Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis

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CRD summary
The review concluded that, in critically ill patients, proton pump inhibitors seemed more effective than histamine 2 receptor antagonists in preventing clinically important and overt upper gastrointestinal bleeding, but limitations in the evidence mean that these findings should not be considered as being robust. The authors' conclusions are likely to be reliable.

Authors' objectives
To determine the efficacy and safety of proton pump inhibitors compared with histamine 2 receptor antagonists for the prevention of upper gastrointestinal bleeding in critically ill patients.

Searching
MEDLINE, EMBASE, ACPJC, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions up to March 2012. Three online trials registries, conference proceedings databases and reference lists of relevant articles were also searched. Search strategy details were available in an online appendix.

Study selection
Parallel-group randomised controlled trials (RCTs) that compared proton pump inhibitors with histamine 2 receptor antagonists in critically-ill adults in intensive care were eligible. Studies had to report clinically important upper gastrointestinal bleeding or overt upper gastrointestinal bleeding.

Both the types and the doses of the proton pump inhibitors and histamine 2 receptor antagonists varied considerably, though many studies used omeprazole and/or ranitidine. Trial population characteristics (for example, medical or surgical patients) and the bleeding definitions used also varied widely. Half the studies were performed in the USA.

Two reviewers selected studies for inclusion.

Assessment of study quality
The Cochrane risk of bias tool was used by two reviewers independently, with disagreements resolved by discussion. The GRADE approach was also used to evaluate the quality of evidence.

Data extraction
Data were extracted to calculate relative risks or mean differences with 95% confidence intervals. Trial authors were contacted for additional or clarifying information when necessary. Two reviewers independently extracted data, with disagreements resolved by discussion.

Methods of synthesis
Meta-analyses were performed using a random-effects model. Heterogeneity was assessed using $X^2$ and $I^2$. Five different sub-group analyses were pre-specified. Publication bias was assessed using a funnel plot and Egger's test.

Results of the review
Fourteen trials (1,720 patients) were included. Three trials were judged to be at low risk of bias, six trials had high risk of bias and five had an unclear risk of bias. Most of the high risk was due to inadequate blinding (though further details on this were not presented). Four trials were published in abstract form only.

Proton pump inhibitors appeared more effective than histamine 2 receptor antagonists at reducing clinically important upper gastrointestinal bleeding (RR 0.36, 95% CI 0.19 to 0.68; 12 RCTs, five without any events; $I^2=0\%$) and overt upper gastrointestinal bleeding (RR 0.35; 95% CI 0.21 to 0.59, 14 RCTs, five without any events; $I^2=15\%$). There was
evidence of publication bias for the clinically important bleeding outcome.

For both of the above outcomes, trials at low risk of bias were significantly associated with a smaller treatment effect when compared with trials having a high or unclear risk of bias; when results from only the low risk of bias studies were pooled there were no statistically significant differences between treatments for both outcomes. When absolute risk difference was used as an effect estimate (in a sensitivity analysis), statistically significant heterogeneity was evident. There were no subgroup differences when investigating the effect of: route of proton pump inhibitor administration, frequency of proton pump inhibitor dosing, intensive care unit type, or trial setting (Asian versus non-Asian).

There were no differences in the risk of nosocomial pneumonia (eight RCTs), intensive care unit mortality (eight RCTs), or intensive care unit length of stay (five RCTs). No trials reported on *C. difficile* infection.

**Authors’ conclusions**
In critically ill patients, proton pump inhibitors seemed more effective than histamine 2 receptor antagonists in preventing clinically important and overt upper gastrointestinal bleeding. The robustness of this conclusion was limited by the trial methodology, differences between lower and higher quality trials, sparse data and possible publication bias. There were no differences between drugs in the risk of pneumonia, death or intensive care unit length of stay.

**CRD commentary**
The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify all relevant studies in any language were undertaken using various appropriate methods. Suitable methods (for example, independent duplicate processes) were used to reduce the risk of reviewer error and bias throughout the review.

Risk of bias was assessed and was used in interpreting the results of the review. Funnel plots also indicated that small study effects may have biased the pooled results. Adequate primary study details were provided. Appropriate methods were used to pool data and to assess heterogeneity. The authors’ conclusions appropriately reflect the limitations of the available evidence, and they appear likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated a need for more research into current gastrointestinal bleeding rates, and the role of acid suppression in predisposing to *C difficile* infection in the intensive care unit.

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