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Editorial

Acid suppression in critically ill patients: is there any real benefit?

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Patients hospitalized in intensive care units (ICU) usually experience a great physiologic stress due to their illness. These patients frequently develop a stress-related mucosal disease (SRMD) in the upper gastrointestinal tract that may result in significant complications if not prevented. SRMD refers to the gastric mucosal injury that develops as a result of severe physiologic stress in other organ systems. The mucosal damage varies greatly from superficial gastritis to deep ulceration. SRMD is a frequent event in critically ill patients occurring in 75% - 100% of individuals within the first 24 hours of admission in ICU.[1] Fortunately, most of these lesions are located only at the superficial layers of gastric mucosa, heal easily and rarely lead to further complications. However, lesions affecting deeper mucosal layers and possibly involving large caliber vessels lead to overt and /or clinically important gastrointestinal (GI) bleeding.

The incidence of upper GI bleeding in critically ill patients is estimated to be approximately 5%.[1] Upper GI hemorrhage appears as either hematemesis, vomiting of fresh blood or coffee- grounds, melena or hematochezia, but not all of them are clinically important. ICU have set criteria in order to stratify this. Thus, any overt bleeding associated with one extra feature of the following, is an important hemorrhage: a) spontaneous decrease in systolic or diastolic blood pressure of = 20 mm Hg within 24 hours of upper GI bleeding. b) an increase of pulse rate of 20 beats /min and a decrease in systolic blood pressure of 10 mmHg on orthostatic change. c) a decrease in hemoglobin of = 2 g/dl in 24 hrs and transfusion of 2 units of packed red blood cells within 24 hrs of bleeding. d) failure of hemoglobin to increase by at least the number of units transfused minus 2 g/dl.[2,3] Having set the above criteria, the incidence of such an important upper GI bleeding lowers to 1% to 2%.[1,4,5] Critically ill patients that suffer a bleeding due to SRMD demonstrate a higher mortality of 50%, compared with matched control patients.[1] In the USA that equals to an extra charge for the ongoing hospitalization of these patients of 7000 $ or even more.[6]

Although the pathophysiology of SRMD is not completely understood, factors that may play an etiological role are mucosal integrity, gastric acid secretion, GI motility and ischemia.[7] The basic mechanism that leads to SMRD seems to be an inability of gastric mucosal barrier to resist against the irritate action of hydrogen in the setting of a relative mucosal ischemia. Hypoperfusion leading to ischemia, is the core of both inducible nitric oxide and oxygen free radical overproduction as well as tissue prostaglandin synthesis decrease.[1] Although critically ill patients do not hypersecrete gastric acid, the presence of acid is mandatory for injury. Thus, by increasing gastric pH above 3.5-5, SRMD could be avoided.[1,5] Additionally, GI motor function of critically ill patients is greatly disturbed. Migrating motor complex (MMC) activity fails to originate and as a result the stomach presents hypokinesia and a delayed emptying.[8,9] These abnormalities can be as frequent as 50%.[8] All the above factors coming together can eventually lead to SRMD. Clinical risk factors for SRMD have thoroughly been studied. Thus, patients at high risk are these who need mechanical ventilation for more than 48 hrs, patients with concomitant coagulopathy, low platelets, shock, sepsis, multiorgan failure, burns and head injury.[2,10] Patients admitted to ICU for cardiac or pulmonary disease and do not need mechanical ventilation are not in high risk for SRMD.

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Therefore, care should be taken towards both prophylactic measures and of course therapy of SRMD in the above subset of critically ill patients. Both targets can be achieved by raising intragastric pH. Either histamine 2-receptor antagonists (H2RAs) or antacids or sucralfate or proton pump inhibitors (PPIs) can accomplish this aim. In the 1990s, Cook et al[4] in a landmark meta-analysis, although did not state the cause of illness, reported on successful prophylactic antisecretory therapy with H2RAs in 7,218 critically ill patients at high risk for stress ulcer, odds ratio (OR), 0.44; 95% CI: 0.22 to 0.88. However, Messori et al in a subsequent meta-analysis failed to confirm the effectiveness of ranitidine on stress-related mucosa (SRM) bleeding prophylaxis, but reported that cimetidine (the only H2RA approved by the USA, Food and Drugs Administration, for this indication) did appear to be superior to placebo OR, 0.37; 95% CI: 0.23-0.60.[11] In the largest randomised controlled trial ever reported, 1,200 mechanically ventilated patients were involved and determined that ranitidine was significantly better than sucralfate for reducing clinically important SRM bleeding OR, 0.44; 95% confidence interval CI: 0.21-0.92. [10] H2RAs and antacids are associated with a weak trend toward lower clinically important bleeding rates than sucralfate.[4] Up to date, there have been no trials directly comparing individual H2RAs with each other, so conclusions regarding individual superiority are not possible, on the basis of existing data.

Because of their more potent antisecretory properties PPIs have been evaluated for stress ulcer prophylaxis in a number of studies. [12,13,14] Unfortunately, these trials that have examined whether acid suppression with (PPIs) reduces the incidence of SRM bleeding have yielded discordant results, likely due to significant differences in study methodology, including small patient numbers, antisecretory agents and doses used, and the definitions of the clinical endpoints studied (intragastric pH). As the incidence of stress ulcer in critical ill patients is low (2%) large trials should practically be warranted to address this issue. Interestingly, Laine and colleagues[14] reported on the results of a randomised trial of 359 patients administered bolus nasogastric-tube dosing of omeprazole suspension compared with continuous-infusion cimetidine in mechanically ventilated critically ill patients. Omeprazole suspension maintained gastric pH > 4, 86% of the time compared with 70.7% for cimetidine ($P < 0.005$), and was associated with similar rates of "clinically significant bleeding" (3.9% vs. 5.5%) and pneumonia (7.9% vs. 6.1%).

To summarise, the bulk of evidence regarding acid suppression for prophylaxis of SRM-related bleeding appears to support its use in selected, high-risk patients, and this conclusion is reflected in current guidelines.[6] The exact degree of protection conferred remains unclear, but a reasonable estimate is approximately 50%.[16] The optimal agent, dose, and route of administration, remains unclear, but current evidence indicates use of acid suppression in high-risk critically ill subpopulation of ICU, with H2RAs representing first-line agents and PPIs coming next. Currently, cimetidine is the only acid-suppressing agent approved by the USA Food and Drugs Administration Office for stress ulcer prophylaxis.

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