Neuroanesthesia and Intensive Care

Best evidence in critical care medicine

Stress ulcer prophylaxis in the intensive care unit: damned if you do, damned if you don't

Article appraised

Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. N Engl J Med 1998; 338: 791–7.

Structured abstract

Background: Intensive care unit patients requiring mechanical ventilation are at risk of stress ulcers and gastrointestinal hemorrhage. Agents used to prevent bleeding in this population have included sucralfate and H₂-receptor antagonists. The efficacy of these interventions is poorly quantified, and concern has arisen that suppression of gastric acid may predispose to ventilator-associated pneumonia.

Design: This was a multicentre, randomized, blinded trial of sucralfate *vs* ranitidine for the prevention of upper gastrointestinal hemorrhage in patients requiring mechanical ventilation. The trial was powered to detect a 25% difference in rates of nosocomial pneumonia between treatment groups.

Patients: 1,200 consecutively admitted intensive care unit patients, expected to require at least 48 hr of mechanical ventilation, were enrolled, out of a total of 7,986 assessed. Patients were excluded who were admitted with a diagnosis of pneumonia or gastrointestinal bleeding, who had previous gastrectomies, who were not expected to survive, or who had received either study therapy in open-label form. Baseline characteristics were similar between groups.

Intervention: Patients received either active ranitidine (50 mg *iv* every eight hours) and placebo sucralfate, or active sucralfate suspension (1 g orally or by nasogastric tube every six hours) and placebo ranitidine. There was no study group that did not receive either active intervention.

Primary endpoint: Clinically-important gastrointestinal bleeding was compared between groups, and

was defined as overt hemorrhage plus one of four measures of severity (defined decreases in hemoglobin or hemodynamic changes). Rates of mortality while in intensive care, and rates of ventilator-associated pneumonia (defined by Centers for Disease Control criteria) were also compared. Implicit in the introduction is that these were co-primary endpoints. No *a priori* hypothesis was stated.

Results: Rates of clinically-significant gastrointestinal hemorrhage were 1.7% in patients receiving ranitidine, as compared with 3.8% in patients receiving sucralfate (RR = 0.44; *P* = 0.02). Mortality rates were 23.5% in the ranitidine group *vs* 22.8% in the sucralfate group (*P* = NS). Rates of ventilator-associated pneumonia were 19.1% in the ranitidine group *vs* 16.2% in the sucralfate group (RR = 1.18; *P* = 0.19).

Conclusion: Ranitidine prophylaxis decreases clinically-significant gastrointestinal hemorrhage as compared with sucralfate prophylaxis, with no statistically significant difference in mortality.

Commentary by R.M. Penner, P.G. Brindley and M.J. Jacka

Any clinician posing the question: "Should my intubated patient receive stress-ulcer prophylaxis, and if so, with what medication?" will be disappointed if expecting a definitive answer from the current literature. Studies have been small and of variable quality, and meta-analyses have reached differing conclusions. In 1996, before the trial reviewed above, Cook *et al.* addressed multiple questions via a detailed, and highly inclusive meta-analysis.¹ They found that H₂-receptor antagonists were superior to placebo in reducing the incidence of clinically-significant gastrointestinal bleed, but the advantage of ranitidine as compared to sucralfate or antacids did not reach statistical significance. Their review showed that sucralfate prophylaxis was associated with a trend towards decreased pneumonia, and a similar mortality rate, as compared

with H₂ blocker prophylaxis. The mortality rate with sucralfate prophylaxis was significantly lower than with antacids.

The randomized controlled trial (RCT) by Cook *et al.*, that is the subject of this review, was no doubt motivated by the questions that remained unanswered from their meta-analysis. The reduction in mortality associated with sucralfate and antacids, and the increased efficacy of gastrointestinal bleed prophylaxis by ranitidine, would seem to make a sucralfate-*vs*-ranitidine trial the final chapter in this clinical conundrum. Unfortunately, not all authors were in agreement with Cook's study design and conclusions, and therefore her RCT was criticized for the lack of a placebo group.²

Despite the aforementioned criticism, Cook's RCT has come to dominate the literature, and has led to widespread *iv* and oral H₂ antagonists for intubated patients. In a subsequent meta-analysis by Messori *et al.*,³ Cook's RCT alone constituted 1,200 patients, out of a total of less than 2,700, and occupied sole first place in terms of trial quality. Importantly, though perhaps surprisingly, Messori's meta-analysis found that neither sucralfate nor ranitidine were superior in the prevention of bleeding as compared with placebo. They further found that ranitidine-treated patients had significantly increased rates of pneumonia as compared with sucralfate (a result largely driven by the trend in Cook's RCT, which did not reach statistical significance in that RCT alone, but did when combined with other studies).

Based upon these results, clinicians can support any of three different prophylactic strategies:

- 1) Routine ranitidine prophylaxis: a single strong RCT suggests that ranitidine is superior to sucralfate. However, this strategy is worrisome because of increased rates of ventilator-associated pneumonia (in Cook's RCT, the ranitidine group had 15 more ventilator associated pneumonias, and 13 less gastrointestinal bleeds than sucralfate).
- 2) Routine sucralfate prophylaxis: mortality data show sucralfate to be superior when compared to antacids, and associated with lower rates of pneumonia when compared to ranitidine. However, sucralfate is inferior to ranitidine for bleed prevention.
- 3) No prophylaxis: given the axiom of "first do no harm," and the lack of consistent or substantial mortality benefit from sucralfate or H₂ blockers.

In conclusion, routine prophylaxis against stress ulcers in the intensive care unit is not well justified by the current evidence. In general though, sucralfate is

safe and has demonstrated a mortality benefit in certain settings. Stronger acid suppression, such as with ranitidine, may be justified in patients at particularly high risk of gastrointestinal hemorrhage, or in those where bleeding would be catastrophic. Any further study of prophylaxis should include proton pump inhibitors, given their widespread use, and must include a placebo arm. In addition, efforts should be geared towards expediting enteral feeding (given its associated protective effects), as well as strategies that treat the underlying critical illness or facilitate earlier extubation.

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References

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