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Gastrointestinal stress ulcer prophylaxis in the intensive care unit, where is the data?

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Abstract

Stress-induced gastrointestinal ulcers are common among patients admitted to the intensive care unit (ICU). These ulcers impose significant morbidity and mortality, therefore, stress ulcer prophylaxis (SUP) is a common clinical practice among healthcare providers dealing with these critically-ill patients. Several strategies for SUP have been suggested over the past four decades, with acid suppressive therapies being the most commonly used in the ICU. Whether SUP is effective and safe, or not, remains a topic of controversy. The data is still conflicting, and provision of a simple answer is not feasible at the present time. Recently, a large phase IV, multicenter, randomized clinical trial (SUP-ICU), negated the benefits (and harms) of proton pump inhibitors as SUP. This article

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reviews some of these controversies.

Key words: Gastrointestinal stress ulcers; Proton pump inhibitors; H2-antagonists; Prophylaxis; Complications

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Core tips: Stress ulcer prophylaxis (SUP) is a prevalent clinical practice in patients admitted to intensive care unit (ICU). However, there is no high-quality evidence to support its use. Indeed, current data on its efficacy and complications remains conflictive at best, and until an explicit evidence becomes available, health care providers working in the ICU must carefully analyze the advantages and disadvantages of SUP based on each patient's presentation and comorbidities.

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GASTROINTESTINAL STRESS ULCER PROPHYLAXIS IN THE INTENSIVE CARE UNIT, WHERE IS THE DATA?

Patients with major illnesses (*i.e.*, trauma, shock, sepsis, head injury) are at risk of developing a variety of erosions or erosive lesions in the mucosa of the gastroduodenal tract (known as stress ulcers)^[1]. These erosions are usually acute, multiple, superficial, and occur mainly in the fundus and body of the stomach, which makes them present as a distinct clinicopathological entity different from other types of ulcers (*i.e.*, reactivation of chronic peptic ulcers, Cushing's ulcers due to head trauma, or drug-induced gastritis)^[1]. Endoscopic evaluation has revealed that more than 75% of critically ill patients develop gross gastric lesions within 72 h of admission to the intensive care unit (ICU), and almost 100% of them among extremely critical patients^[2]. However, only a minority of these ulcerations bleed. Indeed, overt bleeding (manifested as bloody nasogastric aspirate, hematemesis, or melena), is reported in 20% of patients without stress ulcer prophylaxis (SUP), while < 5% develop clinically significant bleeding (CSB), defined as overt bleeding with transfusion, hemodynamic instability, and/or the need for intervention^[2]. These lesions usually remain superficial, and cause sub-epithelial hemorrhages^[3]. The occurrence of significant bleeding usually indicates a breach of the submucosa and the development of a true ulcer, and it is associated with increased mortality (RR = 2.9, 95% CI = 1.6-5.5), and significant morbidity (increased ICU stay of 6.2 d, 95% CI = 1.0-11.4 d)^[4].

It is well known that the most important factor in any gastric ulcer formation is the disruption of balance between gastric acid and gastric wall protective mechanisms, and stress ulcers are no exception. In critically ill patients, activation of sympathetic nervous system, increased catecholamine release and vasoconstriction, hypovolemia, decreased cardiac output, and release of proinflammatory cytokines result in splanchnic hypoperfusion^[5]. Subsequently, this hypoperfusion leads to a number of deleterious effects including, ischemic damage to the gastric wall integrity, bicarbonate secretion, gastric hypomotility resulting in delayed emptying of acid, delayed mucosal healing, and reperfusion injury after restoration of splanchnic circulation^[5]. In addition, these effects make the gastric wall vulnerable to damage and ulceration by acid, even if it is within a "normal" pH range.

The compelling morbidity and mortality of gastric ulcers have entailed a prompt action to prevent them among critically ill patients. Acid suppressive therapies seemed to be reasonable options after showing efficacy in decreasing the rate of overt and clinically important bleeding^[6,7]. They rapidly became a standard critical care practice. A survey of 58 ICUs in North America, mainly in university teaching hospitals, revealed that 84% of patients admitted to the ICUs received SUP, with proton pump inhibitors being the most commonly used agents^[8]. It also seems that different proton pump inhibitors (PPIs) have similar efficacies in this clinical setting. Messori *et al*^[9] conducted a meta-analysis and equivalence testing to assess the

difference between intravenous omeprazole and pantoprazole, and they found that these two agents are equivalent according to reasonable equivalence margins. Moreover, several studies have shown that oral and intravenous routes of PPIs administration showed comparable efficacies in suppressing gastric acid secretion^[10-12].

However, later clinical evidence had shown that this therapeutic and prophylactic intervention failed to improve the overall clinical outcomes, and a wide debate has started. Ben-Menachem *et al*^[13] found that SUP with histamine receptor 2 (H2) antagonists neither improved all-cause mortality nor reduced length of stay in ICU patients, when compared to placebo or no intervention. Likewise, Kantorova *et al*^[14] studied the effect of proton pump inhibitors and H2 antagonists as SUP therapies and found no statistically significant difference in length of ICU stay or mortality. Moreover, the routine use of acid suppressive therapies not only might not improve clinical outcomes, but rather has been reported to cause a variety of potential effects. Gastric acid, in addition to its role in digestion, serves as an important sterilizer of the stomach, and its suppression leads to bacterial and fungal overgrowth and predisposes to nosocomial infections^[15]. A large prospective study enrolling 63878 in-hospital non-ventilated patients found that acid suppressive therapies were associated with a 30% increase in hospital acquired pneumonia^[16]. Similarly, several clinical studies have found that acid suppressive therapies are associated with increased risk of *Clostridioides difficile* (*C. difficile*) diarrhea Leonard *et al*^[17] in a meta-analysis evaluating 2948 patients, revealed a statistically significant association between both PPI and H2 antagonists use and hospital-acquired *C. difficile* infection (OR 1.95, 95%CI: 1.48–2.58). However, this association with *C. difficile* was not established in a larger meta-analysis that enrolled 70862 patients with sepsis, and found no statistically significant correlation between *C. difficile* infection and SUP^[18]. This conclusion can be reasonable, especially as *C. difficile* spores, are acid resistant and remain viable at gastric pH^[19]. In addition, the cost of treatment should be considered as well. In one study, the use of acid suppressive therapy in ICU patients showed a cost of 8026 US Dollars per patient^[20]. Given the number of ICU admissions in the United States alone (5.6 million ICU admissions in 2011), this constitutes an unnecessary heavy economic burden, had this preventive measure been ineffective^[21].

A recent multi-center phase IV randomized clinical trial (SUP-ICU) that involved 3298 patients in multiple European countries revealed that intravenous pantoprazole-receiving patients in the ICU were similar to the placebo group in 90-d mortality, rate of *C. Difficile* infection, rate of pneumonia, and surprisingly even in rate of CSB^[22]. However, the study had several limitations, such as clinical (rather than endoscopic) diagnosis of stress ulcer, limited power to detect differences in the subgroup analyses, and more importantly, the study was powered to detect an absolute mortality reduction of 5%, which is quite high and generally implausible in critical patients^[23]. Moreover, the incidence of clinically important bleeding in critically ill patients has been reported to be as low as 2.6% in a large multicenter prospective study, further confirming that absolute reduction of mortality of 5% is unreasonable^[24].

The large number of conflicting studies make it difficult to draw a simple conclusion regarding the effectiveness of this preventive therapy; therefore, systematic reviews would be suitable means to provide the answer. Several systematic reviews have been conducted. A recent Cochrane systematic review and meta-analysis that included 129 clinical studies, found that SUP interventions, compared to placebo or no intervention, in general decreased the rate of clinically important bleeding, but did not have any effect in the risk of nosocomial pneumonia, all-cause mortality, length of ICU stay, or length of intubation^[25]. It also concluded that PPIs were superior to H2 antagonists by decreasing CSB.

Another systematic review and network meta-analysis by Alhazzani *et al*^[26] showed that PPIs are the most effective agents to decrease CSB, followed by H2 antagonists. However, they found that neither PPIs nor H2 antagonists did improve the all-cause mortality or the risk of pneumonia compared to placebo or no prophylaxis^[26]. Furthermore, a very recent systematic review with meta-analysis and trial sequential analysis (TSA) included 41 trials (included the previously described SUP-ICU) further confirmed previous results, that SUP decreases GI bleeding (overt and clinically important) but not all-cause mortality. However, TSA showed that the evidence of reduction of overt GI bleeding (but not clinically important) was firm. In addition, TSA showed that the required information size to assess the risks of pneumonia and *C. difficile* enteritis had not been reached, therefore, establishing relations is not plausible yet.

Other options have also been sought to prevent stress ulcers. To avoid disrupting the protective mechanism of the acid, ulcer-protective agents without altering gastric pH have been suggested as SUP. Sucralfate, for example, binds to gastric ulcers and erosions and protects them from damaging effects of gastric acid. López-Herce *et al*^[27]

found that sucralfate had similar effect to H2 antagonists in decreasing the rate of clinically important bleeding in pediatric patients admitted to ICU ($P < 0.01$), when compared to placebo. However, this option didn't hold up enough. Another clinical study, comparing sucralfate to no intervention in patients with head trauma, did not show any statistical difference in risk of gastrointestinal bleeding^[28]. Moreover, Alhazzani *et al*^[26] in their meta-analysis, among other studies, found that sucralfate did not improve the rate of clinically important bleeding when compared to placebo.

Although current level of evidence strongly suggests no improvement in all-cause mortality from SUP, some authors argued that cause-specific mortality reduction, rather than all-cause mortality reduction, should be considered when investigating preventive therapies^[29]. Indeed, had all-cause (rather than cause-specific) mortality used as a measure to determine the efficacy of radiotherapy in the management of breast cancer (a valuable intervention with substantial improvement in overall survival), this intervention might never have been introduced, because initial all-cause mortality reduction was insignificant due equivalent deaths from cardiovascular complications of therapy, that were later abolished with subsequent modifications to radio beam which ensured less exposure of the heart and the major vessels to radiation^[29]. Meanwhile, recent evidence-based improvements in critical care practice, such as optimal fluid resuscitation (improving splanchnic hypoperfusion) and early provision of enteral feeding, have led to a substantial decrease in rate of CSB, and questions the efficacy of SUP to further decrease the risk of GI bleeding. In a systematic review, Huang and associates analyzed if SUP provided any protections to patients receiving enteral feeding and found no statistically significant difference in rate of gastrointestinal bleeding, mortality, *C. difficile* infection, length of ICU stay, and duration of mechanical ventilation^[30]. Therefore, we believe that a large scale clinical trial comparing cause-specific mortality and morbidity between a group with early enteral feeding plus SUP to controls with early enteral feeding alone will adequately address this clinical issue. In a nutshell, the current data is neither satisfactory to prove the efficacy of this preventive measure nor to deny it, and until further evidence becomes available, it is at the discretion of the healthcare provider whether to administer SUP to critical patients.

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