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Role of erosive and ulcerative gastric lesions in the development of hemorrhagic complications in liver cirrhosis

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We present the results of the treatment of 135 patients with a hepatic form of portal hypertension (liver cirrhosis) that have been hospitalized in the clinic of the Department of Surgery No. 2 in Bogomolets National Medical University within the period from 2011 to 2020. The aim of our study was to reveal the factors of the development of erosive and ulcerative gastric lesions in liver cirrhosis and their role in the occurrence of hemorrhagic complications. Based on studies of the rheological properties of gastric mucus, it was found that one of the leading factors in the development of erosive and ulcerative stomach lesions in portal hypertension is increased transcapillary filtration in the edematous-ascitic stage of liver cirrhosis. As a result, portal stagnation and reduced colloid mucus-bicarbonate barrier of the stomach led to the development of actual gastric ulcers. Erosive and ulcerative lesions on a part of the gastric mucosa were found in 66 (48.9%) of patients with cirrhosis of the liver, and in 45.2% of cases (28 persons) they were complicated by gastric bleeding development. Pathogenetic treatment of gastric ulcer-erosive bleeding in portal hypertension, against the background of the use of endoscopic hemostasis, should be aimed at strengthening the protective properties of the mucous-bicarbonate barrier of the stomach. Successful results of surgical treatment were achieved in 64.3% of patients. The overall mortality in liver cirrhosis complicated by gastric bleeding from ulcerative lesions of the stomach was 21.4% (6 patients died), and postoperative mortality was 25% (2 patients died).

Key words: stomach; erosive and ulcerative lesions; rheological properties of gastric mucus; liver cirrhosis; gastric bleeding.

INTRODUCTION

A significant and systemic increase in portal pressure is accompanied by the development of varicose veins of the esophagus and the cardiac part of the stomach, which are often complicated by gastric bleeding (GB) due to their rupture. However, it was found that this genesis of bleeding is diagnosed in 42% of patients with portal hypertension (PH), and in 58% of patients, bleeding was caused by erosive and ulcerative lesions in the stomach (erosion, ulcer, gastropathy) [1]. It is well known that primary profuse GB causes the death of every fourth patient, while after the recurrence of bleeding only about 50% of patients survive. It is in PH in comparison with peptic ulcer disease GB is profuse 5 times more often. This type of bleeding leads to irreversible disorders of the coagulation system [2], which cause the death of this category of patients [3].

The leading factor of erosive and ulcerative lesions in the stomach, which are usually complicated by GB is an acid-peptic factor that has a direct effect on varicose veins of the stomach, causing their erosion. At the same time at PH subepithelial capillaries which are easily damaged even without considerable trauma sharply expand [4, 5]. In addition, cirrhosis of the liver significantly increases the permeability to the blood of digestive and bacterial antigens with the formation of immune complexes, which is associated with a violation of the barrier function of the mucous membrane

of the stomach and intestines. Settling in the submucosal layer and gastric mucosa, these complexes potentiate both the inflammatory process and gastric lesions (GL) in the form of acute ulcers and erosions [6]. Quite typical for PH is the occurrence of portal gastropathy (PGP), which is manifested by single petechial hemorrhages (moderate PGP) and numerous hemorrhagic erosions (severe PGP). According to the literature, PGP was detected in 43.6% of patients, including severe PGP - in 24% of cases [7]. Typical during upper endoscopy are changes in the venous blood flow of the gastric mucosa in the form of isolated venous hypertension in the bottom and upper part of the stomach (in the lower parts of the stomach they were unexpressed). In addition, in the upper parts of the stomach, a regional hyperdynamic state of blood circulation is formed due to the development of hyperdynamic blood circulation in the arterial and venous vessels of the spleen. In turn, the arterio-venous discharge of blood to the veins of the gastric floor increases due to arterio-venous and venous shunting in the submucosal base of the stomach, which causes depletion of blood flow to the mucosa and its ischemia [8]. Thus, ways to find new mechanisms of gastric ulcers in PH require further study.

The aim of the study was to study the factors of the development of erosive and ulcerative gastric lesions in liver cirrhosis and their role in the occurrence of hemorrhagic complications.

METHODS

There were studied results of the treatment of 135 patients with a hepatic form of PH (liver cirrhosis) who were hospitalized in the clinic of the Department of Surgery No. 2 of the Bogomolets National Medical University in the period from 2011 to 2020. The age of patients ranged from 28 to 62 years, the mean age was 43.2 ± 2.3 years. The cause of liver cirrhosis in 57 (42%) patients was viral hepatitis, in 47 (34%) - alcoholism, in 31 (24%) - chemical (including drugs) factors.

Examination of the patients, in addition to the medical examination, included laboratory blood tests, ultrasound of the abdominal organs, and upper endoscopy. The liver functional reserve was assessed on the Child-Pugh scale by changes in bilirubin, albumin, prothrombin index, ascites, and encephalopathy [9]. Patients according to the specified classification were divided into three groups depending on the stage of the disease (on a scale): the stage of compensation (class A) (43 persons (31.8%), subcompensation (class B) (57 persons (42.2%) and decompensation (class C) (35 (26%). Varicose veins of the esophagus were diagnosed in 115 patients (85.2%), splenomegaly - in 59 (43.7%), and ascites were detected in 43 patients (31.8%). In the vast majority of patients (23 people (53.5%) ascites was detected at a stable stage, and in 15 people (34.9%) - in progressive, only 5 people (11.6%) it was transient. Symptoms of hypersplenism occurred in 49 patients (36.3)%, and jaundice - in 31 (22.9%).

GL during upper endoscopy were found in 66 patients (48.9%): in 22 patients 33.4%) – PGP, in 21 patients (31.8%) - gastric erosions, in 23 (34.8%) - gastric ulcers. There were 62 (45.9%) patients with cirrhosis of the liver and GB, and according to the Child-Pugh scale, the vast majority of patients were in the stage of decompensation (55 people (88.7%). GL were the cause of GB in 28 patients (45.2%): erosive gastritis - in 11 (39.3%) patients, gastric ulcer - in 12 patients (42.8%), PGP - in 5 patients (17.9%). In 16 patients (57.1%) the first clinical sign of GB was dizziness, in 26 (92.8%) - vomiting blood or «coffee grounds». Melena was found in all studied patients. Symptoms of hemorrhagic shock (sharp pallor of the skin, accelerated heart rate, cold sticky sweat, hypotension, and short-term loss of consciousness) were registered in 21.4% of cases (6 people). The severity of bleeding was determined by changes in the shock index, hematocrit, hemoglobin, erythrocytes, heart rate, blood pressure, and central venous pressure. Mild GB (circulating

blood volume deficit, below 20%) was found in 7 patients (25%), moderate (circulating blood volume deficit, 20-30%) was in 13 (46.4%) and severe (circulating blood volume deficit more than 30%) was in 8 patients (28.6%). Chronic gastric lesions accounted for 64.3% (18 people), acute - 35.7% (10 people).

Gastric mucus was obtained during upper endoscopy, followed by its homogenization and centrifugation for 30 min at a speed of 3000 revolutions per min. At the same time, a precipitate was obtained, which was a model of a native mucous gel. The rheological properties of gastric mucus (the limit of elasticity of the mucus gel, and the viscosity of the mucus) were studied using a precision rotary viscometer Rheotest-2 (Germany). Two indicators of mucus viscosity were determined: the initial viscosity of intact mucus (η1) and the viscosity of mucus after the destruction of its gel structure (η2) [10]. In order to compare the rheological changes of gastric mucus, all studied patients with GL (66 people) were combined into the main group. The comparison group consisted of 50 healthy individuals.

Treatment tactics in patients with GB in portal hypertension is still extremely difficult and not completely solved. Thus, the use of standard drugs for the treatment of bleeding from ulcerative lesions of the stomach on the background of liver cirrhosis can only slow the progression of the disease and surgical treatment is even less effective. The choice of treatment method depended on the degree of blood loss, the patient's age, and the general condition of the body. Treatment of each patient began with conservative measures while specifying the degree of its activity according to the endoscopic classification of Forest. The main direction in the treatment of ulcerative-erosive bleeding in patients with liver cirrhosis is upper endoscopy, which has long been not only a diagnostic but also a therapeutic technique. We have widely used local hemostasis using hemostatic solutions (Caproferr, etc.), coagulation, and clipping of bleeding vessels. The objectives of conservative treatment were to restore circulatory volume deficit, stop bleeding by using systemic hemostatic drugs, reduce gastric secretion and prevent the development of acute liver failure. It should be remembered that against the background of profound disorders of the coagulation system in patients with cirrhosis of the liver, the use of traditional hemostatic agents does not give the desired effect in the correction of hemostasis. Therefore, somatostatin analogs were preferred. The mechanism of action of somatostatin is based on the selective vasoconstriction of internal organs, associated with inhibition of the activity of endogenous vasodilators (in particular, glucagon and vasoactive intestinal peptide), which leads to a decrease in pressure in the portal system by 20-25% [11]. Antiulcer treatment included the use of modern antisecretory drugs (proton pump inhibitors (Esomeprazole, etc), H_2-histamine receptor blockers (Famotidine), and antacids (magnesium-aluminum combination) with a sequential transition from their parenteral to oral administration. The treatment regimens necessarily included drugs cytoprotection (synthetic prostaglandins, bismuth preparation, Sucralfatum) and reparative action (Erbisol, Solcoseril, Etaden), as the most pathogenetically justified in degenerative changes in the gastric mucosa in PH.

There were operated 8 patients (28.6%) with bleeding from GL on the background of liver cirrhosis at the stage of compensation and subcompensation: urgently (according to vital signs) - 5 patients (62.5%) (emergency surgery was performed in 2 patients, urgent - 3). Early delayed surgical interventions (according to absolute indications) were performed in 3 patients (37.5%). The operation of choice for ulcerative gastric bleeding is considered economy (partial) gastric resection. In the postoperative period, patients were prescribed a course of antirelapse treatment (antisecretory drugs, prokinetics (Metoclopramide), cytoprotectors, etc.).

Statistical analysis. Statistical analysis was performed using the program SSPS 22, and the

normality of the data distribution was determined by the Shapiro-Wilk test. In the case of parametric distribution of the analyzed data, the results were presented as averages and their standard deviation (M ± SD), in nonparametric - as the median and quartile (Me [Q1, Q3]). The difference between the groups was established using Student's t-test for independent samples by parametric and Mann-Whitney by nonparametric distribution. Differences between indicators were considered significant at $P < 0.05$.

RESULTS

The dynamics of changes in the rheological parameters of gastric mucus in normal and in patients with GL are presented in the Table.

Patients with gastric ulcers are characterized by the most pronounced violations of the rheological properties of gastric mucus. In them, the elastic limit of the mucous gel was twice lower than in healthy individuals, the initial viscosity of intact mucus was 2.5 times lower and the viscosity of mucus after the destruction of its gel structure was 2.2 times lower. In patients with gastric erosions, the elastic limit of the mucous gel was 1.7 times lower than normal, the initial viscosity of intact mucus was 2.2 times lower and the viscosity of mucus after the destruction of its gel structure was 2 times lower, and in patients with PGP 1.5, 2 and 1.8 times, respectively. Thus, the rheological properties of gastric mucus were reduced in 19 patients (90.5%) with gastric ulcers, 20 (87%) - with gastric erosions, and 18 (81.8%) - with PGP.

The efficiency of endoscopic hemostasis with the help of hemostatic agents in patients with GB from erosive-ulcerative lesions of the stomach was 85.7% (24 people). Three patients who achieved endoscopic hemostasis had a recurrence of bleeding and underwent surgery.

Pathogenetically justified in this case we consider the appointment of cytoprotective drugs (1) stimulants of mucus formation; 2) forming a protective layer; 3) enveloping, astringents, and reparative drugs that increase the protective properties of the mucous-bicarbonate barrier of the gastric mucosa and contribute to the rapid healing of ulcerations. The use of this pathogenetic drug treatment allowed to effectively eliminate not only GB but also to eliminate the morphological substrate of the disease (GL healing) in 25 patients (89.3%) with liver cirrhosis within 4 weeks of conservative treatment. In the remaining patients, in whom the GB was stopped endoscopically and the ulcer did not heal for a long time, antirelapse treatment regimens were adjusted, resulting in scarring of the gastric ulcer at a later date (within 10-12 weeks). Good results of surgical treatment (18 people; 64.3%) were achieved by patients following all our recommendations (provided that patients undergo a full course of antirelapse drug treatment in the early postoperative period).

The overall mortality in liver cirrhosis complicated by GB from ulcerative lesions of the stomach was 21.4% (6 patients died), and postoperative mortality was 25% (2 patients died). The death of patients (both not operated and operated) occurred, despite the cessation

Rheological parameters of gastric mucus in normal and in patients with erosive and ulcerative gastric lesions

Groups of subjects	N	The limit of elasticity τ, (n = 300-800 dynes/cm^2)	Viscosity of mucus	
			η1, (n = 2000-4700 SP)	η2, (n = 16-20 SP)
Control	50	541 [503; 579]	3321 [3154; 3488]	18.1 [17.2; 19.0]
Main:	66	311 [296; 326] *	1476 [1351; 1601]*	9.2 [8.6; 9.8]*
PGP	21	347 [328; 366] *	1623 [1485; 1761]*	10.5 [9.9; 11.1]*
Erosions	23	321 [307; 335] *	1484 [1360; 1608]*	9.1 [8.3; 9.9]*
Ulcers	22	264 [253; 275] *	1323 [1211; 1435]*	8.2 [7.6; 8.8]*

Note: *$P < 0.01$ compared to control

of GB conservatively or surgically, due to the progression of liver failure.

DISCUSSION

Given the polymorphism of erosive and ulcerative lesions in the stomach in patients with liver cirrhosis (acid-peptic factor, immune complexes, restructuring of venous blood flow in its upper parts), the syndrome of PH is one of the important causes of ulcerative lesions of the stomach [12]. However, we disagree with some authors who believe that cirrhosis of the liver and PH are the cause of symptomatic duodenal ulcers [13]. The negative impact on the mucosa-bicarbonate barrier of the gastric mucosa and duodenal venous stasis in these organs is demonstrated by a significant frequency of erosions and ulcers (according to our data – 48.9% of cases), which are found in PH and heart failure [14]. These changes are especially pronounced during the development of edema-ascites syndrome in this category of patients. At the same time, due to portal stagnation and reduction of colloid-osmotic properties of blood, transudation through the capillary wall in the stomach increases, which causes an increase in the aggressiveness of gastric juice. In addition, there is a «leaching» of bicarbonate, reduced viscosity, and concentration of mucus, which leads to a decrease in the protective properties of the mucosa-bicarbonate barrier of the gastric mucosa [15]. This, in our opinion, explains why in the edematous-ascitic stage of liver cirrhosis the frequency of ulcerative-erosive lesions of the stomach is the highest, and in the prehepatic form of PH is almost no different from the general population. Therefore, in the mechanism of development of GL at liver cirrhosis, the leading factor is not actually PH, and increase of transcapillary filtration at an edematous-ascitic stage of liver cirrhosis. It is this mechanism that we consider the main in the development of «cyrogenic» or «hepatogenic» erosive and ulcerative gastric lesions, which was confirmed by our research (GL was detected in 48.9% of patients). Given that GB is the most frequent complication of liver cirrhosis, and the frequency of development of hemorrhagic complications is on average 30%, the frequency of development of this complication in liver cirrhosis was also investigated [16]. It was established that in cirrhosis of the liver, the frequency of GB caused by GL is 45.9%, and, according to the Child-Pugh scale, the vast majority of patients were at the stage of decompensation (55 people; 88.7%).

CONCLUSIONS

1. In the development of erosive and ulcerative gastric lesions in liver cirrhosis the leading factor is not actual hypertension, but increased transcapillary filtration in the edematous-ascitic stage of liver cirrhosis, which, due to portal stagnation and reduced colloid-osmotic properties of blood, causes a decrease in protective properties of mucosal bicarbonate barrier causes the development of destructive lesions of the actual gastric localization.

2. Erosive and ulcerative gastric lesions during upper endoscopy were found in 48.9% of patients with cirrhosis of the liver and in 45.2% of cases, they are complicated by the development of gastric bleeding.

3. The use of drugs aimed at strengthening the protective properties of the mucous-bicarbonate barrier of the stomach with the basic use of endoscopic hemostasis techniques for erosive and ulcerative gastric changes at liver cirrhosis is promising but requires a separate and more thorough study.

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РОЛЬ ЕРОЗИВНО-ВИРАЗКОВИХ УРАЖЕНЬ ШЛУНКА У РОЗВИТКУ ГЕМОРАГІЧНИХ УСКЛАДНЕНЬ ПРИ ЦИРОЗІ ПЕЧІНКИ

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Досліджували фактори розвитку ерозивно-виразкових уражень шлунка при цирозі печінки у 135 хворих на печінкову форму портальної гіпертензії (цироз печінки) та їх роль у виникненні геморагічних ускладнень. На основі вивчення реологічних властивостей шлункового слизу було встановлено, що одним із провідних факторів розвитку ерозивно-виразкових уражень шлунка при портальній гіпертензії є підвищення транскапілярної фільтрації при набряково-асцитичній стадії цирозу печінки, яка внаслідок портального застою і зниження колоїдно-осмотичних властивостей крові спричинює зниження захисних властивостей слизово-бікарбонатного бар'єра шлунка та зумовлює розвиток власне шлункових виразок. Ерозивно-виразкові ураження слизової оболонки шлунка під час верхньої ендоскопії виявлено у 66 (48,9%) хворих на цироз печінки, причому в 45,2% випадків (28 осіб) вони ускладнюються розвитком шлункової кровотечі. Патогенетичне лікування ерозивно-виразкових кровотеч шлунка при портальній гіпертензії, на фоні застосування засобів ендоскопічного гемостазу, повинно бути направлене на посилення захисних властивостей слизово-бікарбонатного бар'єра шлунка. Таким чином, поєднання новітніх методик ендоскопічного гемостазу, з застосуванням сучасних медикаментозних засобів, які не тільки знижують шлункову секрецію, а й сприяють відновленню слизово-бікарбонатного бар'єра слизової шлунка, а також органозберігаючих оперативних втручань (у разі неефективності зазначених вище методів), дає змогу значно покращити результати лікування хворих на цироз печінки, ускладнений ерозивно-виразковими кровотечами шлунка, та знизити летальність у цієї надзвичайно важкої категорії хворих.

Ключові слова: шлунок; ерозивно-виразкові ураження; реологічні властивості шлункового слизу; цироз печінки; шлункова кровотеча.

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