REVISITING CAUSES AND FEATURES OF TREATMENT FOR EROSIVE AND ULCERATIVE GASTRODUODENAL BLEEDING IN PATIENTS WITH ACUTE CARDIAC DISEASES (A REVIEW OF LITERATURE)

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BACKGROUND	Erosive and ulcerative gastroduodenal bleedings observed in patients with cardiac disease, are associated with a high rate of mortality and significantly complicate the course of the underlying disease. Studying the etiology of erosive and ulcerative lesions of the upper gastrointestinal tract mucosa in these patients may serve as a basis for the development of preventive measures for gastroduodenal hemorrhage. The multiple treatment of patients with erosive and ulcerative gastroduodenal bleeding complicating a cardiac disease should be carried out with the interaction of antisecretory drugs and antiplatelet drugs.
Keywords:	erosive and ulcerative gastroduodenal bleeding, cardiac diseases, treatment, prevention.

AC – artificial circulation
ASA – acetylsalicylic acid
GIT – gastrointestinal tract
IABC – intra-aortic baloon counter-pulsation
LP – lipid peroxidation
MI – myocardial infarction
PPI – proton pump inhibitors

THE RELEVANCE

Erosive and ulcerative gastroduodenal bleedings in patients who underwent surgeries on the heart and the aorta, or experienced myocardial infarction (MI) is considered to be one of the most severe complications significantly affecting mortality rates. The literature presents various data on the incidence of bleeding in these patients. According to these data, gastroduodenal bleedings were observed in 1.8-3.3% of cases [1, 2] and in 0.1-3% after surgery on the heart and the aorta in patients with acute myocardial infarction [3-6]. Diagnostic studies in cardiac surgical patients showed erosive and ulcerative lesions of the upper gastrointestinal tract (GIT) (without signs of bleeding) in 25.3-48.7% of cases [3, 7, 8]. Mortality in patients with a cardiac impairment complicated with gastroduodenal bleeding remains high and varies from 9.6 to 80%, reaching the highest numbers in elderly and senile patients despite the advances in recent years [7, 9-11].

DISCUSSION

In the literature, the issue of gastroduodenal bleedings in critically ill patients is widely described. The sourcees of bleeding are usually erosive and ulcerative lesions of the mucous membrane of the upper GIT, which is called *SRES - stress-related erosive syndrome* in the literature [12].

The pathogenesis of acute erosive and ulcerative lesions is described as multifactorial, but most authors point out that the basis of the latter one is an imbalance between factors of aggression and protective factors, which most important are acid-peptic production and state of the gastric mucosal blood flow [13]. The fact that reduction of gastric blood flow is the most important mechanism in the development of gastroduodenal ulcers, has been confirmed by numerous experimental studies [14]. It is noted that reduction of blood flow in the gastric mucosa promotes local acidosis leading to *SRES* through several mechanisms: increasing levels of free radicals, reduction of acid buffer capacity, and reduction of mucus secretion and bicarbonates as well as regeneration defect of epithelial cells [12, 15]. The final result of these processes is an increase of back diffusion of H + ions and the destruction of the epithelial *barrier. R.G. Fiddian-Green et al.* [16] made a direct correlation between the level of intramural pH and development of erosive and ulcerative massive gastrointestinal bleeding.

Regarding the erosive and ulcerative lesions in patients with cardiac impairement, some authors suppose that hypoperfusion, hypoxia and microcirculatory disorders in the digestive system play the leading role in their pathogenesis [5, 11, 17-19]. The effect of hypoperfusion in patients after surgeries on the heart and the aorta is usually caused by the development of low cardiac output syndrome and hypovolemia [6]. In addition, the use of hypothermia and artificial circulation (AC) with pulsatile and non-pulsatile blood flow, as well as circulatory support with the use of intra-aortic balloon counter-pulsation (IABC), according to some authors, is the reason for the reduction of perfusion of the gastric mucosa [20, 21]. Use of adrenaline, dopamine, dobutamine in the treatment of patients with acute heart failure also relates to the factors potentiating decrease in perfusion of the stomach through the development of persistent vasoconstriction and reduction of tissue oxygenation [20].

Analyzing the causes and mechanisms of erosive and ulcerative gastroduodenal lesions in cardiac patients, L.A. Bokeria et al. [4] studied correlation between factors of surgical aggression during heart surgery and refractive intramucosal gastric pH (pHi). The authors concluded that there was a different degree of negative correlation between pHi and factors such as the duration of the AC, aortic cross-clamping time, the use of IABC, the temperature gradient in the esophagus and rectum during hypothermic AC, the use of sympathomimetics and serum lactate level in blood.

In addition, arising ischemia of the gastric mucosa under the influence of all these factors leads to the release of vasoactive amines, causing persistent vasospasm, further aggravating tissue hypoxia [22]. According to some authors, developing ischemia and hypoxia of the stomach wall lead to a shift in the ratio of aerobic and anaerobic metabolic processes in favor of the latter one, activation of lipid peroxidation (LP), depletion of tissue antioxidants and increased peroxidation products in the stomach tissue with the development of tissue acidosis. All this becomes a pathogenetic link of erosive and ulcerative lesions of the mucous membranes of the upper GI tract [23]. The mechanism of the

pathological effects of lipid peroxidation products in cells of the mucous layer of the stomach is the damage of biological membranes by interfering protein-lipid and lipid-lipid bonds and suppression of the activity of membrane-bound enzymes, which change the selective permeability of the mucosa for ions. In addition, oxygen radicals are agents directly damaging the gastric mucosa [24].

According to some authors [14], the role of pepsin and hydrochloric acid is not evident in the formation of stress ulcers, as reduction of blood flow leads to significant reduction of gastric secretion. An important role in initiation of acute ulcers formation is given to the energy deficit in ischemia of the mucosa. According to A.N. Kurygin et al., the basis of the acute necrotizing ulcer genesis is a destructive process with inflammatory lymph and leukocytic infiltration associated with microcirculation disorders [7].

Studies have shown that tissue ischemia under reduction of blood flow greatly slowed purification of mucosa from back-diffusion of hydrogen ions. Under these conditions the balance between concentration of hydrogen ions in the gastric lumen and gastric mucosal blood flow is disturbed. Local hypoxia of its parts leads to interstitial edema and acidosis, which occurs as a result of increased capillary permeability, observed if protective mucosal barrier is damaged [25].

Summarizing the opinions of the authors on the pathogenesis of erosive and ulcerative lesions in patients with cardiac abnormalities, A.A. Shchegolev et al. [20] recommend that the risk factors for their occurrence are the following:

- heart failure, which requires the infusion of adrenaline, dobutamine, dopamine;
- prolonged AC (more than 120 min);
- circulatory support – IABC;
- arterial hypoxemia, acute respiratory failure;
- development of postoperative bleeding excessing 10% of circulating blood;
- prolonged artificial ventilation (more than 2 days);
- development of postoperative multiple organ dysfunction syndrome, sepsis;
- development of disseminated intravascular coagulation.

In addition to these factors, there is a risk of erosive and ulcerative gastroduodenal bleedings in patients with cardiac impairment associated with the need for continuous antiplatelet therapy, or its combination with anticoagulants (including unfractionated heparin, low molecular weight heparin and warfarin). The latter is used after surgery on valves and has a 50% higher risk of gastroduodenal bleeding than antiplatelet therapy alone [26-28]. Studies on the large amount of clinical observations of patients with acute coronary syndrome showed that treatment with a combination of warfarin with acetylsalicylic acid (ASA) increased the risk of major bleeding from the gastrointestinal tract twice compared to monotherapy with ASA [29]. Currently, ulcerogenic mechanism of action of the latter one has been already studied. According to scientists, it occurs due to inhibition of ASA and other nonsteroidal anti-inflammatory drugs on cyclooxygenase – thee enzyme involved in formation of prostaglandins from arachidonic acid, which gastroprotective effect is well understood [30]. In addition, some authors suggest ulcerogenic effect of glucocorticosteroids, widely used in a complex post-operative treatment of patients undergoing heart surgery [5]. According to E.S. Ryss and E.E. Zvartau the basis of this effect is violation of microcirculation and suppression of regenerative processes in the mucosa of the stomach and duodenum [31].

The pathogenic role of *H. pylori* in the formation of erosive and ulcerative lesions in patients with cardiac impairments has not been evidenced. There are studies that indicate a significantly lower level of infection of the gastric mucosa (62.7%) in patients with erosive and ulcerative lesions of the upper GIT compared to infection with *H. pylori* in patients with peptic ulcer disease [8].

Analysis of the causes of erosive and ulcerative lesions of the gastric mucosa and duodenum in cardiac patients allows determining methods for their prevention and treatment. According to the unanimous opinion of various authors [4], patients with impending heart surgery should necessarily undergo esophagogastroduodenoscopy to avoid erosive and ulcerative lesions as well as the development of gastroduodenal bleeding in the postoperative period. Postoperatively, these patients should receive massive antisecretory therapy, and the main focus of this drug should be proton pump inhibitors (PPIs). Studies have shown that injectable therapy has the greatest efficiency in treatment and prevention of erosive lesions in the mucous membrane of the stomach and duodenum. In addition, according to the authors, prevention and treatment should include drugs with antioxidant and anti-hypoxic effect and gastroprotectives of various types, including the synthetic prostaglandins (misoprostol), and sucralfate [4, 5, 12]. Enteral nutrition with balanced mixtures has a significant protective effect for patients in the early postoperative period [12].

In recent years, publications pointing to the negative aspects of the use of proton pump inhibitors in cardiac and cardiac patients have appeared. It is known that after transluminal coronary angioplasty with a stent implantation containing drug coverage, the mostly recommended antiplatelet drug for a long-term treatment is clopidogrel in combination with ASA [30]. However, as noted at the 32nd Scientific Meeting of the Society for Cardiovascular Angiography and Interventions, the simultaneous use of clopidogrel and PPIs significantly increases the risk of myocardial infarction, stroke, need for repeated coronary intervention due to the reduced effect of clopidogrel. According to some authors, the negative effect of combination of clopidogrel with proton pump inhibitors occurs due to the fact that some PPIs may inhibit the enzyme cytochrome P-450 2C19, altering the pharmacokinetics of clopidogrel [32]. There are reports indicating adverse effects of interaction between PPIs and warfarin, and some PPIs (omeprazole, esomeprazole) can reduce the clearance of warfarin, thereby resulting in an undesirable increase of anticoagulant effect of warfarin. [30] Studies using various PPIs have found that pantoprazole has the least ability to cause side effects when combined with anticoagulant and antiplatelet drugs, which may be used for antisecretory therapy in patients with cardiac diseases and after heart and coronary vessels surgeries as the drug of choice [30].

CONCLUSION

Thus, it should be noted that causes and pathogenesis of erosive and ulcerative lesions of the upper gastrointestinal mucosa in patients with acute cardiac disease are represented by multiple factors. The use of complex of drugs aimed at treating the underlying cardiac abnormality and having ulcerative effect represents a significant threat of gastroduodenal bleeding development in these patients. All this requires of clinicians to reason the treatment considering the need to prevent the development of erosive and ulcerative gastroduodenal bleeding with proper selection of drugs with antisecretory activity.

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Article received on 10 October, 2014

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