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Prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation

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Introduction

Stress ulcer-related gastrointestinal (GI) bleeding is a serious complication which increases morbidity and mortality in ICU patients. Prophylactic therapy against stress ulcers has focused on neutralisation (antacids), reduction of gastric acid secretion (H_2-antagonists) and more recently on cytoprotection (sucralfate). However, prophylactic therapy is costly and may lead to side effects such as nosocomial pneumonia due to gastric and nasopharyngeal colonisation by aerobic Gram-negative bacilli. Controversy exists concerning whether prophylactic therapy should be routinely used in all ICU patients, or only in some populations at risk. Questions which need to be answered are: What do we consider as an end point to study: overt bleeding or clinically important bleeding? Which are the most reliable risk factors for GI bleeding? Which therapeutic modality (a specific drug or a combination of drugs) offers better protection with fewer side effects, such as the increased incidence of nosocomial pneumonia? These are questions that Cook and co-workers tried to answer in a series of articles.

Cook D, Guyatt G, Marshall J et al. (1998) A comparison of sucralfata and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N Engl J Med 338: 791–797

This multicentre, randomised, blinded, placebo-controlled trial filled a gap in our knowledge by directly comparing sucralfate and the H-2 receptor antagonist ranitidine on the rate of GI bleeding, ventilator-associated pneumonia and mortality. They found no difference between the two drugs concerning the incidence of ventilator-associated pneumonia and mortality. However, ranitidine was more effective than sucralfate in preventing clinically important GI bleeding (1.7 % versus 3.8 % respectively, $p = 0.02$).

Cook D, Fuller H, Guyatt G, et al. (1994) Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med 330: 377–381

This study was conducted in order to identify patients at sufficiently low risk of bleeding to restrain the need for prophylaxis. Two thousand fifty-two patients were included in the study, among them 847 had respiratory failure requiring mechanical ventilation and/or coagulopathy, and 674 received prophylaxis against stress ulcers. Of the 2252 patients, 100 had overt bleeding episodes (4.4 %); among these 100 patients, 87 were receiving prophylaxis (3.8 %). Of the 2252 patients, 33 had clinically important bleeding (1.5 %), 23 out of 33 were receiving prophylaxis (69.7 %). Moreover, of these 33 patients with clinically important bleeding, 31 had respiratory failure and/or coagulopathy (31 out of 847 = 3.7 %). By contrast, the occurrence of clinically important bleeding in the remaining 1405 patients without respiratory failure and/or coagulopathy was only 0.1 % (2 out of 1405). They conclude that the risk of clinically important GI bleeding in critically ill patients is extremely low, therefore prophylaxis can be safely withheld unless the patient has respiratory failure and/or coagulopathy. When the incidence of GI bleeding in the sucralfate group of the more recent study (3.8 %) was compared with the incidence in the non-treatment/control group (3.7 %) in the first prospective multicentre cohort study, the authors speculate that sucralfate has no effect on clinically important bleeding.

Cook D, Witt L, Cook R, Guyatt G (1991) Stress ulcer prophylaxis in the critically ill: a meta-analysis. Am J Med 91: 519–527
In this meta-analysis study of 42 randomised controlled trials, they found that in critically ill patients who have an appreciable risk of bleeding, stress ulcer prophylaxis induced a 50% reduction in clinically important bleeding. In the same study, comparison of various prophylactic drugs and with a placebo/control showed: (1) all drugs do better than a placebo/control; (2) H-2 receptor antagonists are more effective than antacids in reducing overt haemorrhage and they are the only ones able to reduce clinically important bleeding; (3) sucralfate was equivalent to antacids in preventing overt bleeding but the data was insufficient to compare the effect of sucralfate with H-2 receptor antagonists.

Discussion

These studies seem to indicate that the incidence of clinically important bleeding in the critically ill patient is less than 2%. However, this result may reflect a relatively less sick population than in other studies. H2-antagonists are more effective than sucralfate or antacids in preventing clinically important GI bleeding without increasing the incidence of nosocomial pneumonia. Risk factors for GI bleeding are respiratory failure and/or coagulopathy. However, if we accept the evidence that coagulopathy may induce GI bleeding, respiratory failure is not sufficient, per se, to produce bleeding. Other factors that lead to gastric mucosal ischaemia and disruption must be present (sepsis, haemodynamic compromise, etc.). This is supported by Zandstra's study [**Zandstra D et al. (1994) Intensive Care Med 20: 335–340**] who reported the virtual absence (0.6%) of GI bleeding in 167 mechanically ventilated patients without any prophylaxis who were treated with aggressive haemodynamic support and sepsis prevention.

In another study conducted in septic patients [**Labattut AG et al. (1992) Clin Intensive Care 3: 19–25**], 88.9% of the GI bleeding occurred beyond the first 7 days after admission. Similar findings were reported in Cook's studies, where GI bleeding occurred at a mean of 14 days after admission to the ICU, however, the median duration of intubation was between 7 and 8 days. This indicates a population of patients who might bleed if the severity of their primary disease requires a more prolonged ventilatory support. With some reservation, if respiratory failure and/or coagulopathy are the only independent risk factors for GI bleeding, patients without these risk factors have a very low incidence (0.1%) of clinically important bleeding, and this allows a more selective use of prophylaxis against stress ulcers. Mortality was equal between the prophylaxis-treatment groups but higher than in the non-treatment/control group, due to the fact that the severity of illness in the prophylaxis group was higher than in the control group. Moreover, when the incidence of GI bleeding in the sucralfate group of the most recent randomised control study **(N Engl J Med 1998; 338: 791–797)** was compared with the incidence in the non-treatment/control group in the first prospective multicentre cohort study **(N Engl J Med 1994; 330: 377–381)** (3.8 vs. 3.7%), we may speculate that sucralfate has no effect on clinically important bleeding.