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DIAGNOSIS AND TREATMENT OF GASTRODUODENAL ULCER BLEEDING

Gastroduodenal ulcer bleeding remains an urgent problem in emergency surgery. This literature review presents modern data on gastroduodenal bleeding of ulcerative etiology. The review considers the issues of epidemiology and etiology, as well as diagnosis and treatment of ulcerative gastroduodenal bleeding.

Keywords: peptic ulcer bleeding, peptic ulcer bleeding relapse, conservative hemostasis, endoscopic hemostasis.

Acute bleeding from the upper gastrointestinal tract remains one of the most important and complex problems in urgent surgery. Despite a large number of studies and publications, patient's treatment strategy of diagnosing and therapy remains the subject of discussion. The absence of standardized therapeutic and diagnostic algorithms creates a complexity in case management of this particular patient population.

Materials and methods. The analysis of articles in Russian and English languages, investigating ulcerative gastroduodenal bleeding, with a limited publication date of 10 years have been conducted. Articles exceeding a 10-year period were admitted in case of similar articles absence or scientifically valuable research. The literature search was made on the bases of scientific e-libraries, such as PubMed, eLIBRARY, Cyber Leninka, Google Scholar and Cochrane Library.

Epidemiology. Gastric and duodenal ulcers are the major causes of gastrointestinal bleeding. According to Russian authors, the frequency of gastroduodenal bleeding of ulcerative etiology in the bleeding general structure accounts for 56.1% - 59% and it remains the primary cause of gastrointestinal bleeding. Despite significant ulcerative gastroduodenal bleeding diagnosis and treatment progress, unadjusted mortality rate remains extremely high reaching 20.3%. Several factors like elderly and senile

age, co-morbidity, recurrent bleeding with repeated endoscopic hemostasis and surgical treatment aggravates the patienthood. In such a way, the mortality rate of the specified patient's category increases up to 53% [3].

The challenge of health services delivery to patients with gastroduodenal bleeding outside the Russian Federation is no less urgent. In the post-Soviet area, the ulcerative hemorrhages fraction in the structure of gastroduodenal bleeding amounts to 72.8%, while in the structure of emergency surgical care it comes up to 6.3% with a mortality rate reaching 4.4% [1]. In Western Europe and North America, these rates range from 26% to 50.6% with a mortality rate of up to 13.8% [30]. The ratio of male and female in the world is approximately the same (69.9% -75% and 25% -30.1%, respectively) [2].

However, recently, we can trace a decrease in the number of ulcerative bleeding and an increase in the frequency of bleeding of non-ulcer etiology in the general structure of hemorrhages. This fact may be associated with improved diagnosis and differential diagnostics as a result of the widespread introduction of esophagogastroduodenoscopy (EGDS).

Etiology. The major etiological factors are *Helicobacter pylori* infection and NSAIDs.

The discovery of *H. pylori* in 1982 has changed the understanding of the etiology of peptic ulcer disease [26]. The relation of *H. pylori* infection to the development of ulcerative gastroduodenal bleeding has made adjustments to the diagnosis and treatment of the disease. However, neither domestic nor international recommendations on ulcerative gastroduodenal bleeding give clear instructions for clinicians as regards testing for *H. pylori* infection detection in acute hemorrhage conditions [4, 17, 22].

According to a 2006 meta-analysis, it was found that the sensitivity of *H. pylori* tests based on endoscopy (biopsy for rapid urease testing, histology, and seeding) is low in acute stages of ulcerative bleeding. The reasons explaining

this event are not clear. Feces antigen analysis is less accurate and has many false-positive results, probably due to cross-reactions with blood components in the lumen of the gastrointestinal tract, in such a way serological test cannot be recommended as the first diagnostic test for *H. pylori* infection in hemorrhagic conditions. In this connection, the best possible test is the breathing *helicobacter urease* test [16].

It is common knowledge that Nonsteroidal anti-inflammatory drugs and anti-aggregants increase the risk of ulcerative gastroduodenal bleeding development; however, on numerous occasions they are proposed due to the concurrent vascular diseases. At the same time in the cases of ulcerative bleeding drug withdrawal duration as well as the timing of the antiplatelet therapy resumption remain controversial. Currently, if possible, it is applicable not to stop taking aspirin, although if the withdrawal is necessary, the duration of aspirin withdrawal should not exceed 3 days in the cases of ulcerative gastroduodenal bleeding.

Recently, there has been an increase in ulcerative gastroduodenal bleeding caused by idiopathic ulcers not related to *H. pylori* infection and the use of NSAIDs, and can reach approximately 20% of all cases. The main etiological factor of such ulcers is stress. After the earthquake in Japan in 2011, the number of gastroduodenal ulcer bleeding cases increased by 2.2 times, which also indicates the vital role of stress in the development of peptic ulcer disease.

Therefore, peptic ulcer disease is a polyetiological, multifactorial disease that has many development causes which require hard research.

Clinical manifestation. Normally, clinical implications of upper gastrointestinal bleeding are manifestative for clinicians. Core symptoms signaling the bleeding are haematemesis or coffee-ground vomit and melaena. However, if there are no such symptoms, the bleeding diagnosis can be cumbersome. According to the statistics, in almost half of

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upper gastrointestinal tract (GIT) bleeding cases vomiting does not occur, and in 5% of cases there are no pathognomonic symptoms at all. This can lead to delayed initiation of treatment [2].

Endoscopic diagnostics in hematochezia remains a significant dilemma: it is bleeding from the intestine or accelerated transit of blood from the source of the upper gastrointestinal tract. What to do first, colonoscopy or EGDS? Hematochezia can cause hemorrhages from the upper gastrointestinal tract, if the intensity of bleeding is high enough and the digestive enzymes are not enough to convert hemoglobin to hematin hydrochloric acid, occurring in up to 14% of cases [14]. So, in order to determine the therapeutic and diagnostic tactics, it is necessary to conduct prospective studies, although it seems reasonable to perform an EGDS before an endoscopy of the lower gastrointestinal tract.

Diagnosis and endoscopic imaging. Endoscopic imaging is the core diagnostic method for gastroduodenal bleeding. Since gastric lavage is not always effective enough, there is a reasonable ground to use prokinetic therapy as a part of preparation for gastroduodenal ulcer bleeding endoscopic examination.

Recent studies have shown that intravenous erythromycin prior to emergency esophagogastroduodenoscopy improves the gastrointestinal mucosa imaging, reduces the number of repeated examinations and the duration of patients hospitalization [32]. However erythromycin as prokinetic is not yet widespread in national clinics.

The alternative to erythromycin would be the prescription to use metoclopramide 30 minutes prior to the endoscopic examination in patients with upper gastrointestinal bleeding signs. At the same time, there are studies the results of which, on the contrary, show the ineffectiveness of metoclopramide in comparison with placebo [13]. A number of authors point out higher efficiency of erythromycin, so it requires further study with a larger number of participants.

Conservative therapy. One of the first recommendations in the ulcerative gastroduodenal bleeding treatment is hunger; nevertheless, there are no criteria for the duration of the fasting diet, as well as the time for the resumption of oral or enteral alimentation. According to the study results, patients who underwent endoscopic hemostasis for ulcerative gastroduodenal bleeding or those who have a high risk of recurrence should refrain from oral or enteral nutrition for 48 hours. In the case of a low recurrent

bleeding risk, nutrition can be resumed immediately after endoscopic examination [19]. At the same time, the study carried out by M. Khoshbaten points out that oral feeding did not significantly affect the water-electrolyte balance and treatment results in patients with ulcerative gastroduodenal bleeding who underwent endoscopic hemostasis, but it reduced the length of hospitalization [23].

"The gold standard" of the ulcerative gastroduodenal bleeding medical therapy is the usage of Proton-pump inhibitor (PPI).

The primary mechanism of PPI prescription is Hong Kong protocol, which represents bolus IPP dosing followed by intravenous infusion within 72 hours. However, the debating point is the switch from intravenous PPIs to oral ones. On this basis a metaanalysis incorporating six random investigations was performed during the period from 2006 to 2011. In total, 615 patients were randomly assigned to receive PPIs orally (n=302) or intravenous (n=313). According to the results of the analysis, there was no significant difference between oral and intravenous PPIs in terms of recurrent bleeding, average blood transfusion volume, surgical interference demand and all-cause mortality rate. Hospitalization duration was significantly reduced in patients using oral PPIs. In addition, it was emphasized that oral PPIs demonstrated efficiency similar to intravenous PPIs in patients with bleeding ulcerative etiology, but the results were pooled from open-label studies with a limited sample size.

Blood transfusion. The hemoglobin threshold level for red blood cells transfusion in patients with gastrointestinal bleeding is controversial. The general clinical principles are used in order to restore the volume of blood circulation, although it seems that an individual approach to transfusion is inevitable. 2014 Clinical guidelines for ulcerative gastroduodenal bleeding stress that blood transfusion is indicated when hemoglobin level is less than 90 GM/DL [4].

In order to find the better approach scientist conducted a randomized study with two groups of patients: the first one to apply restrictive strategy (blood transfusion with hemoglobin values less than 70 GM/DL) and the second one to apply liberal strategy (blood transfusion with hemoglobin less than 90 GM/DL). A restrictive strategy of maintaining a hemoglobin level of 70-90 GM/DL was as safe and as effective as the traditional goal of reaching a hemoglobin level of 90-110 GM/DL. In patients with bleeding ulcers, there were fewer differences between the two

strategies, although all valuable clinical outcomes were better with the restrictive strategy (mortality 3% versus 5%, recurrent bleeding 10% versus 17%, surgery 2% versus 6%) [35].

Similar results are highlighted in the conducted meta-analysis that combined the results of four studies [36]. In particular, included studies did not specifically examine gastroduodenal ulcer bleeding, but also they had different methodologies, inclusion and exclusion criteria. Nevertheless, the results of the study support the restrictive strategy: there was a significant decrease in mortality and the duration of hospitalization, and the percentage of recurrent bleeding was slightly lower. The exact optimal strategy for blood transfusion is unclear and should always be individualized for each patient.

In addition, the analysis of four published and one unpublished randomized controlled studies, which included 1965 people, showed that the amount of transfused red blood cell mass in the restrictive blood transfusion strategy group was less than in the liberal strategy group. The restrictive strategy was associated with a lower risk of bleeding recurrence and death regardless of all causes [28].

Endoscopic hemostasis. The key method of patients with ulcerative gastroduodenal bleeding treatment is endoscopic hemostasis.

Currently, the methods of endoscopic hemostasis are divided into two types: mechanical and thermal. A meta-analysis carried out in 2009 comprising 75 studies evaluating endoscopic hemostasis methods illustrated that both thermal and mechanical hemostasis methods are effective [25].

Injection hemostasis is the most common method. Injection hemostasis as monotherapy is significantly inferior to combined hemostasis in the form of the adrenaline solution injection combined with other methods of hemostasis [25]. In various medical institutions, adrenaline solution, ethanol, ethoxysclerol, isotonic sodium chloride solution, etc. are preferred as a drug for injectable hemostasis. This choice is justified by the secondary pharmacological effect. However, according to the meta-analysis carried out in 2003 by M. Bardou and co-authors, which included 38 studies, none of the drugs used for injection hemostasis have advantages over others [10].

Existing thermal methods of hemostasis are divided into contact and non-contact methods. The applied methods of contact hemostasis include electrocoagulation and the use of heater probes. Talking about methods of electrocoagula-

tion, the preference is given to bipolar and multipolar probes. Electrocoagulation devices deliver energy in a fixed circuit, heating tissues up to 1000 C, then their action is stopped, limiting the depth of tissue damage, thereby reducing the risk of perforation. The methods of bipolar and multipolar coagulation are easier to use, since they have a local effect, without requirement of patient's grounding. Heating probes maintain a constant temperature of approximately 2500 C for a given time, supplying the required amount of energy, which can cause uncontrolled tissue damage depth and lead to a high risk of an organ paries perforation reaching 3% of cases [24].

Argon plasma coagulation (APC) is a non-contact method of thermal endohemostasis. Since the first description and early experience of using this method, it has become widespread in clinical practice [18]. The unquestioned advantage of this method is the small depth of the coagulation scab (up to 3 mm), which makes it possible to use argon plasma coagulation for bleeding from deep ulcers and with a thin organ paries, since the probability of perforation is much lower than with contact methods of hemostasis. Injection of epinephrine in combination with APC has shown the same efficiency and safety as injection of epinephrine in combination with a heating probe in the process of patients with ulcerative gastroduodenal bleeding treatment.

Recently developed in Japan, the soft coagulation clip forceps method is increasingly applied in the cases of ulcerative bleeding. Thus, soft coagulation turned out to be more effective than coagulation with a thermal probe in achieving endoscopic hemostasis, making it possible to achieve hemostasis in 96% of cases. The use of clip forceps in terms of efficiency and safety is not inferior to APC and is no less successful than clipping in the treatment of patients with ulcerative gastroduodenal bleeding [8]. One of the soft coagulation method's advantages is the reduction of the required time to achieve hemostasis [8].

One of the most fully studied method of mechanical hemostasis is clipping with metal clips. When properly used and positioned, the clips can cause overall hemostasis similar to the surgical deligation of a bleeding vessel. They do not cause significant tissue damage and do not interfere with the healing of ulcerative defects.

Taking into consideration that clips are metal, people also need to remember about their compatibility with magnetic resonance imaging (MRI). Although all

commercially available clips are marked as incompatible with MRI, a study on biological models of pigs showed that MRI can be performed with all available types of clips, with the exception of Tri-Clip, since they separated from the stomach tissue during the experiment, which means they should be considered incompatible with MRI [15].

Combined endoscopic hemostasis is usually the procedure of choice. A 2014 Cochrane review conducted a meta-analysis of 19 randomized controlled trials with 2033 patients, which pointed out that combined hemostasis in the form of an injection of epinephrine and a second method of hemostasis is more effective in comparison with injection hemostasis with epinephrine only. This combination reduces the risk of rebleeding, the need for surgery, and mortality [34]. In a meta-analysis published in 2016, including 2888 patients, the effectiveness of various endoscopic hemostasis methods was studied. In the end, only clipping and combined hemostasis, including adrenaline injection and thermal exposure, were the most effective [9].

Local hemostatic means represent the new method of endoscopic hemostasis. Currently, there are three types of powder available: Hemospray, EndoClot and Ankaferd Blood-Stopper. For instance, Hemospray's combined technical and clinical success rate was 88.5% in humans and 81.8% in pig models studied. Bleeding recurrence was observed in 38 patients within 72 hours after treatment (16.2%) and in three pigs' models (27.3%). No side effects have been associated with the use of Hemospray [11].

There are also other methods of endoscopic hemostasis known in medical practice, such as OVESCO clips, Endoloops, bandage dressing, etc., which require further study in order to assess the possibility and effectiveness of their use in clinical practice.

Roentgen-endovascular treatment methods. Patients with recurrent ulcerative gastroduodenal bleeding, in cases when endoscopic hemostasis is unsuccessful, represent a serious problem. Percutaneous translumbar angiographic embolization can be an alternative to surgical measure.

In patients with bleeding ulcers after unsuccessful endoscopic hemostasis, X-ray endovascular treatments reduce the need for surgery without increasing overall mortality with fewer complications, but the recurrence rate may be higher (up to 34.4%) [37]. A study evaluating five-year experience showed that percutaneous transcatheter embolization

reduced the frequency of rebleeding to 3.4%, and the need for surgical treatment to 10.3% [21].

Operative therapy. The indication for surgical treatment is ongoing bleeding with the ineffectiveness of other hemostasis methods. Operational activity in ulcerative gastroduodenal bleeding reaches 16-33%, and postoperative mortality is up to 32.5% [6]. In case of ulcerous gastroduodenal bleeding, laparotomy should not be finished in all patients with retroclusion of a bleeding vessel, since this tactic is complicated, as according to the statistics, up to 50% of cases end up by recurrent bleeding due to progressive necrosis in the area of the ulcer and arrosion of the bleeding vessel [6]. In critical cases when the risk of surgery is extremely high, repeated endoscopic hemostasis or X-ray endovascular treatment can be considered as an alternative.

Bleeding recurrence. Bleeding recurrence sharply worsens the prognosis of the disease. All mortality causes were significantly lower in patients who underwent only one procedure of endoscopic hemostasis (3%) compared to patients whose cases required more than one endoscopic hemostasis (6%), X-ray endovascular treatment (9%) or surgery (14%) [29].

The etiology of peptic ulcer disease complicated by bleeding is also a significant factor: after hemostasis, idiopathic ulcers showed a higher percentage of bleeding recurrence in comparison with ulcers associated with *H. pylori* infection and those caused by taking NSAIDs (30% versus 7.4% and 2.7%, respectively) [12].

Previously, the Forrest type of ulcer played great importance in predicting bleeding recurrence. However, according to a recent research, the risk of rebleeding for Forrest 1b ulcers is less than for Forrest 2a and 2b ulcers, and may not require high-dose PPI therapy after successful endoscopic hemostasis [20], which casts doubt on this approach.

Many scales have been created in an attempt to predict the risk of recurrent bleeding and the outcome of a patient's treatment. The most frequently used, especially in foreign practice, are the Glasgow-Blatchford and Rockall scales. A research described in the article 'Comparison of Glasgow-Blatchford score and full Rockall score systems to predict clinical out-comes in patients with upper gastrointestinal bleeding' was carried out in order to analyze the data of the scale. Thus, the Glasgow-Blatchford scale performed better in predicting bleeding recurrence [27]. Another international study pointed out in the article 'Comparison of

risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study' indicates that the Glasgow-Blatchford scale is the most accurate for predicting the need for interference, but all available prediction scales have low predictive accuracy for other criteria, including endoscopic therapy and mortality rate, therefore their clinical value for high-risk patient management is somewhat limited [31]. Domestic scales for the prognosis of recurrent bleeding have also been developed. The first one is the system for predicting recurrent bleeding by M.M. Vinokurov and the second ones are the systems developed at the Department of Faculty Surgery of the RUDN University which include the system for predicting recurrent bleeding (SPRK) and an improved system for predicting recurrent bleeding II (SPRK II). According to the results of the study carried out by domestic authors, the most optimal for use in clinical practice is SPRK II [5]. Despite the large number of relapse prediction scales, further work is needed to improve the systems.

Reoccurring endoscopic hemostasis. Endoscopic hemostasis is the basic method for stopping the bleeding in patients with ulcerous gastroduodenal bleeding, but none of the methods allows to achieve the final hemostasis without recurrent bleeding in all cases, which means that the choice of the hemostasis method in case of repeated bleeding is relevant. In accordance with clinical guidelines, emergency surgery is prescribed in patients with ongoing bleeding with ineffective or impossible endoscopic hemostasis, or with relapse [4]. However, at the same time these recommendations point out the possibility of repeated endoscopic hemostasis in case of relapse or the use of endovascular methods. Repeated endoscopic hemostasis, in case of recurrent bleeding, is considered effective in up to 97% of cases, avoiding surgical intervention in up to 84% of recurrence cases [7]. Performing repeated endoscopic hemostasis, as well as the ability to refuse patients surgical treatment, can reliably reduce mortality by 2-3 times [7, 29].

Repeated endoscopic hemostasis should be an alternative to surgical treatment for recurrent ulcer bleeding; at least a second attempt to achieve endohemostasis should be taken, especially in patients with severe comorbidity.

Conclusion. In conclusion, ulcerative gastroduodenal bleeding still remains a vital problem in urgent surgery and is accompanied by high mortality. So, to

create a unified diagnostic and treatment algorithm for gastroduodenal bleeding of ulcerative etiology requires a great amount of research.

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