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Evaluation of Hemostatic Efficacy of Hemoben Gel in Ruptures Of The Gastric Mucosa in An Experiment

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ABSTRACT

The objective of these studies was to experimentally evaluate the possibility of introducing Hemoben gel into the submucosal layer of the stomach with justification for its use in case of rupture of the gastric mucosa at the border of the transition to the esophagus. It was found that for injection using needle injectors, it is sufficient to prepare 2% gel before the procedure by diluting Hemoben powder in saline solution. Experimental morphological studies have shown that no pathological changes in the stomach wall were detected at various observation periods. From the second day after the operation, the mucosal roller formed by the introduction of the gel was no longer determined. Observation for 7 days revealed no signs of necrosis or inflammation of the mucosa after administration of Hemoben gel. In turn, due to its high adhesive properties, the gel provided gluing of the edges of the defect and accelerated regeneration processes with the beginning of proliferation on the 3rd day of the experiment with complete bio dehydration of the substance on the 5th-7th day.

***Key words**: syndrome (MWS) refers, degree and severity of blood loss depends*

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INTRODUCTION

Mallory-Weiss syndrome (MWS) refers to no transmural lacerations in the esophageal-gastric junction due to severe vomiting. The provoking factors of the development of this syndrome are multiple vomiting of various genesis [1]. The degree and severity of blood loss depends on the depth and extent of the rupture of the mucosa, as well as on concomitant diseases that cause coagulopathy. In most cases, bleeding associated with MWS is a benign and self-canceling process. Conservative treatment, including resuscitation and treatment with proton pump inhibitors (PPIs), is quite effective [2, 3]. Nevertheless, in 14-30% of MWS cases, conservative treatment is not enough to solve the problem and endoscopic treatment is necessary.

If the bleeding has already stopped during the endoscopy, further intervention is usually not required. In situations with ongoing active or recurrent bleeding, there are various methods of endoscopic treatment [4, 5]. Local injection of adrenaline (dilution from 1:10,000 to 1:20,000) stops bleeding due to vasoconstriction. Other options in such situations are multipolar electrocoagulation, sclerosant injection, argon plasma coagulation or endoscopic ligation. Surgical intervention is rarely required and is considered necessary after the ineffectiveness of endoscopic procedures [6-8].

Despite the above methods, the problem of long-term hemostasis and the risk of recurrent bleeding persist. This is why specialists are interested in continuing to develop various new techniques for local effects on the mucosa, which should provide both a stop of bleeding and a prolonged hemostatic effect [9, 10]. Taking into account the above, the main objective of this study was an experimental assessment of the hemostatic effect of submucosal administration of Hemoben gel.

MATERIALS AND METHODS

The research was carried out on the basis of the Laboratory of experimental Surgery of the Republican Specialized Scientific and Practical Medical Center for Surgery named after academician V. Vakhidov. The research objectives included the development of a model for the formation of a rupture of the mucous membrane of the esophageal-gastric junction with bleeding. Subsequently, the experiments were continued on white mongrel rats of both sexes to conduct a comparative assessment of the effectiveness of hemostasis from the area of damage to the mucous membrane of the esophageal-gastric junction in the

control and experimental study groups. In the third series of experiments, a new method of hemostasis for ruptures of the mucous zone of the cardio-esophageal junction was tested on mini pigs.

Experimental studies were conducted in compliance with the rules adopted by the European Convention for the Protection of Vertebrates Used for Experiments or Other Scientific Purposes (ETS N 123), Strasbourg, 03/18/1986.

Morphological studies using macro-photographs, as well as histological studies of mucosal biopsies at various times after the intervention were carried out to assess the reaction of tissues and the healing time of mucosal ruptures (Tables 1-2).

Table 1: Groups of experimental animals and terms of research

Rats	1 Day	3 Days	5 Days	7 Days	14 Days	21 Days	Total
Control	3	3	3	3	3	3	18
Experience	4	4	4	4	4	4	24
in total	7	7	7	7	7	7	42

Tab 2: Evaluation of the effectiveness of a new method of hemostasis in ruptures of the gastric mucosa in mini pigs

Mini pigs	1 Day	3 Days	5 Days	7 Days	14 Days	21 Days	Total
Control	2	2	2	2	2	2	2
Experience	3	3	3	3	3	3	2
Total	5	5	5	5	5	5	5

Experimental technique. Experimental evaluation of the harmlessness and safety of submucosal administration of Hemoben gel in various concentrations.

The course of the operation: in a rat under general anesthesia, the hair was cut from the anterior abdominal wall by injecting 0.5ml of ketamine solution. Upper-median laparotomy up to 3 cm long. The stomach is removed into the wound. Along the anterior stack of the stomach, closer to the esophageal-gastric junction, a puncture of the serous-muscular layer of the stomach was performed and Chamoe 0.2-0.3 ml gel was injected into the submucosal layer using a syringe with a needle for intramuscular injections in various concentrations: 2%, 3%, 5%. Higher concentrations of Hemoben gel were injected through the lumen of the needle impossible. In the control group of animals, 0.2-.0.3 ml of 0.001% epinephrine solution was similarly administered.

Experiments to evaluate the effectiveness of Hemoben in healing ruptures of the gastric mucosa. In the available literature, we were unable to find an experimental model of rupture of the mucous membrane of the esophageal-gastric junction. In this regard, we have developed our own methodology:

In a rat under general anesthesia, the hair was cut from the anterior abdominal wall by injecting 0.5ml of ketamine solution. Upper-median laparotomy up to 3 cm long. The stomach is removed into the wound. Dissection of the anterior wall of the stomach up to 1 cm long. Longitudinal dissection of the posterior wall of the gastric mucosa at the site of the gastro-esophageal junction was performed using vascular angle scissors. Bleeding from the vessels of the submucosal layer has been achieved. In the control series in animals, hemostasis was achieved by submucosal administration of epinephrine solution. In the experimental series of animals, hemostasis was carried out by submucosal administration of Hemoben gel. At the time of the study, the animals were removed from the experiment by overdosing on narcotic drugs. A macroscopic picture of the condition of the gastric mucosa was evaluated, and tissue pieces were taken for histological examination.

Methods of research on mini-pigs. In order to study the possibility of submucosal administration of Hemoben gel to stop bleeding from rupture of the gastric mucosa in large experimental animals. The method of the experiment. To perform the experiment, the animals were on a starvation diet for 2 days, while water was provided in unlimited quantities. Premedication was performed by intravenous administration of xylem solution at the rate of 0.5 ml per kg of animal weight. After reaching sedation, the animal was taken to the operating room. Mask anesthesia was carried out by sevoflurane vapors with oxygen supply at a pressure of 2atm. After achieving anesthesia sleep, a restrictive tube with a diameter of 2 cm was inserted into the oral cavity and fixed to the upper jaw. An Olympus endoscopic device with a diameter of 5 mm was inserted through the lumen of the tube to the stomach. After examining the gastric and esophageal mucosa and the absence of pathological changes, the experiment was started. Using biopsy forceps, ruptures of the gastric mucosa were made in the longitudinal direction at a distance of up to 5 cm. At the same time, a gaping gap lumen was achieved with active mixed bleeding from the vessels of the submucosal layer. Hemostasis was carried out by submucosal administration of epinephrine solution (control) and administration of Hemoben gel. In the following periods after the manipulation, repeated endoscopy was performed with taking pieces of mucosa for histological analysis.

Morphological studies. For light microscopy, the material was fixed in 10% neutral Lilly buffered formalin for at least 24 hours. After dehydration in alcohols of ascending concentration according to the generally accepted method, the material was poured into paraffin, sections 5-7 microns thick were stained with hematoxylin - eosin. The obtained results were subjected to statistical processing using the standard Microsoft Excel 2010 software package by the method of variational statistics with an assessment of the significance of the indicators (M ± m) and the differences in the samples under consideration according to the Student's t-criterion. The differences in the compared groups were considered significant at a significance level of 95% ($P<0.05$).

Results and their discussion. Taking into account the main task, the primary study was aimed at assessing the effect of Hemoben gel on the gastric mucosa in experimental animals. It was found that for injection using needle injectors, it is sufficient to prepare 2% gel by diluting Hemoben powder in saline solution. At the beginning of the studies, Hemoben was injected through a puncture of the serous wall of the stomach into the submucosal layer in an amount of up to 0.2-0.3 ml with the formation of a protruding roller. Observation for 7 days revealed no signs of necrosis or inflammation of the mucosa.

In the second series of experiments, a wound of the mucous membrane of the esophageal-gastric junction was formed by gastrotomic access. In the control group of animals, bleeding from a mucosal tear was stopped by injecting an epinephrine solution into the submucosal layer, and in the experimental group by injecting Hemoben gel. During morphological examination of the control group on the 1st day of the experiment, various alterative inflammatory processes prevailed. At the same time, there were "micro-tears" of histological layers of different sizes, tissue edema, areas of moderate necrosis. In the experimental group of animals, the mucosa in the area of previously performed damage is closed, there are no signs of ischemia and necrosis, histologically, the exudative-proliferative process of inflammation prevailed more, edema and lymphocytic focal infiltration were detected in the area where the gel was injected (Fig. 1-4).

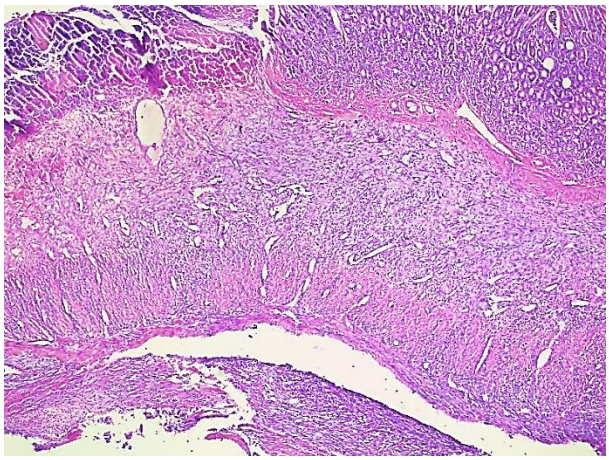

Fig. 1. CAP zone. "Micro-rupture" of layers - histoarchitectonic order of mucous and submucosal cells, tissue edema, submucosal hemorrhages of various sizes. The control group. 1 day. SEE G-E. 10x2

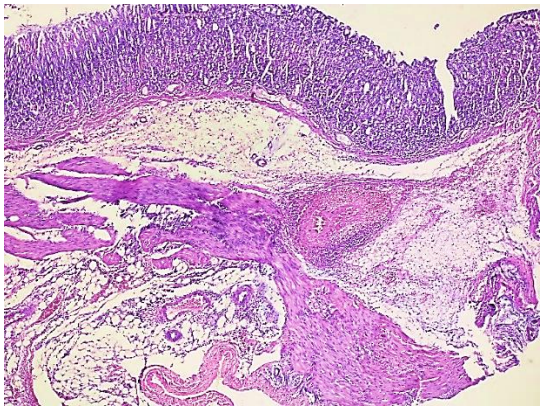

Fig. 2.The cardiac department of the stomach. The layers (more slimy) are "micro-fractured". Submucosal hemorrhages of various sizes. Control group 1 day. SEE G-E.10x2

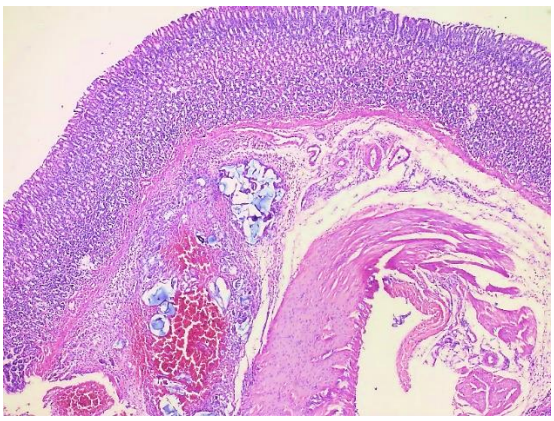

Fig. 3. The zone of gastroesophageal transition. Swelling of submucosal areas at the gel injection sites, homogeneous gel mass and infiltration with lymphocytic foci.An experienced group. 1 day. SEE G-E. 10x2

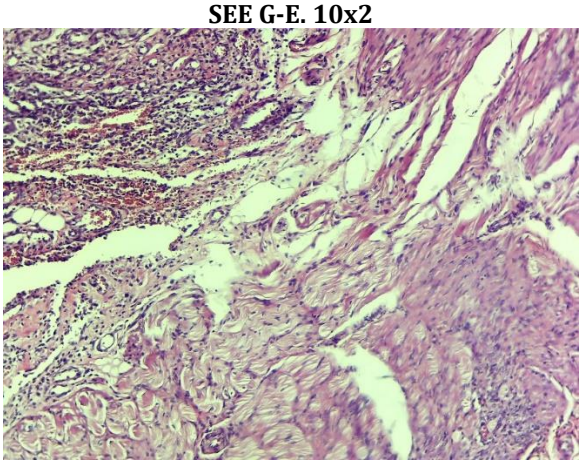

Fig. 4. CAP zone. Fullness of blood vessels around the injection site. Diffuse lymphocytic infiltration of the submucosal layer. An experienced group.1 day. SEE G-E. 10x4

On the 3rd day in the control group, the wound in the form of a narrow line, decreased in size by 2 times, was covered with fibrin, exudative-proliferative inflammatory process prevailed in the mucous and submucosal membranes. In the experimental group, the mucosa in the area of the tear almost completely healed in the form of an elastic scar. Histologically, the fibers of the mucous layer are organized, fibrosis is found in the affected areas. The remains of a homogeneous mass are found in the area of gel administration (Fig. 5-6).

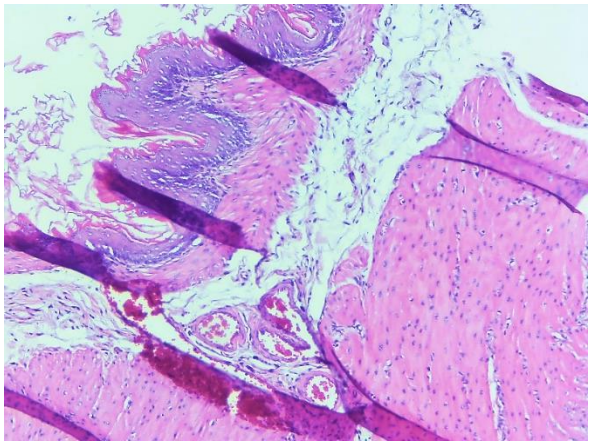

Fig. 5.Layers of the esophagus.Uneven expansion of the connective tissue layer, thickening of the vessel wall, dilation and stasis, edema throughout the layer. Fibroblasts of various lengths were formed in the submucosal and muscular layers. The control group. Day 3. SEE G-E.10x4

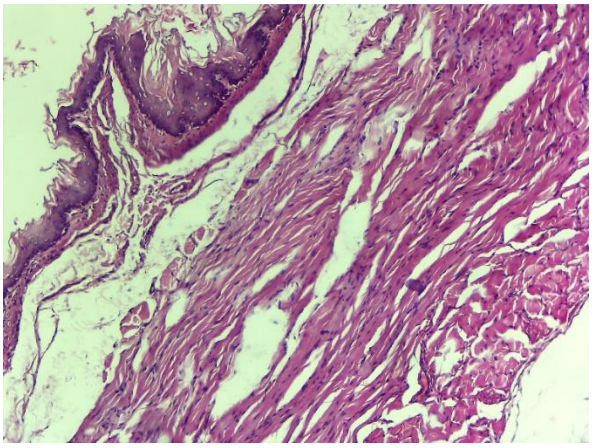

Fig. 6. CAP zone. Esophageal layers. Small fibroblasts formed in the layers where the fibers of the muscle layer were damaged. An experienced group. Day 3. SEE G-E.10x4

In the control group, hemostasis in the vessels of the affected layers was mainly achieved due to vascular spasm. Subsequently, micro hematomas appeared in submucosal areas as a result of diapedesis accumulation of erythrocytes and sludge in the injection area. Their complete resorption was observed after 5-7 days of the experiment. Wound healing mainly in the exudative form began from 5 days. In the experimental group: hemostasis in the vessels in the area of experimental trauma occurred due to Hemoben gel with hardening of damaged vessels. In contrast to the control group, extravascular diapedesis was almost not observed. As for wound healing, due to its adhesiveness, the gel glued the damaged areas and enhanced their regeneration (Fig. 7-9).

Fig. 7.Sludge in the blood vessels in the injection area. Extravascular diapedesis of erythrocytes.The control group.1 day. SEE G-E.10x4

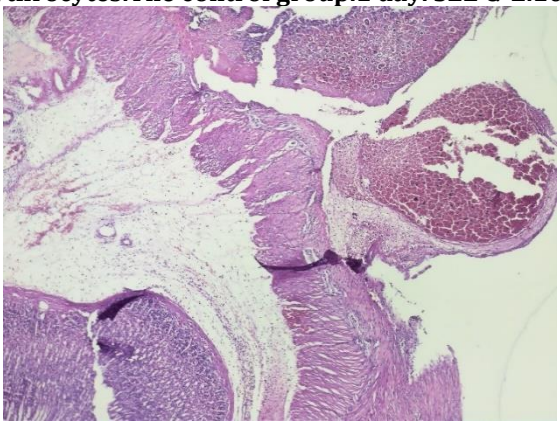

Fig. 8.Microhematoma in the injection area.The control group. 3 days. SEE G-E.10x4

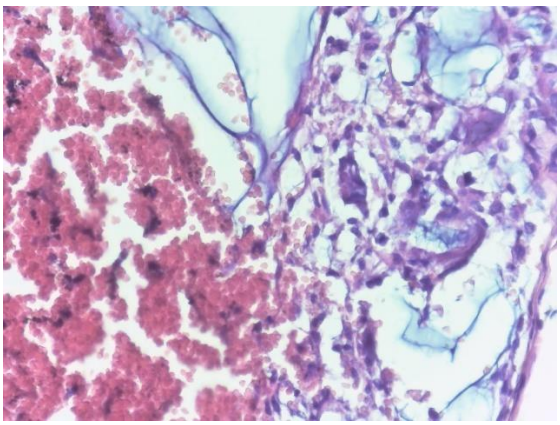

Fig. 9.Homogeneous gel elements in the area of experimental trauma. Microthrombs as a result of erythrocyte sludge in the places of contact with the gel. An experienced group. 3 days. SEE G-E.10x4

On the 7th day in the control group of animals, macroscopically, the wound of the gastric mucosa completely healed by forming a scar. However, microscopically, a layer of fibroblasts continued to form in the area of damage, especially in the area of damaged histological layers. In the experimental group, the regeneration of the histological layers of the lesion zone was completed within these terms. A small number of soft-fibrous connective tissue elements are observed in the affected layers, while all layers have recovered to their morph physiological state.

Thus, in this part of the experiment, the possibility of stopping bleeding using a gel from the domestic hemostatic drug Chamoe was tested. The dynamics of resorption of gel injected into the submucosal layer of the stomach and the ability to stop bleeding were investigated. This made it possible to conduct the next part of experimental studies close to the clinical situation. For this purpose, a model of the formation of a longitudinal rupture of the gastric mucosa by endoscopic method in mini-pigs was used. In the control group, bleeding was stopped by injecting up to 20 ml of epinephrine solution. In the experimental group, Hemoben gel was injected in an amount of up to 10 ml (Fig. 10-13).

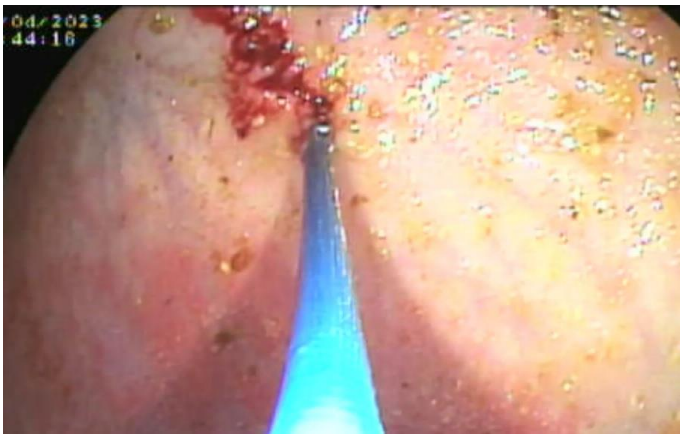

Fig. 10. The beginning of the formation of a rupture of the gastric mucosa using endoscopic forceps

Fig. 11.Formed rupture of the gastric mucosa with gaping edges and leakage of blood from the vessels of the submucosal layer.

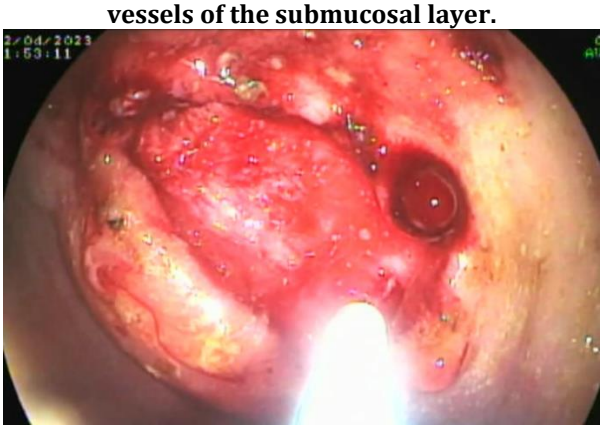

Fig. 12.The condition of rupture of the gastric mucosa after administration of epinephrine solution.

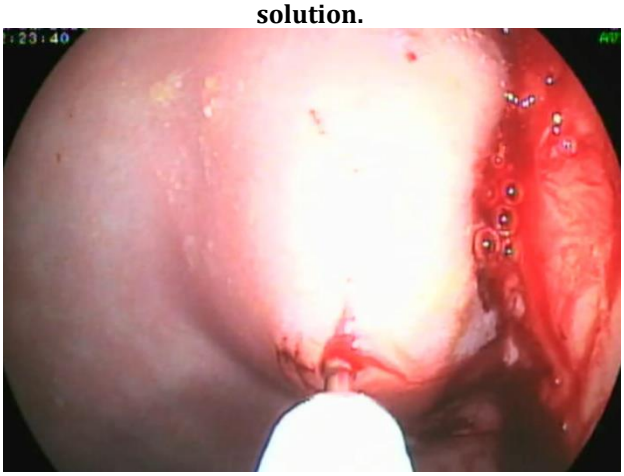

Fig 13. Introduction of Hemoben gel into the submucosal layer of the stomach around the rupture.

10 minutes after the bleeding stopped, there was almost complete resorption of the injected epinephrine solution with a gaping lumen of the wound. The resumption of bleeding occurred only in one case, which was stopped by repeated administration of epinephrine solution (Fig. 14). In the experimental group, in addition to achieving complete hemostasis, the introduction of the gel contributed to the closure of the edges of the rupture of the mucosa due to the formed mucosal roller. 10 minutes after the procedure, the edges of the wound remained closed, no blood leakage was observed (Fig. 15).

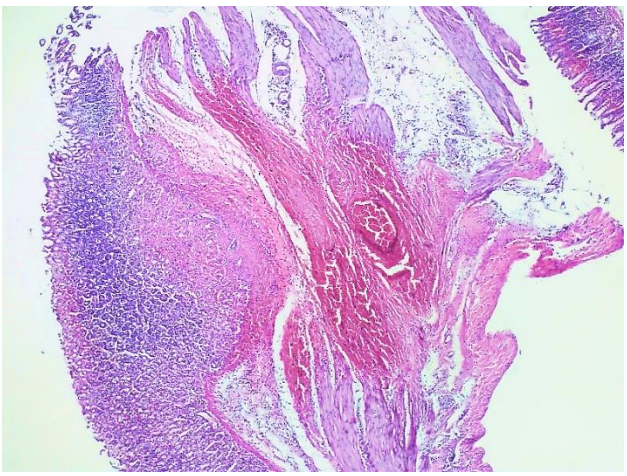

Fig. 14.Epinephrine injection zone. Diffuse submucosal microhematoma of the experimental wound area. The control group. 10 minutes. SEE G-E.10x2

Fig. 15.Experience. The condition of the gastric mucosa 10 minutes after the introduction of Hemoben gel into the submucosal layer

According to endoscopic studies performed at various times after surgery, it was found that in the control group of animals by 6 days, the wound of the mucosa remained almost the same size and was covered with fibrin. The edges of the wound had a gaping character. Partial healing of the mucosal wound was observed by 10-18 days. In the experimental group of animals, on the 6th day, the wound of the gastric mucosa practically healed, while it shrank by 3 times and had the character of a linear wound (Fig. 16-17).

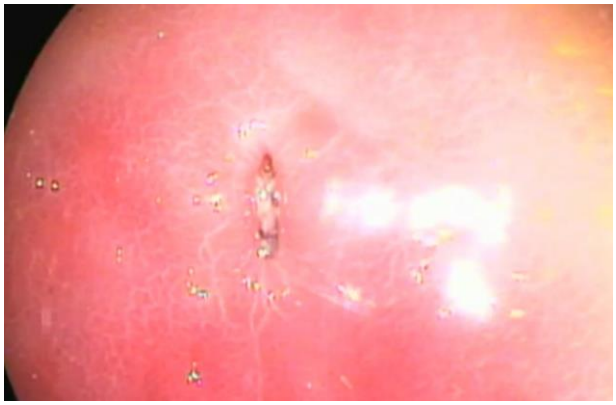

Fig. 16.Experience. Almost complete healing of the rupture of the gastric mucosa on the 6th day after the introduction of Hemoben gel. The wound shrank by 3 times, without infiltration. The bottom of the wound is covered with fibrin.

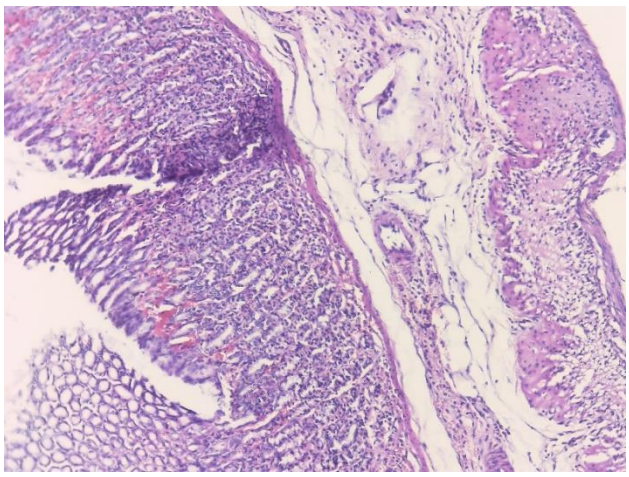

Fig. 17.Signs of wound healing in the area of gel application.Signs of stasis in the vessels of the submucosal region.Signs of minor fibrosis in the wound area.

Stable hemostasis occurred in the affected histomorphological layers due to the homogeneous distribution of the gel. In contrast to the control group, extravascular diapedesis was practically absent in this group.

DISCUSSION AND CONCLUSION

The objective of these studies was to evaluate the possibility of introducing Hemoben gel into the submucosal layer of the stomach and to substantiate the possibility of its use in experimental rupture of the gastric mucosa at the border of the transition to the esophagus. It was found that for injection using needle injectors, it is sufficient to prepare 2% gel before the procedure by diluting Hemoben powder in saline solution. At the beginning of the research, we injected Hemoben through a puncture of the serous wall of the stomach into the submucosal layer in an amount of up to 0.2-0.3 ml with the formation of a protruding roller. At the same time, there was some paling of the stomach wall due to stretching of the mucous membrane. No pathological changes in the stomach wall at the macroscopic level were detected in the subsequent observation periods. From the second day after the operation, the mucosal roller formed by the introduction of the gel was no longer determined. Observation for 7 days revealed no signs of necrosis or inflammation of the mucosa after administration of Hemoben gel.

In the second series of experiments, a wound of the mucous membrane of the esophageal-gastric junction was formed by gastrotomic access. In the control group of animals, bleeding from a mucosal tear was stopped by injecting an epinephrine solution into the submucosal layer, and in the experimental group by injecting Hemoben gel.

Dynamic observation of the condition of animals and visual assessment of the condition of the gastric mucosa in the area of mucosal tear allowed us to conclude that the submucosal administration of Hemoben gel does not cause a violation of the trophic gastric mucosa, does not enhance the inflammatory response of tissues, and also does not contribute to the spread of the defect zone to the serous surface of the stomach. Even in cases of puncture of the stomach wall and the introduction of gel outside the organ, there were no cases of leakage of stomach contents into the abdominal cavity and perforation of the organ.

Unlike the introduction of adrenaline, hemostasis using injections and application of gel to the bottom of the rupture led to an instant stop of bleeding, closure of the edges of the mucosa and healing of the stomach wound within 3 days, whereas with the introduction of an adrenaline solution, the healing of the defect area occurred 5-7 days after surgery.

In the control group: hemostasis in the vessels of the affected layers was mainly achieved due to spasm and rheology of blood in the vessels. In the future (especially on 1-2 days of observation) microhematomas appeared in submucosal areas as a result of dipedial accumulation of erythrocytes and sludge in the injection area and began to dissolve from the 3rd day of the experiment. Complete resorption was observed after 5-7 days of the experiment. Wound healing mainly in the exudative form occurred from the 5th day of the experiment.

In the experimental group: hemostasis in the vessels in the area of experimental trauma occurred due to Hemoben gel with hardening of damaged vessels due to calcium ions contained in it. In contrast to the control group, extravascular diapedesis was almost not observed. As for wound healing, because of its adhesiveness, the gel glued the damaged areas and enhanced their regeneration. As a result, wound

healing began in a proliferative form on the 3rd day of the experiment. The presence of homogeneous gel elements in the wound area even after 3 days of the experiment caused its persistent hemostatic effect.
In experiments on mini pigs, a rupture of the gastric mucosa was formed using endoscopic technique. The rupture length was up to 5 cm with active mixed bleeding from the vessels of the submucosal layer. As a rule, the rupture had ragged edges, and the divergence of the edges of the wound led to a gaping lumen. Immediately after the formation of the stomach wound in the control group of animals, hemostasis was carried out using an epinephrine solution (1 ml per 20 ml of saline solution). After the introduction of an epinephrine solution into the submucosal layer around the perimeter of the wound, bleeding stopped, but the gap gap remained gaping. 10 minutes after the bleeding stopped, there was almost complete resorption of the injected solution with a gaping lumen of the wound. The resumption of bleeding took place only in one case, which was stopped by repeated administration of an epinephrine solution. In the experimental group of animals, a 2% Hemobene solution diluted in saline solution was injected into the submucosal layer of mucosal rupture. Up to 10 ml of Hemoben gel was required to stop bleeding in this group of animals. In addition to achieving complete hemostasis, the introduction of the gel contributed to the closure of the edges of the rupture of the mucosa due to the formed mucosal roller. 10 minutes after the procedure, the edges of the wound remained closed, no blood leakage was observed.
In the control group of animals, anesthesia was performed after surgery using a tablet form of omeprozole 0.5 t x2 times a day. Nevertheless, the animals remained sedentary, refrained from eating for 3-4 days. At the same time, the weight loss was 2-3kg. The restoration of appetite and physical activity was observed 7-10 days after the operation, but the initial weight did not recover in these terms.
In the experimental group of animals, against the background of treatment of the control group, the restoration of physical activity was observed for 2 days with the loss of 500 grams of weight and restriction of food intake. In the following periods, the animals recovered quickly and reached a similar weight by 5 days after the operation.
According to endoscopic studies performed at various times after surgery, it was found that in the control group of animals by 6 days, the wound of the mucosa remained almost the same size and was covered with fibrin. The edges of the wound had a gaping character. Partial healing of the mucosal wound was observed by 10-18 days after surgery.
In the morphological study of this group, the same results were obtained as in the experimental rats in the previous chapter. At the same time, in the control group, hemostasis in the vessels of the affected layers increased mainly due to spasm and rheology of blood in the vessels. In the future (especially on the 1st-2nd day of observation) micro hematomas appeared in submucosal areas as a result of diapiric accumulation of erythrocytes and sludge in the injection area and began to dissolve from the 3rd day of the experiment. Full absorption was observed on the 5th day of the experiment and explicit on the 6th-7th day. Wound healing, mainly exudative, occurred from the 5th day of the experiment.
In the experimental group of animals, on the 6th day after surgery, the wound of the gastric mucosa practically healed, while it shrank by 3 times and had the character of a linear wound, the bottom of which is covered with fibrin.
In the experimental group, hemostasis in the vessels in the area of experimental damage was caused by the introduction of gel, stable hemostasis occurred in the affected histomorphological layers due to the homogeneous distribution of the gel and the presence of calcium ions contained in the damaged vessels. In contrast to the control group, extravascular diapedesis was practically absent in this group.
As for wound healing, thanks to its adhesiveness, the gel glued the damaged areas, and also accelerated the regeneration processes. As a result, wound healing began in a proliferative form after 3 days of the experiment. Another feature is that after 3 days of the experiment, homogeneous gel elements are found in the wound area, which indicates its persistent hemostatic effect. From the 5th-7th day of the experiment, the gel does not remain in the tissue due to complete decomposition and absorption due to biodegradation. This prevents the development of late responses to a foreign body.
Thus, 2% Hemben gel can be injected into the submucosal layer of the stomach. The advantage of introducing Hemoben gel is to achieve closure of the edges of the mucosal defect, which lasts for a long time. This contributes to a more favorable course of the postoperative period and wound healing for 6-10 days after surgery, which is 2-3 times faster than when using an adrenaline solution (14-18 days).

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