Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis

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CRD summary
This well-conducted review concluded that the quality and quantity of evidence supporting the use of stress ulcer prophylaxis was low. The authors' conclusion that there was no firm evidence of benefit or harm accurately reflects the presented evidence.

Authors' objectives
To assess the effects of stress ulcer prophylaxis in adult patients in intensive care units.

Searching
MEDLINE, EMBASE, and The Cochrane Library were searched to March 2013; search terms were reported. Reference lists of included randomised controlled trials (RCTs) and other relevant systematic reviews were checked. No language or publication restrictions were applied.

Study selection
RCTs of adult intensive care unit patients receiving stress ulcer prophylaxis versus proton pump inhibitors or histamine 2 receptor antagonists were eligible for inclusion. Trials could have more than one intervention group; control groups had to receive placebo or no prophylaxis.

Included RCTs were published from 1977 to 2004 and were conducted in USA, Canada, UK, Germany, The Netherlands, Italy, Spain, Switzerland, Czech Republic and India; four were multicentre RCTs. Trials were in surgical, medical or mixed intensive care units, with mainly high-risk patients. Intravenous cimetidine, ranitidine, omeprazole and metiamide were used as the prophylaxis intervention, with the exception of one trial where cimetidine was delivered intravenously or orally. Over half of the trials used a placebo control. Patients were fed enterally in some of the trials.

Two reviewers independently assessed studies for inclusion; disagreements were resolved by a third reviewer.

Assessment of study quality
Two reviewers independently assessed the quality of included trials using the Cochrane risk of bias tool.

Data extraction
Outcomes (all-cause mortality, gastrointestinal bleeding, and hospital-acquired pneumonia) were extracted from each trial to calculate relative risks with 95% confidence intervals.

Two reviewers independently extracted data.

Methods of synthesis
Trials were pooled using a fixed-effect model, if there was no statistical heterogeneity, measured by $I^2$ ($I^2=0\%$). If $I^2$ was higher than 0%, results for both fixed-effect and random-effects models were reported. Trial sequential analysis was used to investigate whether the sample size of the meta-analysis was sufficient to detect an effect. Continuity correction in trials with zero events was applied in sensitivity analyses.

Subgroup analyses were: high versus low risk of bias; adequate versus inadequate random sequence generation, allocation concealment and blinding; protein pump inhibitors versus histamine 2 receptor antagonists; medical versus surgical versus mixed intensive care unit; enteral nutrition versus no enteral nutrition; and placebo trials versus no prophylaxis trials.
Funnel plot analysis was used to assess publication bias.

**Results of the review**

Twenty RCTs were included (1,971 intensive care unit patients, range 25 to 208). Length of follow up ranged from seven to 29 months. All of the trials were judged to be at high risk of bias. Few trials reported adequate randomisation methods, allocation concealment or blinding.

There was a significant difference in gastrointestinal bleeding in favour of stress ulcer prophylaxis (random-effects RR 0.44, 95% CI 0.28 to 0.68; 20 RCTs; I²=48%; fixed-effect results similar). This beneficial effect was not found in any of the subgroup analyses or trial sequential analysis.

There were no significant differences in all-cause mortality (fixed-effect RR 1.00, 95% CI 0.84 to 1.20; 15 RCTs; I²=0%) or hospital-acquired pneumonia (random-effects RR 1.23, 95% CI 0.86 to 1.78; seven RCTs; I²=19%; fixed-effect results similar) between patients treated with stress ulcer prophylaxis and those treated with placebo or no prophylaxis.

Results of subgroup analyses and trial sequential analysis did not differ for these two outcomes. Sensitivity analysis did not change the results for any outcome. Trial sequential analysis showed that there were insufficient numbers of patients included to detect a clinically meaningful difference in the meta-analysis for all three outcomes.

There was possible publication bias for the all-cause mortality outcome.

**Authors' conclusions**

There was no firm evidence for benefit or harm of stress ulcer prophylaxis compared with placebo or no prophylaxis.

**CRD commentary**

The review question and inclusion criteria were clear. Several sources were searched, with no language or publication status limitations. Efforts were made to reduce the potential for reviewer error and bias in the review process.

Trial quality was assessed using an appropriate tool; the results for each trial were reported. Reporting a random-effects model was appropriate for those outcomes where there was statistical heterogeneity, which may be explained by differences in trial authors' definitions of the outcomes. All of the included trials were at high risk of bias, which may affect the reliability of the results. The trials were small with some reporting few or zero events for some outcomes. Trial sequential analysis highlighted the sparseness of the data.

The conclusions of this well-conducted review accurately reflect the presented evidence.

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

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

**Research:** The authors stated that large robust RCTs should be conducted to determine whether critically-ill patients in intensive care unit should be treated with stress ulcer prophylaxis.

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