The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis

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CRD summary
This review found there were no differences in outcomes between treatment with proton pump inhibitors and histamine-2 receptor antagonists for critical care patients in intensive care units. The authors' cautious conclusions reflect the evidence presented, but the poor quality of the included trials and the potential for publication and language biases should be considered when interpreting the results.

Authors' objectives
To evaluate the safety and efficacy of proton pump inhibitors compared with histamine-2 receptor antagonists for stress-related upper gastrointestinal bleeding prophylaxis in critical-care patients admitted to intensive care units.

Searching
PubMed, EMBASE, the Cochrane Library and Clinicaltrials.gov were searched from inception to May 2008 for English language studies; search terms were reported. Searches were repeated to identify new research until October 2009. Reference lists of review articles and identified articles were checked for additional references.

Study selection
Randomised and quasi-randomised controlled trials that compared proton pump inhibitors with histamine-2 receptor antagonists in adult patients admitted to medical or surgical intensive care units for upper gastrointestinal tract bleeding prophylaxis were eligible for inclusion. Pharmacokinetic studies and studies that used intragastric pH as the only outcome of interest were excluded, as were studies that did not clearly specify the admission of patients to intensive care units.

The primary outcome was the incidence of stress-related upper gastrointestinal tract bleeding. Secondary outcomes were the incidence of pneumonia and intensive care unit mortality.

The settings for the included trials were general medical and surgical intensive care units. The mean age of the patients ranged from 40.8 to 57.1 years (where reported). Definitions of upper gastrointestinal bleeding varied. The proton pump inhibitors included were intravenous omeprazole (40 to 120mg/day), enteral omeprazole simplified suspension or capsule (20 to 40mg/day), or intravenous pantoprazole (40 to 240 mg/day). The histamine-2 receptor antagonists were intravenous ranitidine (150 to 200mg/day), intravenous cimetidine infusion (50mg/hr), or intravenous famotidine (80 mg/day). Enteral nutrition varied from almost nothing given by mouth up to 42% (where reported).

Two reviewers independently performed the study selection.

Assessment of study quality
Two reviewers independently evaluated methodological quality using the Jadad 5-point scale assessing randomisation, concealment, blinding and follow-up. Trials that scored fewer than 3 points were deemed to be low quality. Any disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted data to calculate risk differences (RD) and 95% confidence intervals (CI) for the outcomes. In the event that data were missing, the authors of the included trial were contacted. Any disagreements between the reviewers were resolved by discussion.

Methods of synthesis
Pooled risk differences and 95% confidence intervals were calculated using a random-effects model. Heterogeneity was assessed using the Cochran's Q-statistic and quantified using $I^2$. Potential sources of heterogeneity were investigated in
sensitivity and subgroup analyses. Publication bias was assessed by examining funnel plots for asymmetry.

Results of the review
Seven trials (n=936) were included in the review, comprising five fully published trials and two abstracts. Sample sizes ranged from 31 to 359 patients. Three trials were assigned Jadad quality scores of 1 point, two trials scored 3, one trial scored 4 and one trial scored the maximum Jadad score of 5 points.

There were no significant differences between proton pump inhibitors and histamine-2 receptor antagonists in stress-related upper gastrointestinal bleeding prophylaxis (seven trials; n=936 patients; I²=66%), pneumonia (six trials; n=905 patients; I²=0%) and mortality (three trials; n=569 patients; I²=0%) in patients admitted to intensive care units. Removal of one trial reduced the between-trial heterogeneity for the analysis of stress-related upper gastrointestinal bleeding (I²=26%).

There were no differences between proton pump inhibitors and histamine-2 receptor antagonists in subgroups analyses that evaluated the requirement for mechanical ventilation as an inclusion criterion, reporting of baseline characteristics, route of administration, trial quality, whether upper gastrointestinal bleeding was well defined or otherwise, and the type or dose of proton pump inhibitor. Trials published prior to 2000 showed significant benefits with proton pump inhibitor treatment (RD -0.11, 95% CI -0.21 to -0.01, three trials; I²=54%; supplementary details published online, see URL for additional data).

The funnel plot showed some evidence of publication bias, language bias and inflated estimates of effect because of flawed methodology in smaller included trials.

Authors’ conclusions
There was no evidence of differences in outcomes in patients in intensive care units who were treated with proton pump inhibitors compared with those treated with histamine-2 receptor antagonists in stress-related upper gastrointestinal tract bleeding prophylaxis, pneumonia, and mortality. Further well-designed trials are required as the results of this review remain inconclusive.

CRD commentary
The review addressed a clearly defined question. Criteria for the inclusion of studies were clearly stipulated. The review was restricted to trials published in English language only, which meant there was a risk of language bias; formal analysis suggested evidence for this. Although there were some attempts to identify unpublished literature, there was some evidence of publication bias reported. The reviewers took a number of steps to minimise errors and biases at each stage of the review process.

Trial quality was assessed using an appropriate tool; the results of this assessment showed that most of the trials were of poor quality. The authors’ decision to pool the results of the trials appeared to be justified. Potential sources of heterogeneity were appropriately explored.

The authors’ cautious conclusions reflect the evidence presented, but the poor quality of the included trials and the potential for publication and language biases should be considered when interpreting the results.

Implications of the review for practice and research
**Practice:** The authors stated that if decisions are made to suppress gastric secretion, patients should be treated on the basis of their individual risk of gastrointestinal bleeding from stress ulcers and that treatment decisions also account for the convenience of drug administration, potential drug interactions and cost.

**Research:** The authors stated that well-designed and sufficiently powered randomised controlled trials are required, because the evidence for this review remains inconclusive. They also stated that stratification of patients by risk factors is required to explore optimal regimens in terms of drug, dosage, mode of administration, timing and treatment duration among patients with different levels of risk.
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