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A New Composite Hemostatic Plate in Parenchymal Organ Surgery

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Abstract **The aim** of the study was to improve the results of stopping parenchymal bleeding in abdominal surgery by developing and clinically evaluating the efficiency of a new domestic composite hemostatic plate. The article presents the experimental and histomorphological studies results of the use of composite hemostatic plate. A pronounced hemostatic property of the plate in the vessels in the wound area was proved by the results of the study. Due to the fact that inflammatory reactions in the wound area are predominantly proliferative in nature, hemostasis plate restores the histoarchitectonics of wound tissue in the wound area in the early stages and prevents rough scarring due to the lack of a response to foreign bodies, prevents the occurrence of complications.

Keywords Parenchymal organ, Bleeding, Hemostatic plate

1. Introduction

Bleeding and hemorrhagic shock are the cause for 30-40% of traumatic deaths. Besides, perioperative and examination-related procedures may lead to a risk of bleeding [8,10]. Electrocoagulation, argon, microwave, laser and radiofrequency coagulation, contact infrared radiation, ultrasonic, harmonic, jet scalpels, plasma streams, radiofrequency ablation are used among the physical methods of hemostasis in surgery of parenchymal organs. Achieving a hemostatic effect by physical methods of influencing the wound surface and bleeding vessels of the parenchyma is rational mainly with its shallow and superficial injuries [6]. An increase in exposure and energy exposure is required to stop bleeding from parenchymal vessels with a diameter of more than 1.0 mm, which inevitably leads to the injury of the organ stromal elements and increases the area of parenchymal necrosis to a depth of 4-8 mm, and the coagulation scab formed in this case often serves as a substrate for infection and recurrence of bleeding [7]. Physical methods of hemostasis during surgeries on parenchymal organs do not meet the requirements of the "ideal method", which should be accompanied by minimal blood loss or its absence, minimal necrosis of the parenchyma and a reduction of the suregry time [4].

A study of surgeons' opinion conducted by Bondarev et al. (2020) on the use of local hemostatic agents showed that 30% of 135 doctors of various surgical specialties resorted to hemostatic sutures and 27% used local hemostatics, splenectomy was performed in 13%, electrocoagulation in 18% [2].

Particular attention is paid to issues related to indications for the use of local hemostatic agents. According to 50% of respondents, local remedies were used as the main method of stopping bleeding in case of parenchymal organ injury of the first degree. In cases of injuries of I-III-degree, local hemostatics can be used as an additional method of stopping bleeding. At the same time, 42% of surgeons believe that hemostatic suture should be covered with hemostatic material from above after its application; 26% placed the implant under the suture, and then tied a knot on it; 10% believe that it is necessary to place a hemostatic in the wound, and 22% of respondents believe that it makes no sense to combine the use of a local hemostatic agent with a hemostatic suture of a parenchymal organ.

The final part of the questionnaire was devoted to assessing the opinion of surgeons on what should be the ideal local hemostatic agent. Как показал опрос, 95% of respondents believe that the hemostatic material should have such properties as antibacterial activity, non-pyrogenicity 60.9%, high adhesive ability 58.6%, biodegradation within 5-10 days after implantation 36.1%, hemostatic effect within 2 min after application 60%, 5-10 min 27%. At the same time, 84% of respondents believe that the speed of stopping bleeding is not significant, the main thing is the reliability of stopping bleeding [2].

The use of hemostatic agents is essential to prevent serious bleeding and death from excessive bleeding during surgery or in emergency situations. Cellulose oxide is an excellent biodegradable and biocompatible derivative of cellulose and has become one of the most important hemostatic agents used in surgical procedures. There is still no comprehensive

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report on the evaluation of cellulose-based hemostatic substances, although the preparation for oxidation, the origin and structure of cellulose, as well as the biodegradability and safety of cellulose oxide have been considered. Hemostatic mechanisms of various forms, variations and currently commercially available cellulose products are comprehensively discussed, which highlights the most important development in the recent scientific literature [1,3,5,9,11].

The aim of the study was to improve the results of stopping parenchymal bleeding in abdominal surgery by developing and clinically evaluating the efficiency of a new domestic composite hemostatic plate.

2. Material and Methods

In previous studies, the entire range of necessary preclinical researches was carried out in the experimental department of the Republican Specialized Scientific and Practical Medical Center of Surgery named after V. V.Vakhidov, the results of which allowed to substantiate the hemostatic efficiency of the new domestic implant in the form of a plate, taking into account the determination of the basic physical and chemical properties and the proven absence of toxic effects (according to the requirements for conducting studies of similar composite materials). The optimal composition of a biodegradable hemostatic plate was developed and experimental studies were conducted on small experimental animals (rats). This article presents the results of the second series of experimental studies on large animals (dogs, pigs).

The results of experimental and morphological studies allowed to obtain the permission of the Ethics Committee to conduct the first clinical trial, followed by the preparation of all necessary documentation for the registration of a new domestic hemostatic implant in the Pharmaceutical Committee of the Republic of Uzbekistan with the possibility of subsequent serial production.

This study was conducted to evaluate the hemostatic effect of the new plate coating on large-sized liver defects (experimental liver injury in large animals). This will allow us to determine the efficiency of the claimed properties of the implant in extensive areas of parenchymal bleeding. Hemostatic efficacy in spleen injuries was also additionally studied.

Currently, the evaluation of the medicines' efficiency and in particular, hemostatic agents, is carried out on small laboratory animals. These experiments are easy to model, low-cost and allow to trace the dynamics of the pathological process and evaluate the efficacy of treatment. However, in real conditions it is impossible to fully reflect the peculiarity of hemostasis which takes place in clinical practice. In this regard, for the development of recommendations and a real assessment of the efficacy of hemostatic agents, the most adequate model is an experiment on large experimental animals. Mongrel dogs are used for this purpose, as well as recently mini pigs. The mini-pig is an ideal model for evaluating the efficiency of hemostatic drugs, since they correspond to a human in many functional and anatomical parameters.

The objective of these studies was to develop a model of parenchymal bleeding in large animals (dogs, pigs), as well as to evaluate the efficiency of the domestic coating – composite plate.

Course of the surgery: Hemostasis in case of liver injury. After removing the coat from the anterior abdominal wall, an upper-middle-median laparotomy was performed. After dilution of the wound edges with a retractor, the right lobe of the liver was removed into the surgical field (Fig. 1). Using an abdominal scalpel, the liver parenchyma up to 3x4 cm in area was injured with the development of mixed bleeding (Fig. 2).

Figure 1. Simulation of liver injury in the experiment. The right lobe of the liver was brought into the wound

Figure 2. Liver wound formation

Subsequently, a hemostatic sponge (control) or a hemostatic plate (experiment) was applied to the wound surface of the liver and held until complete hemostasis. The reliability of hemostasis was assessed by monitoring the state of the wound for 30 minutes.

3. Results

Control. A hemostatic sponge made of bovine collagen manufactured by "Turon Silk Pharm" LLC is a porous plate of light-yellow color. To stop bleeding from the liver, its fragment 3x4 cm in size was used. After drying wound surface of the liver, the sponge was immediately applied and pressed against the wound (Fig. 3). The sponge was held by hand for 2 minutes. Subsequently, due to the lack of adhesive ability, the sponge was kept on the liver surface by tamponing with a gauze napkin (Fig. 4).

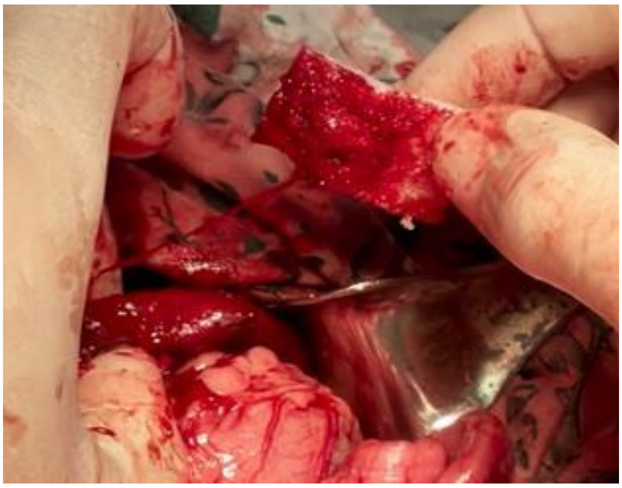


Figure 3. Partial hemostatic effect of collagen sponge

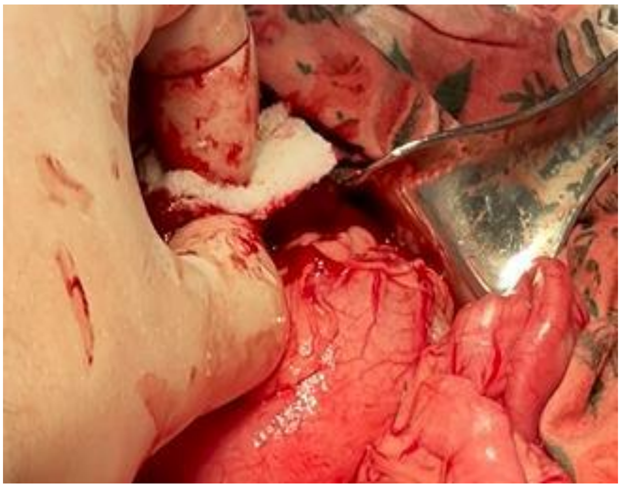


Figure 4. Hemostasis of the liver wound surface with a hemostatic sponge

The results of using a hemostatic sponge showed that even with a 5-minute exposure, only partial hemostasis from capillary vessels was achieved. While bleeding from small venous vessels continued. In 2 cases blood began to flow through a blood-soaked hemostatic sponge, which served as the basis for removing the sponge and applying another one. After repeated use of the sponge, hemostasis was achieved within 6 minutes. It should be noted that during a 30-minute observation, there was no dense adhesion of the sponge to the liver wound surface. This circumstance does not exclude the risk of resumption of bleeding at a later period.

The results of evaluating the efficiency of a hemostatic plate in bleeding from a liver wound (experiment). Modeling of a 3x4 cm planar liver wound was performed as described above. Bleeding was achieved, which had the character of mixed with copious impregnation of a gauze napkin. After drying the liver wound with a napkin, a 4x5cm hemostatic plate was immediately attached to it. During the contact of the plate with blood, it became more flexible and well in contact with the uneven wound surface (Fig. 5).

Figure 5. Experiment. The moment of applying the hemostatic plate to the wound surface of the liver

Figure 6. Experiment. An attempt to remove the hemostatic plate from the surface of the liver wound. The plate does not come off from the wound when pulled up with tweezers

After fixation for 30 seconds, adhesion to the wound surface occurred with a complete stop of bleeding. Over time, at least 30 minutes, the plate was a transparent coating resembling a Glisson capsule in character. The wound surface was viewed through the plate, which allowed to eliminate the risk of hematoma accumulation under the plate's surface (Fig. 6). Thus, the use of a hemostatic plate in case of liver injury allowed to achieve its complete adhesion to the wound surface with a complete stop of bleeding for a short time (0.5-1 minute). The effect of hemostasis was stable with minimizing the risk of recurrent hemorrhage.

Hemostasis in case of spleen injury. According to the experimental procedure, the spleen was removed into the laparotomic wound in mongrel dogs under anesthesia. Using an abdominal scalpel, the spleen parenchyma was injured with active mixed bleeding. Bleeding was of sufficient intensity, which did not tend to stop on its own or with the use of napkins (Fig. 7). When bleeding from the spleen wound was stopped in 4 experimental animals, it was noted that over time, within 5-10 minutes, in all cases, the sponge was completely soaked with blood, followed by blood seepage through the sponge (Fig. 8).

Figure 7. Simulation of the spleen injury. A planar wound of the spleen is formed using an abdominal scalpel

Figure 8. Control. The result after repeated application of the hemostatic sponge to the spleen wound surface. Final hemostasis was not achieved

In the experimental group, a planar wound of the spleen with active bleeding was similarly formed. A 5x5 cm hemostatic plate was cut out or hemostasis for hemostasis. After drying the accumulated blood on the spleen wound surface, a hemostatic plate was immediately applied and pressed with fingers for 30 seconds to 1 minute (Fig. 9).

Figure 9. The moment of applying the hemostatic plate to the spleen wound surface

Observation of the hemostasis stability for 30 minutes allowed us to establish the achievement of a complete hemostatic effect. The plate adhered well to the surface of the wound and was not detached with tweezers, the wound was visible through it, which allowsed to state the absence of a hematoma under the surface of the plate (Fig. 10).

Figure 10. Experiment. A complete adhesion of the hemostatic plate to the spleen wound surface with final hemostasis was after 30 minutes

The morphological evaluation of the materials obtained during our experiment compared the condition of the vessels in the area of contact with the polycomposite hemostatic plate (PHP) or sinusoidal vessels in the liver parenchyma, the interaction of hemostatic materials with the wound and the inflammatory reaction. From the 1st day of the experiment, signs of necrobiotic processes with an alterative effect in the area of liver tissue significantly prevailed in the field of exposure to polycomposite hemostatic plate. But a characteristic feature is that in the sinusoidal veins of the sinuses in contact with the polycomposite hemostatic plate (PHP), the microthrombotic elements of the vessels are filled with sludge, and around these vessels the diapedesis of erythrocytes, lymphocytic (mainly eosinophilic) infiltrates began to appear (Fig. 11).

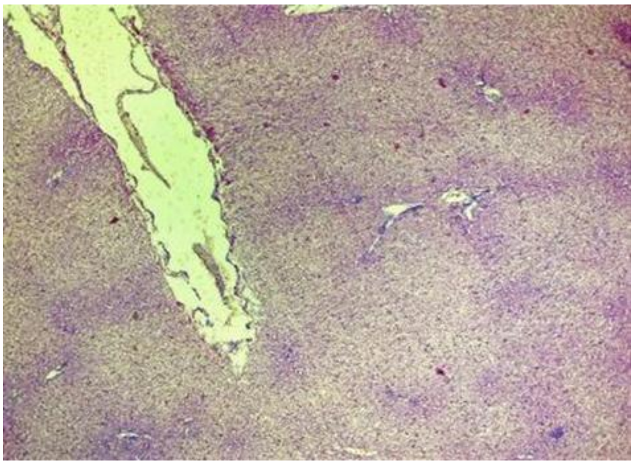


Figure 11. Experimental liver injury and the field of action of the hemostatic plate. The predominance of alteration and inflammation stage, edema in the tissue. The 1st day of the experiment. CM. Stain with H-E x200

On the 3rd day of the experiment, it was found that the inflammatory process decreased in the area of PHP exposure, hematopoietic elements, especially erythrocytes, were in a state of stasis and sludge in most vessels and almost all vessels of the sinusoidal type. Blood clots were found around and inside some large vessels in the area of contact with PHP (Fig. 12).

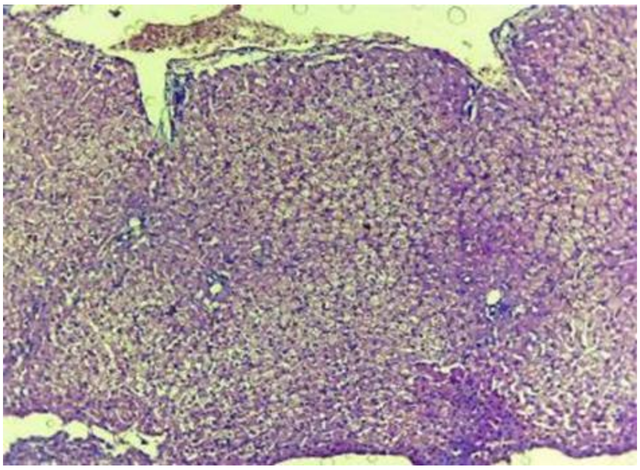


Figure 12. Liver with a contact zone of PHP exposure. Stasis and sludge-state of red blood cells. Blood clots in the PHP area. The 3rd day of experience. CM. Stain with H-E x100

By the 14^{th} day of the experiment, in the area of liver contact with PHP, microscopic examination revealed a response with unexpressed elements of cellular inflammation, a rare macrophage reaction, minimal capillary proliferation, and the formation of a moderate fibrous layer of connective tissue. Fat infiltration was not observed (Fig. 13).

On the 21^{st} and 30^{th} days of the experiment, the experimental animals were histologically noted an increase in the regenerative process in the parenchyma in the area of contact with injured liver tissue and PHP, especially in the area of injury, which indicated the restoration of the beam structure of the liver, the disappearance of edema and fullness, a decrease in the thickness of the fibrous layer of the liver. Минимальная клеточно-воспалительная и тканевая реакция на PHP. PHP implant marks were determined (Fig. 14).

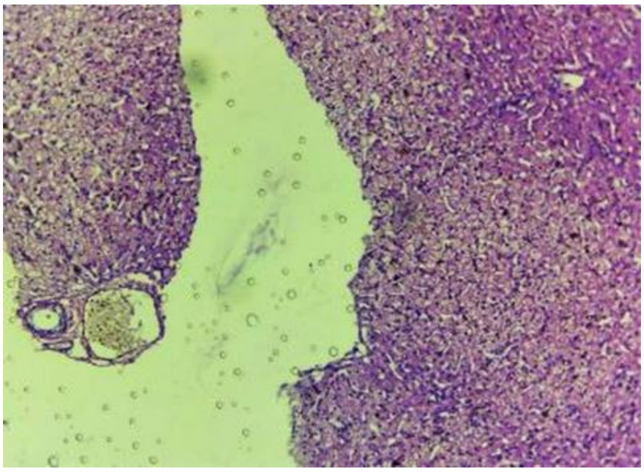


Figure 13. The area of contact of the liver with PHP. Weak macrophage reaction. Proliferation of a small number of capillary vessels. Sludges of hematopoietic elements in the vessels. The 14th day of experience. CM. Stain with H-E x100

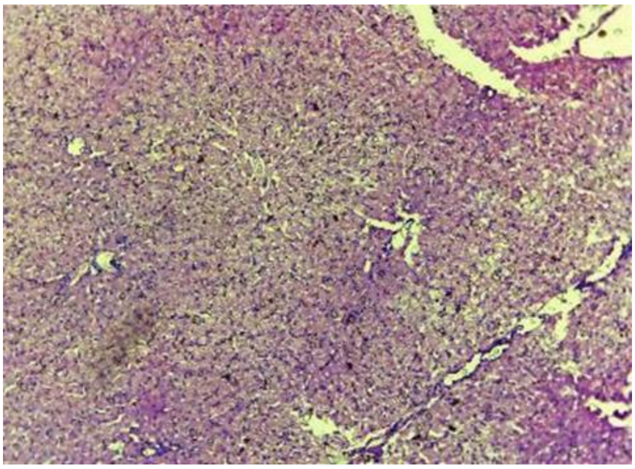
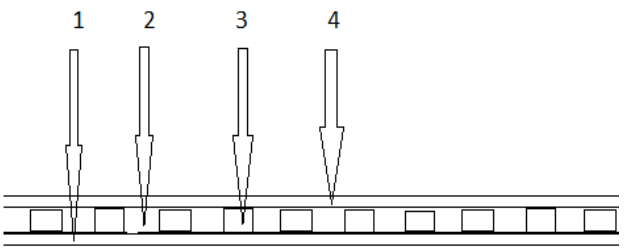


Figure 14. Control. 30 days. Fragments of stacks of oxidized cellulose are encapsulated. The fibers are indistinguishable. CM. Stain with H-E x100

On the 21-30th day after implantation of the plate on the surface of the liver, the experimental animals were practically healthy. During euthanasia, complete wound healing was established. There were no pathological changes in the abdominal cavity. The liver was not enlarged. The surface was smooth. The wound has healed. In the region of the edge of the liver a site of limited fibrosis was determined, which was connected with the surrounding tissues and the omentum by thin adhesive cords. When dissecting the fibrosis site, the remnants and fragments of the mesh were not detected, which confirms the biodegradation property of the implant.

The experimental studies carried out made it possible to develop the first domestic composite hemostatic plate for use in surgery of parenchymal organs, which includes several layers based on biologically absorbable polymer derivatives (cellulose, viscose and calcium), the combination of which ensures the local hemostatic efficiency of the implant. The hemostatic preparation in the form of a finely dispersed powder is made from water-soluble cellulose derivatives and has the ability to induce hemostasis within a few seconds, has the ability to actively absorb moisture, and has a high adhesive ability to wet tissues. Collagen plate is made from purified medical grade collagen and has weak antigenic properties. The film has a weak adhesive ability and therefore does not stick to the hands of the surgeon during use. It has the property of biodegradation within 3-4 weeks.

At active bleeding from the surface of the parenchymal organ, at first, with the help of available methods (coagulation, stitching), active arterial bleeding from large vessels is stopped. Subsequently, the surface of the organ is drained and with continued bleeding from small venous and capillary vessels, a hemostatic plate is applied to the wound surface with an active layer and is hold for 1-2 minutes. The degree of compression corresponds to the pressure in the bleeding vessel. Due to the high adhesion of the powder to the wet surface of the tissues, no additional actions are required to fix the plate.



Note: *1 - the inner (in contact with the wound) plate layer is up to 100 microns thick. It provides high adhesion to the wet wound surface, and also protects against the scattering of powdered hemostatic; 2 - a plate with a high hemostatic effect, prepared from cellulose derivatives, which provides local hemostasis by tightly closing with the first layer and the wound surface, provides tensile strength and holds the desired shape of the structure. It has perforating holes with a diameter of up to 2 mm and a depth of up to 400-800 microns; 3 - perforating holes in the plate filled with hemostatic powder from cellulose derivatives which has the ability to absorb the liquid part of the blood and form a dense thrombus within 1-2 minutes; 4 - the outer plate made from collagen with a thickness of up to 100 microns. It provides high tensile strength of the plate, protects the fingers of surgeon from sticking to the plate, protects the active layer of the plate from moisture and enzymes of the body, providing a prolonged effect.*

Figure 15. Schematic structure of a composite plate for hemostasis and tissue strengthening

According to the results of the experimental study and comparative data, it can be concluded that the proposed method of hemostatic therapy contributes to a significant acceleration of the healing of liver tissue in the experimental group, and ensures complete wound regeneration. An application for a patent for a utility model of this development has been filed to the Agency for Intellectual Property under the Ministry of Justice of the Republic of Uzbekistan "Composite hemostatic plate for the use in surgery of parenchymal organs" FAP No. 0337 dated by September 23, 2022.

4. Conclusions

The conducted experimental studies allowed to develop the first domestic composite hemostatic plate for the use in parenchymal organs surgery, which includes several layers based on biologically absorbable polymer derivatives (cellulose, viscose and calcium), the combination of which provides local hemostatic efficiency of the implant.

Due to its properties, the use of a composite hemostatic plate in the wound area causes rapid histoarchitectonic remodeling of tissues in the area of contact with the organ.

The plate after topical application does not cause a strong tissue and response reaction as a foreign body, which makes it biocompatible.

Ca^{2+} ions in the polycomposite structure of the implant have a direct and indirect effect on the blood clotting process, which in turn provides a stable hemostatic property on the wound surface.

The authors declare no conflict of interest.

This study does not include the involvement of any budgetary, grant or other funds.

The article is published for the first time and is part of a scientific work.

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