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## **RISK FACTORS FOR STRESS-INDUCED ULCER BLEEDING IN SEVERE TRAUMA AND CRITICALLY ILL PATIENTS**

**SUMMARY:** A hemorrhaging stress-induced ulcer is a mucosal lesion that develops as a result of a broken mucosal barrier in patients with severe trauma and those who are critically ill, and it poses a threat for potentially lethal complications. Prophylactic treatment administered to patients with risk factors dramatically reduced the incidence of hemorrhaging. Prophylactic treatment reduces the stress ulcer hemorrhage by more than 90% with respect to the assessed risk. Among patients who required surgery, total mortality rate is still about 34%. Patients with sepsis are at the highest risk, as are those who are on long-term ventilation. The choice of a prophylactic agent in this field, particularly for the group with a medical history of ulcerations or gastrointestinal bleeding, still remains to be addressed.

**Keywords:** acute mucosal lesion, hemorrhage, prophylaxis, severe trauma patients, critically ill patients

Stress ulcer or stress-induced mucosal lesion is a mucosal lesion occurring in two forms: a diffuse superficial mucosal damage or deep focal lesions penetrating in the submucosa and appearing mostly on the stomach corpus or fundus. Such lesions occur so often in the critically ill patients that certain authors claim that 75% to 100% of patients have a form of a verifiable gastrointestinal lesion in the initial 24 hours. Clinically relevant forms of such lesions (bleeding, and much less frequent perforations, requiring blood transfusion or surgical treatment) occur in 6–10% of patients in intensive care units<sup>1</sup>. Both the etiology and pathophysiology of the lesions are related to multiple factors and have not been sufficiently explained. Ischemia and reperfusion lead to the mucosal barrier rupture. Under such conditions the destruction of mucosal layer serving to eliminate any potential toxins also occurs and a reduction

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in the synthesis of prostaglandin ensues. Increased concentration of oxygen radicals causes inflammation, cell death and further production of inflammatory cytokines. The risk factors for gastrointestinal bleeding from such a lesion are: artificial ventilation lasting for more than 48 hours, coagulopathy, significant hypotension, sepsis, long-term presence of a nasogastric tube and no peroral ingestion<sup>2</sup>, acute liver failure, chronic kidney failure, severe head trauma, burns covering more than 30% of the body, chronic alcoholism, long and extensive surgical procedures, treatment involving corticosteroids and some anticoagulants, organ transplant. These patients and the patients past 65 years of age or those who have a history of gastritis or ulcers are candidates for prophylactic stress-induced ulcer treatment.

Clinically, apart from the occurrence of blood in the nasogastric tube contents, melena or unexplained hypotension (spontaneous drop in systolic tension by 20 mmHg or more), an increase in heart rate by more than 20 beats per minute and a drop of more than 2g/dL in the hemoglobin levels are probable predictors of a gastrointestinal hemorrhage<sup>1,3</sup>. Another likely indicator for bleeding is the number of blood transfusions that, if reduced by 2, do not result in the corresponding increase in the level of hemoglobin.

Hemorrhage prophylaxis involves clinical parameters and blood and electrolyte test results monitoring, avoidance of local irritation (tubes, anti-inflammatory medications, aspirin), and restricted administration of vasopressors, if possible, as they may exacerbate gastrointestinal ischemia. Vasopressors cause an increase in arterial tension at the expense of mesenteric perfusion. Numerous studies have demonstrated that enteral ingestion initiated in the first 24 hours after trauma or onset of illness has the same effect as does the H<sub>2</sub>-receptor or PPI prophylaxis. Such claims, however, have not been confirmed in multicenter or meta-analytic studies<sup>2,4</sup>. In addition, it is a known fact that many surgical patients simply cannot be subjected to enteral ingestion in the first 24 hours (e.g. patients with acute pancreatitis, patients who have undergone invasive surgical procedures on the digestive tract etc.).

The American Pharmacists Association has prepared guidelines for pharmacological prophylactic treatment against the occurrence of stress ulcer and its complications. Pharmacological prophylaxis is advised for all adult patients in intensive care units who:

1. have coagulopathy,
2. require mechanical ventilation for more than 48 hours,
3. have had a history of gastrointestinal ulcers or bleeding in the previous 3 years,
4. have at least two of the following risk factors:
  - sepsis
  - stay in the ICU for more than 7 days,
  - acute hemorrhage over a period of more than 5 days,
  - 250-mg hydrocortisone (or another equivalent corticosteroid) treatment<sup>1,3,5</sup>.

The most widely used medications for stress ulcer prevention at Level I Trauma Centers in the USA are H2-receptor antagonists (67%) and PPI just for patients with a history of gastrointestinal ulcer disease and/or bleeding from upper gastrointestinal region. Sucralfate is used in a significant 24% of cases. Omeprazole and Pantoprazole are used for prevention in more than 10% of cases in total, and this is only for patients at high risk of bleeding according to Zinner. For high-risk patients (coagulopathy, respiratory failure), proton pump inhibitors (PPI) are increasingly the preferred choice, with potentially favorable results. PPIs exhibit certain pharmacokinetic qualities that give them advantage over other medications, although the published series remain inconclusive<sup>5</sup>.

Care provided in the intensive care units for patients who are at a risk of stress ulcer bleeding is a vital part of the treatment. Therefore, the ICU nurses must be highly qualified in their area of expertise in order to be able to recognize a patient at high risk, as well as pay attention when handling such a patient (nasogastric suction, contents aspiration, enteral nutrition), and notice any possible signs of hemorrhage in order to promptly advise a physician.

Regardless of the prophylactic treatment of choice, if any, a very small number of patients require surgical treatment for stress ulcer hemorrhage (more than 2%). Of such patients, about 47% are found in surgery with old ulcerations or ulcer scars, so that only slightly above 1.5% of patients who have had mucosal lesions or bleedings require surgical treatment.

Sepsis patients present a different problem and challenge for prophylaxis and treatment of gastrointestinal bleeding caused by mucosal lesions. In sepsis patients, the underlying condition or trauma in itself usually favors such hemorrhaging, as does a long-term stay in intensive care units and a release of multiple inflammatory mediators in large concentrations, as well as aggressive therapy that sepsis treatment demands (vasopressors, mechanical ventilation, corticosteroids)<sup>6</sup>.

Gastrointestinal bleeding from acute mucosal lesions in severe trauma and critically ill patients usually results from multiple risk factors, the initial ones being hypotension, hypoxia and the resulting mucosal ischemia. The hemorrhage combined with sepsis and artificial ventilation occurs within two weeks from trauma or onset of illness.

Sepsis coupled with the long-term respiratory support has been the most frequent causative factor for stress-induced ulcer bleeding number of studies corresponded to the results published by many authors. Jang et al. specify that in a group of 574 patients who had severe trauma complications resulting in sepsis, 10.8% had a manifestation of stress ulcer hemorrhage compared to 0.3% from the group of patients who did not develop sepsis. The total mortality in various studies is 22.5% in average. Bleeding is a contributing cause of death in less than 3% of cases, which corresponds to the results of a cohort study conducted on 2252 patients (Cook et al). Fadaak cites that in

more than 50% of severe trauma patients and patients with burns that covered more than 33% of the body who died, a mucosal lesion ranging from a superficial change to deep submucosal necrosis was discovered at the autopsy<sup>3,4,5</sup>.

Number of studies provide different information on the number of patients with clinically relevant bleeding. In 27 randomized studies, the incidence of hemorrhage ranges from 2 to 3%. Prospective cohort studies and six randomized studies cite the same risk factors for bleeding; however, there are insufficient studies on the prediction of bleeding in individual patients. Published studies demonstrates that the specified factors are reasonable hemorrhage risk predictors<sup>6,7</sup>. In addition, the severity of trauma/illness represents the primary hemorrhage risk factor due to hypoxias, reperfusion and release of high concentration of inflammatory mediators.

Zinner's score is a good predictor for the stress ulcer bleeding. It is obvious that prophylaxis has a significant effect on the reduction in bleeding from mucosal lesions, as specified by authors of studies published in the last 10-15 years. For example, series of patients, in the group I according to Zinner, among 27.3% of patients who were at risk of hemorrhage, 4.9% experienced bleeding, while in the group II 7%, and in the group III 13% of patients had bleeding. Therefore, the total incidence of hemorrhage was 8.5%<sup>1,7</sup>.

The choice of a prophylactic agent may also be an important factor for hemorrhage prevention, particularly in cases with a medical history of hemorrhage in the previous year or a history of ulcers, and these records should be insisted upon. Prophylactic treatment should be continued for several weeks after the risk factors have resolved, particularly if the risks were combined. Starting early with enteral ingestion is important, since the presence of food has a stimulatory effect on mucosal proliferation and splanchnic circulation, which serves as excellent prevention against particularly profuse stress-induced ulcer bleeding<sup>8</sup>.

Data show that the prophylaxis reduces the number of patients bleeding from stress ulcers, although it does not affect the mortality in patients who have already had bleeding manifestation, regardless of the prophylaxis. In these patients, the mortality rate is still exceptionally high (34.5%), especially if a surgical procedure is required, when the rate exceeds 50%. For that reason, the surgical risk is quite high. Risk factors for a surgical procedure are: HGB < 80 g/L, BP < 80 mmHg, HR > 120 bpm, CRP > 200, D-dimer > 1000, APACHE II > 10, earlier repeated interventions<sup>9</sup>.

## ***Conclusion***

Prophylactic treatment significantly reduces the incidence of clinically relevant stress-induced ulcer hemorrhage in severe trauma and critically ill patients, and each ICU should have a prophylaxis administration protocol for different critical groups. Bleeding from acute mucosal lesion still poses a threat for a potentially lethal com-

plication of severe trauma or critical conditions. Special attention should be paid to the choice of prophylactic agents for individual patients, as the studies conducted thus far do not provide any explicit suggestions as to the approach to prophylactic agent selection.

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