Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses

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Authors' objectives
To provide estimates of the effect of stress ulcer prophylaxis on gastrointestinal bleeding, pneumonia, and mortality in critically-ill patients.

Searching
MEDLINE and EMBASE were searched from 1966 to January 1 1995 using the MeSH terms provided. Additional published studies were located by identifying frequently cited references, using SciSearch to locate further studies cited in these articles, and by examining reference lists of all identified articles.

Unpublished material was identified through personal files, conference abstracts, and contact with authors of primary studies and pharmaceutical companies marketing prophylactic drugs. In addition, the National Institutes of Health and the Medical Research Council of Canada were contacted to identify research projects funded in this area, and the Federal Research in Progress database, Medical Research Directory, IEP, NTIS, Microlog, Conference Papers Index, and BIOSIS Previews were searched. Studies in all languages were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were considered.

Specific interventions included in the review
One or more prophylactic drugs (antacids, histamine-H2-receptor antagonists, or sucralfate) in comparison with each other, or a placebo or untreated control group.

Participants included in the review
Critically-ill patients were included.

Outcomes assessed in the review
The outcomes were gastrointestinal bleeding (overt and clinically important, both defined), pneumonia and mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the titles and abstracts. Articles identified as meeting the study design, target population and outcome measure criteria by one or both reviewers were retrieved, and the criteria independently applied to the full text.

Assessment of study quality
The primary studies were assessed for patient selection, group comparability, method of randomisation, blinding and definition of outcomes (bleeding and pneumonia). Methodological quality was graded for each item on a scale of 0 to 2; the maximum score available was 12. Two reviewers independently evaluated each study. All authors were asked to check the completed quality assessment forms for accuracy and to provide missing information.

Data extraction
Two reviewers independently extracted the data from each study. For abstracts, data were coded from the full manuscripts which were obtained from the authors whenever possible. Authors were asked to check the completed data extraction forms.
Methods of synthesis
How were the studies combined?
The drug effects were summarised using the weighted average of the odds ratio (OR) of individual studies. Two-tailed p-values and 95% confidence intervals (CIs) were calculated using a fixed-effect model.

How were differences between studies investigated?
The trials were grouped according to treatment comparisons and heterogeneity was assessed using the method described by Fleiss (see Other Publications of Related Interest no.1).

Results of the review
Sixty-three RCTs (n=7,218) were included.

The mean overall score for methodology was 5.3.

Overt bleeding: histamine-H2-receptor antagonists significantly reduced overt bleeding in comparison to both placebo or no therapy, OR 0.58 (95% CI: 0.42, 0.79) (trials were shown to be statistically heterogeneous), and antacid therapy, OR 0.44 (95% CI: 0.37, 0.84). Sucralfate significantly decreased overt bleeding in comparison to no prophylaxis, OR 0.58 (95% CI: 0.34, 0.99). A strong trend in favour of antacids over placebo or no therapy was demonstrated, but not found to be statistically significant. There was no evidence to suggest a differential effectiveness of sucralfate versus either antacids or histamine-H2-receptor antagonists for overt bleeding.

Clinically-important bleeding: histamine-H2-receptor antagonists were shown to be statistically-significantly superior to placebo or no therapy, OR 0.44 (95% CI: 0.22, 0.88). No other statistically-significant differences were demonstrated, although there was a trend in favour of histamine-H2-receptor antagonists versus antacids in the prevention of clinically-important bleeding.

Pneumonia: a trend toward a lower incidence of pneumonia was demonstrated when sucralfate was compared to either antacid therapy or histamine-H2-receptor antagonists. Histamine-H2-receptor antagonists were associated with an increased incidence of pneumonia in comparison with no prophylaxis. This difference was not statistically significant.

Mortality: sucralfate was associated with a statistically-significant reduction in mortality when compared to antacids, OR 0.73 (95% CI: 0.54, 0.97). A trend in favour of sucralfate over histamine-H2-receptor antagonists was also demonstrated.

Authors' conclusions
There is strong evidence of reduced clinically-important gastrointestinal bleeding with histamine-H2-receptor antagonists. Sucralfate may be as effective in reducing bleeding as gastric pH-altering drugs, and is associated with lower rates of pneumonia and mortality. However, the data are insufficient to determine the net effect of sucralfate compared with no prophylaxis.

CRD commentary
This was a thorough and well-documented review.

Implications of the review for practice and research
A full economic evaluation, incorporating both costs and consequences, would help in the development of evidence-based clinical practice guidelines regarding the administration of prophylactic agents to critically-ill patients.

Bibliographic details
Other publications of related interest

This additional published commentary may also be of interest. Ranitidine and gastrointestinal bleeding in intensive care. BMJ 2001;322:995.

Indexing Status
Subject indexing assigned by NLM

MeSH
Antacids /therapeutic use; Anti-Ulcer Agents /therapeutic use; Critical Care; Critical Illness /mortality /therapy; Female; Gastrointestinal Hemorrhage /mortality /prevention & control; Histamine H2 Antagonists /therapeutic use; Humans; Male; Peptic Ulcer /prevention & control; Pneumonia /mortality; Randomized Controlled Trials as Topic; Risk Factors; Stress, Physiological; Sucralfate /therapeutic use

AccessionNumber
11996008048

Date bibliographic record published
31/07/1997

Date abstract record published
31/07/1997

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.