THE USE OF PROTON PUMP INHIBITORS IN INTENSIVE CARE UNITS

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UPOTREBA INHIBITORA PROTONSKE PUMPE U JEDINICAMA INTENZIVNOG LEČENJA

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ABSTRACT

The bleeding from the upper gastrointestinal tract represent a significant medical but also socio-economic problem. A special group of patients et increased risk consists of critically ill patients in intensive care units. Particularly significant cause of bleeding in intensive care unit patients is bleeding resulting from the stress ulcers caused by damage of the mucosa of the stomach and duodenum.

The purpose of this review is to present current experience in prevention of upper gastrointestinal tract bleeding using proton pump inhibitors in intensive care units.

Combination of endoscopic hemostatic methods and proton pump inhibitors represents golden standard in most cases.

Despite some adverse effects treatment with proton pump blockers is essential when upper gastrointestinal tract bleeding appears in critically ill patients in intensive care units. Proton pump inhibitors are more effective in acid suppression, as well as in the prevention of recurrent bleeding after endoscopic hemostasis than histamine 2 receptor blockers. The efficacy of proton pump blockers is higher in the case of a continuous intravenous infusion than in the intermittent mode of administration of the drug. The need for highly elaborate strategy for the prophylaxis of bleeding from the upper parts of gastrointestinal tract in intensive care units is essential, because when it occurs in intensive care units, mortality is high, and therapeutic options become narrow.

Keywords: *proton pump inhibitors, acid suppression, upper gastrointestinal tract, bleeding, prophylaxis*

SAŽETAK

Krvarenje iz gornjih partija gastrointestinalnog trakta predstavlja značajan medicinski, ali i socio-ekonomski problem. Posebna grupa pacijenata pod povećanim rizikom sastoji se od kritično obolelih pacijenata u jedinicama intenzivne nege. Značajan uzrok krvarenja u jedinicama intenzivne nege predstavljaju krvarenja nastala usled stres ulceracija uzrokovanih oštećenjem sluznice želuca i duodenuma.

Svrha ovog pregleda je predstaviti aktuelna iskustva u prevenciji krvarenja iz gornjih partija gastrointestinalnog trakta upotrebom inhibitora protonske pumpe u jedinicama intenzivne nege.

Kombinacija endoskopskih hemostatskih metoda i inhibitora protonske pumpe predstavlja zlatni standard u većini slučajeva.

Uprkos nekim neželjenim efektima blokatori protonske pumpe su od suštinskog značaja kada je u pitanju krvarenje iz gornjih partija gastrointestinalnog trakta kod kritično bolesnih pacijenata u jedinicama intenzivne nege. Inhibitori protonske pumpe su efikasniji u supresiji lučenja kiseline, kao i za sprečavanje ponovnog krvarenja posle endoskopske hemostaze od blokatora histamin 2 receptora. Efikasnost blokatora protonske pumpe je veća u slučaju kontinuirane intravenske infuzije nego u intermitentnom modalitetu primene leka. Dobro razvijena strategija profilakse krvarenja iz gornjih delova gastrointestinalnog trakta u jedinicama intenzivne nege je veoma bitna, jer kada se javi kod teško obolelih pacijenata u jedinicama intenzivne nege, smrtnost je velika, a terapeutske opcije postaju uske.

Ključne reči: *inhibitori protonske pumpe, supresija lučenja kiseline, gornje partije gastrointestinalnog trakta, krvarenje, profilaksa*

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INTRODUCTION

The bleeding from the upper gastrointestinal tract

Evidence based medicine is the concept of scientific thinking and processing results and involves rational interpretation and use of the currently best available, scientifically proven and evidence-based approaches in the treatment of patients. The methodology of evidence-based medicine can be successfully demonstrated evaluating studies that have observed the occurrence of bleeding from the upper gastrointestinal tract, acid suppression and application of proton pump inhibitors in critically ill patients in intensive care units (1).

The bleeding from the upper gastrointestinal tract represent a significant medical but also socio-economic problem of our time. It is estimated that each year about 4 million people are diagnosed with peptic ulcer disease worldwide (2). Previously, bleeding from the digestive tract ulcer was a common cause of surgical treatment, but this is a rarity today, thanks to advances in pharmacological therapy. On the other hand, the way of life of modern man certainly contributes to the increase of diseases such as gastric and duodenal ulcers. A special group of patients consists of critically ill patients in intensive care units who are at increased risk for the occurrence of stress ulcer and consecutive bleeding from the upper gastrointestinal tract. Together with the underlying disease and comorbidities bleeding from the digestive tract is often life-threatening when patients are concerned. Many clinical trials have focused on acid suppression treatment and prevention of stress ulcer but it is still a common problem and a major challenge for clinicians who deal with treatment of critically ill patients in intensive care units worldwide (3).

There is a big difference between the group of patients who had signs of acute bleeding from the upper gastrointestinal tract at the time of admission and the group of patients who bleeding from the upper gastrointestinal tract developed after hospitalization. Mortality in the first group is about 9.1% and the mortality rate in the second group is about 50% (4).

Causes of gastrointestinal bleeding

The causes of bleeding from the upper gastrointestinal tract are differ not only in place and the pathogenesis, as well as by the intensity, dynamics of occurrence and possible consequences. The main cause of gastrointestinal bleeding in critically ill patients are the varices of the distal esophagus and proximal stomach with hyperacidity related causes such as peptic ulcer disease and stress-related damage to the lining of the gastrointestinal tract. Particularly significant cause of bleeding in intensive care units patients is bleeding resulting from the stress ulcers caused by damage of the mucosa of the stomach and duodenum.

The pathophysiological mechanisms by which stress leads to lesions of gastric and duodenal mucosa are numerous, often mutually complementary and the most significant are: hypotension with hypo perfusion of mucosa, tachycardia, anemia, hypoproteinemia, etc... Hyperacidity inhibits platelet aggregation and activate pepsin, so that it has a double negative effect. Decreased platelet aggregation leads to increased bleeding tendency due to the difficulty or inability to create the formation of blood clot while by acid activated pepsin can lyse clots that already formed (5). The causes of bleeding from the upper gastrointestinal tract may be relatively rare conditions such as Mallory-Weiss syndrome, coagulopathy, vascular lesions.

Treatment of patients with acute gastrointestinal bleeding

The initial treatment of patients with signs of acute bleeding from the upper gastrointestinal tract is generally identical in all patients, and reduced to the basic resuscitation and resuscitation. Particular attention should be paid to the protection of the airway during massive hemorrhage, restoration of circulating blood volume, correction of comorbidity. After stabilization of vital functions some of the methods of hemostasis should be carried out as causal treatment (6).

According to several studies performed mechanical ventilation is one of the most provocative factor when for bleeding from the upper gastrointestinal tract in critically ill patients in intensive care units (5).

H. pylori infection is the main cause of chronic gastritis type B and duodenal ulcer. Its presence can be detected in a biopsy sample of intestinal mucosa during gastroduodenoscopy, serology or breath test. Although it has long been known for its role in the development of gastric and duodenal ulcers, its role in the occurrence of acute bleeding from the upper gastrointestinal tract is still unclear. Results from the studies are contradictory. There are studies that indicate that eradication of H. pylori significantly reduces the incidence of ulcer recurrence or occurrence at a recurrent bleeding after already achieved hemostasis in patients with duodenal ulcer (7). There are also studies that have shown that there is no statistically significant correlation between the presence of H. pylori and gastrointestinal bleeding in critically ill patients. On the other hand, in the same studies a causal relationship with the bleeding by applying mechanical ventilation has been confirmed, which is already previously known (8).

The therapeutic modalities in case of bleeding from the upper parts of the gastrointestinal tract are pharmacotherapy, endoscopic intervention methods and operative treatment.

Development of interventional endoscopic procedures has significantly reduced the need for surgical intervention in case of bleeding peptic ulcers. Endoscopic hemostatic methods have numerous advantages as compared to other treatment modalities. First of all, trauma is significantly lower compared to surgery, which is very important for seriously ill patients who usually except the bleeding

Table 1. Pre-Endoscopy Rockall Score for Risk Assessment after Upper Gastrointestinal Tract Bleeding

Age	< 60 years	0
	60-79 years	+1
	≥ 80 years	+2
Shock	No shock (SBP ≥100 AND HR <100	0
	Tachycardia (SBP ≥100 AND HR ≥100)	+1
	Hypotension (SBP <100)	+2
Comorbidities	No major comorbidity	0
	Any comorbidity EXCEPT renal failure, liver failure, and/or disseminated malignancy	+2
	Renal failure, liver failure, and/or disseminated malignancy	+3

from the digestive tract have life-threatening underlying disease. On the other hand, interventional endoscopic hemostasis is a significantly faster than pharmacological methods. However, the aforementioned methods of treatment are not competing but are complementary. When establishing hemostasis by endoscopy emphasis is placed on prevention of recurrent bleeding, which occurs in about 20% of patients (9). The main endoscopic techniques for establishing hemostasis in case of bleeding from the upper gastrointestinal tract are injection therapy and termocoagulation and these two techniques are complementary. The injection therapy is most commonly used solution with adrenaline which has vasoconstrictor effect (10). The two most commonly used techniques are the method of heating and bipolar coagulation methods (11). One of widely used scoring systems for risk assessment after acute upper gastrointestinal hemorrhage is the Rockall score (Table 1 and 2) (12-14).

Acid suppressive agents such as histamine-2 receptor antagonists have been for many years in use. The first drug of this type, which is set to use in the US was cimetidine, which went into service in 1977. The fact that drugs in this group had a great effectiveness in the treatment of peptic ulcer disease is a prerequisite that they enter into wider use in the field of prevention of repeated bleeding after already achieved hemostasis. However, histamine 2 receptor blockers have not met the expectations in this regard and did not show a statistically significant effect on reducing the number of required transfusion, duration of bleeding, repeated bleeding or the need for surgical intervention, as proven by numerous studies (15, 16).

Proton pump inhibitors

Proton pump inhibitors belong to the group of benzimidazole drugs in chemical composition. Omeprazole (Prilosec®, AstraZeneca, Wilmington, DE) was approved by the FDA in 1989 and was the first drug from a group of PPI approved for use in the United States; and then followed lansoprazole, pantoprazole, rabeprazole, esomeprazole, omeprazole bicarbonate, naproxen and esomeprazole-dekslansoprazol. These drugs inhibit H + / K + -ATP-ase and reduce gastric acid secretion. Some of the indications for use of proton pump inhibitors include gastroesophageal reflux disease (GERD), erosive esophagitis, gastric ulcer, Helicobacter pylori eradication, as well as the treatment of gastric ulcers caused by excessive use of non-steroidal anti-inflammatory drugs (17). Application of proton pump inhibitors in critically ill patients with signs of bleeding from the upper gastrointestinal tract has led to significant advances in treatment, which has proven by randomized, double-blind, placebo-controlled studies (18, 19). H +, K + -ATP-ase is the key enzyme in the process of acid secretion (20). It is mainly localized in idle parietal cells and it is mobilized in a situation when it comes to the activation of the parietal cells by some of stimuli such as histamine, acetylcholine or gastrin (21). Proton pump blockers such as lansoprazole [2 - [[[3-methyl-4- (2, 2, 2-trifluoroethoxy) -2-pyridyl] methyl] sulfinyl] -1H-benzimidazole), omeprazole, rabeprazole and pantoprazole inhibit gastric H +, K + -ATP-ase covalent attachment to the sulfhydryl group, thus inhibiting the secretion of acid (22). Although proton pump inhibitors show a powerful acid suppression activity, still many pharmaceutical laboratories try to improve the pharmacological properties of the drug, as proton pump inhibitors bind only for the activated H +, K + -ATP-ase, so that it takes 4-5 days to achieve maximal therapeutic effect (23). Proton pump inhibitors alter its molecular configuration and therefore acid suppression activity depends on pH conditions, i.e. acidity of the environment, so that their activity is considerably lower at a neutral pH environment.

Table 2. Complete Rockall Score for Risk Assessment after Upper Gastrointestinal Tract Bleeding

Age	< 60 years	0
	60-79 years	+1
	≥ 80 years	+2
Shock	No shock (SBP ≥100 AND HR <100	0
	Tachycardia (SBP ≥100 AND HR ≥100)	+1
	Hypotension (SBP <100)	+2
Comorbidities	No major comorbidity	0
	Any comorbidity EXCEPT renal failure, liver failure, and/or disseminated malignancy	+2
	Renal failure, liver failure, and/or disseminated malignancy	+3
Diagnosis	Mallory-Weiss tear	0
	No lesion identified and no stigmata of recent hemorrhage	0
	All other diagnoses	+1
	Malignancy of upper GI tract	+2
Mallory -Weiss tear0	None	0
	Dark spot only	0
	Blood in upper GI tract	+2
	Adherent clot	+2
	Visible or spurting vessel	+2

Proton pump inhibitors have a relatively short plasma half-life period, so their activity over night is in question, even in the repeated bolus administration (24). Proton pump inhibitors have adverse effects including development of life threatening Clostridium difficile colitis. Some novel studies declare that proton pump inhibitors do not affect risk for Clostridium difficile infection in the intensive care unit, but it is still unclear (25-27).

In order to improve the pharmacodynamics a new group of drugs has been proposed. In contrast to the proton pump inhibitors, a novel class of medicaments, known as potassium-competitive blockers of acid suppression (P-CABs) or acid pump antagonists inhibit the gastric H +, K + -ATP-ase K + -competition, through reversible mechanism (28). 3- (Cyanomethyl) -2-methyl, 8- (phenylmethoxy) imidazo (1, 2-a) pyridine (SCH28080) is the prototype of the P-CAB classes of drugs. It binds to fosfoenzim monovalent cation sites (E2P) on H +, K + -ATP-ase and it is strictly K + -competitive (Mendlein and Sachs, 1990). This mechanism allows the rapid inhibition of the pump without the need for an acidic medium. Several structural imidazopyridine derivatives, pyrimidine, imidazonaphthyridine and pirolopiridazin have been studied as a P-CABs. These compounds are stable at low pH values. Therefore, P-CABs are highly concentrated in the extremely acidic environment of gastric parietal cells on the luminal surface of the H +, K + -ATP-ase, and their effectiveness is less variable, because, unlike the proton pump inhibitor does not require a gastro protective formulations (29). P-CABs show rapid development of acid inhibition based on the rapid achievement of therapeutic doses in plasma, so that the maximum effect is already achieved during the first day of implementation (30). However, P-CABs group of drugs has its drawbacks, primarily hepatotoxicity (31).

CONCLUSION

Based on studies on a large number of patients as scientifically valid the following conclusions can be imposed:

Although the stress ulcers of the digestive tract in critically ill patients are common, clinically significant acute bleeding from the upper gastrointestinal tract is not so often (32). During the first 24 hours of admission to the intensive care unit, 75% to 100% of critically ill patients develop endoscopically visible damage of the mucosa of the upper gastrointestinal tract, however, relatively few of them, 1% to 4% develop clinically overt bleeding (33).

Clinically significant acute bleeding from the upper gastrointestinal tract caused by mucosal stress damage is accompanied by signs of hemodynamic instability and the need for transfusion, but need for surgical intervention is relatively rare, even when viewed from only a sample of patients in intensive care units. Also it is in constant decline which is associated with the progress of medicine and therapeutic possibilities as well as a better understanding of the pathophysiology of the problem (34).

The need for highly elaborate strategy for the prophylaxis of bleeding from the upper parts of GIT is essential, because when it occurs in intensive care units, mortality is high, and therapeutic options become narrow (35).

Treatment with proton pump blockers is essential when upper gastrointestinal tract bleeding appears in critically ill patients in intensive care units.

Proton pump inhibitors are more effective in acid suppression, as well as in the prevention of recurrent bleeding after endoscopic hemostasis than histamine 2 receptor blockers (6).

Prophylaxis of stress ulcers has led to a reduction of frequency of clinically significant bleeding, but it has not been proven to increase the survival rate (36).

The cause of death of critically ill patients who developed stress ulcer bleeding is often one or more preexisting comorbidities, while bleeding from the upper parts of GIT represents only contributing, additional factor. Therefore, it is recommended that each institution has a guide which determines what the patient has enough factors of risk and is in need of acid suppression prophylaxis (37).

Acid suppression therapy has its adverse effects. There is evidence to suggest that this therapy is associated with increased risk of hip fracture, but this connection is likely to apply only to patients who already have some of the other risk factors, such as osteoporosis (38).

The efficacy of proton pump blockers is higher in the case of a continuous intravenous infusion than in the intermittent mode of administration of the drug (39).

Although the price of the proton pump inhibitor is greater than the price of histamine 2 receptor blockers, there is a clear benefit from their use not only in medical terms but also in terms of economic profitability because costs are much higher if the treatment with lower efficiency histamine 2 receptor blockers contributes to the formation of stress ulcers and consequent bleeding from the upper gastrointestinal tract (6).

As proton pump inhibitors should be considered as serious risk factor for Clostridium Difficile infection some of prevention methods mustn't be neglected, such as reducing use of broad–spectrum antimicrobials, probiotics administration, isolation of cases and personal protective equipment (40).

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Conflict of interest

The authors have declared that no competing interests exist.

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