation day 4, these values had returned to within normal limits. No significant differences were found in the coagulation parameters (aPTT, PT, and PTI) before and after the surgical procedure.

On postoperative day 30, repeat laparoscopy was performed to assess the injury site. Adhesion formation and encapsulation of the hemostatic material at the trauma site were recorded. The remaining abdominal organs and peritoneum appeared normal.

On postoperative day 60, laparotomy was conducted, followed by euthanasia. The encapsulated material was found between the liver injury site and peritoneum (Fig. 2). The volume of this material was slightly smaller than that of the material originally placed into the abdominal cavity to achieve hemostasis, indicating a low biodegradation rate.

Microscopic evaluation of the histological sections revealed a broad layer of mature granulation connective tissue with a surrounding lymphocytic infiltrative rim adjacent to the hemostatic sponge. The granulation tissue, which was rich in blood vessels and inflammatory cells, was densely infiltrated by leukocytes and multinucleated

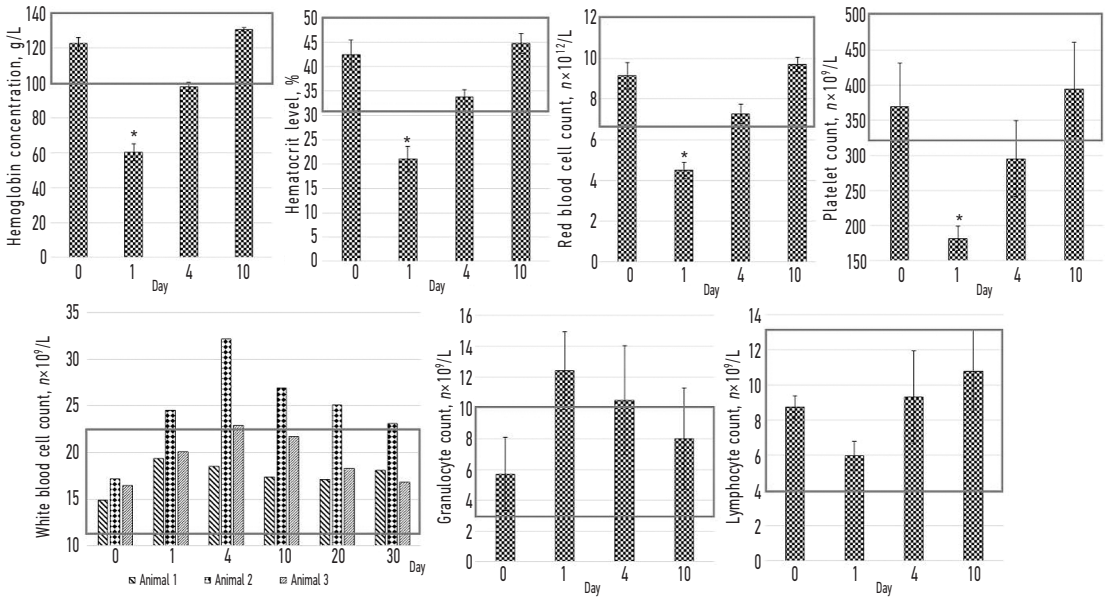

Fig. 1. Complete blood count results, **p* <0.05 compared to normal values.
Рис. 1. Результаты общего анализа крови; **p* <0,05 по сравнению с показателем нормы.

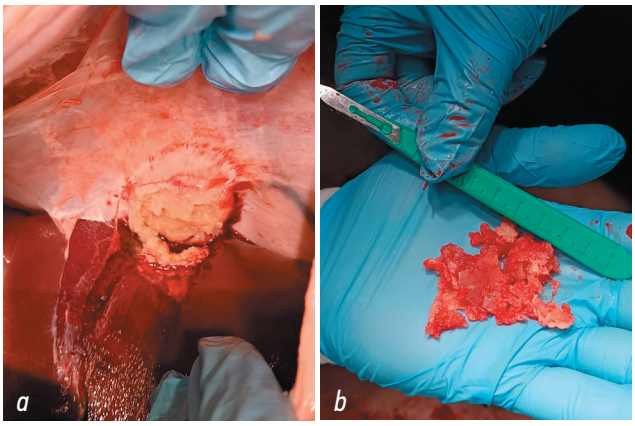

Fig. 2. Macroscopic appearance of the hemostatic sponge on day 60: *a*, hemostatic sponge on the liver wound after adhesiolysis; *b*, removed hemostatic sponge.
Рис. 2. Внешний вид гемостатической губки через 60 сут: *a* — материал на ране печени после разрезания спайки; *b* — извлеченный материал гемостатической губки.

giant macrophages forming foreign body granulomas (Fig. 3). Furthermore, microscopic findings indicate active maturation of granulomatous connective tissue adjacent to the liver at the site of contact with the chitosan-based hemostatic sponge.

The liver injury model is widely used to assess the hemostatic efficacy of medical products based on polymers capable of arresting bleeding [14, 15]. However, most chitosan-based sponges, films, and other formulations have been developed for external use. Moreover, such studies are often limited to 30-day observation periods [16]. Similar studies assessing the efficacy and safety of such prototype medical products using laparoscopy are scarce. The present study identified only a few scientific publications related to the use of chitosan-based hemostatic formulations for parenchymal bleeding control.

In one study, the long-term safety and efficacy of a chitosan-based hemostatic dressing were evaluated in a laparoscopic partial nephrectomy model in pigs [17]. The high efficacy of the material was confirmed; however, higher levels of inflammation parameters were observed compared with the use of a composite hemostatic formulation based on oxidized cellulose and blood proteins (Surgicel® and Tisseel®). The chitosan-based material remained in the body for 12 months and caused local inflammation. However, no physiological abnormalities nor clinically significant symptoms were observed.

To enhance biodegradation, chitosan is subjected to chemical modifications, which allow adjustment of its physicochemical and biochemical properties [18, 19]. For example, a thermosensitive hydroxybutyl chitosan

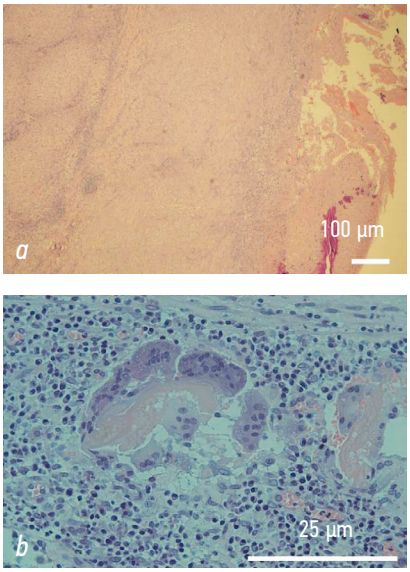

Fig. 3. Liver tissue morphology on day 60 after hemostasis using a chitosan lactate–based hemostatic sponge (hematoxylin and eosin staining): *a*, interface between the sponge and liver tissue; *b*, cellular infiltration in granulation tissue.
Рис. 3. Морфология тканей печени через 60 сут после остановки кровотечения с помощью гемостатической губки на основе лактата хитозана, окрашивание гематоксилином и эозином: *a* — граница взаимодействия губки и тканей печени; *b* — скопление клеток в грануляционной ткани.

derivative was developed to prevent postoperative abdominal cavity adhesions. This chitosan derivative was shown to be effective in adhesion prevention in a rat model of lateral cecal wall defect [20].

In the present study, a prototype based on a water-soluble chitosan salt was used. The hemostatic efficacy of the sponge was confirmed in a laparoscopic intervention model of large laboratory animals. After recovery from anesthesia, the animals showed high locomotor activity and fully recovered from surgery within 2 days. No bleeding recurrence was observed. Accordingly, the chitosan lactate-based sponge ensured stable hemostasis. However, biodegradation of the product was not observed, as the material remained in the abdominal cavity at 60 days. Nevertheless, sponge presence in the peritoneal cavity was safe for the animals and did not induce toxicological effects. Thus, the results support existing data on the potential use of chitosan-based biomaterials in abdominal surgical procedures.

CONCLUSION

The developed chitosan lactate-based hemostatic sponge is capable of arresting intense parenchymal bleeding and may be left in the abdominal cavity for a short period, for example, during casualty evacuation. The material used is biocompatible and does not cause clinically significant adverse reactions. However, the use of a water-soluble chitosan salt does not result in a substantial increase in the biodegradation rate of the material. Therefore, the sponge should be removed after use. Further experiments are required to determine the maximum period before medical product removal from the abdominal cavity becomes crucial.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: A.B. Yudin, editing the manuscript, observing animals; A.M. Nosov, drafting a study plan, analysis of the obtained data; M.V. Volkova, developing and preparing samples, manuscript writing; K.N. Demchenko, observation of animals during the experiment; A.V. Zhabin, implementing the operational regime for animals; D.A. Zaychikov, conducting morphological studies; N.Yu. Andreev, assisting at the start of operations; Ya.B. Kovalevsky, development and provision of samples.
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Competing interests. The authors declare that they have no competing interests. (The search and analytical work was carried out at the personal expense of the author's team.)
Consent for publication. Written consent was obtained from the patients for publication of relevant medical information within the manuscript.
Ethical expertise. The study was approved by the local ethics committee of the S.M. Kirov Military Medical Academy of the Ministry of Defense of the Russian Federation (protocol No. 279 from June, 27, 2023).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования. (Поисково-аналитическая работа проведена на личные средства авторского коллектива.)

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