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Stress ulcer prophylaxis versus placebo in critically ill patients: a systematic review of randomised trials with meta-analysis and trial sequential analysis

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Review question(s)

The aim of the present systematic review is to assess the effects of SUP versus placebo or no treatment on all-cause mortality, GI bleeding and hospital-acquired pneumonia in critically ill patients in the ICU.

Research question: Is SUP in critically ill patients in the ICU superior to placebo or no treatment?

Searches

We will search the Cochrane Library, MEDLINE, and EMBASE.

We will also hand search the reference lists of relevant trials and other systematic reviews of SUP in the critically ill patients.

Types of study to be included

We will include randomized clinical trials of human subjects without consideration of publication status, blinding status or language.

Condition or domain being studied

SUP with proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA).

Participants/ population

Adult critically ill patients in the ICU.

Trials of animals or healthy human subjects will be excluded.

Intervention(s), exposure(s)

PPIs.

H2RAs.

Comparator(s)/ control

Placebo.

No treatment.

Outcome(s)

Primary outcomes

All-cause mortality.

Secondary outcomes

GI bleeding.

Hospital-acquired pneumonia.

Data extraction, (selection and coding)

Two persons will independently extract and collect the data on a standardized paper form. We will not be blinded to the author, institution, or the publication source of trials.

Risk of bias (quality) assessment

We will use the risk of bias table described in the Cochrane Handbook section 8.5 as a tool for assessing risk of bias in included studies.

The risk of bias will be evaluated according to the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance, bias due to vested financial interest and academic bias.

Strategy for data synthesis

We will use Review Manager software (RevMan 5.0) as statistical software. We will calculate the RR with 95% confidence interval (CI). We will use D-squared and I-squared to describe heterogeneity among the included trials. We will explore causes of substantial heterogeneity by meta-regression. We will use the chi-squared test to provide an indication of heterogeneity between studies, with P = 0.10 considered significant. We will use Egger's test to measure funnel plot asymmetry. Most meta-analytic software packages do not include options for analysis including trials with 'zero event' in both arms (intervention versus control) when calculating RR. Exempting these trials from the calculation of RR and CI may lead to overestimation of a treatment effect as the control event proportion may be overestimated. Thus we will perform a sensitivity analysis by applying empirical continuity corrections to our zero event trials as proposed by Sweeting et al. by applying an imaginary, small mortality in both arms.

Meta-analyses may result in type 1 errors due to sparse data and repeated significance testing when meta-analyses are updated with new trials. Systematic errors from trials with high-risk of bias, outcome reporting bias, publication bias, early stopping for benefit, and small trial bias may result in spurious P-values. In a single trial, interim analysis increases the risk of type 1 errors. To avoid type 1 errors, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P value, that is the cumulative Z-curve crosses the monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses as well, called trial sequential monitoring boundaries. In 'trial sequential analysis' (TSA) the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to decide whether additional trials are needed. So far several meta-analyses and reviews have been published including an increasing number of trial results as new trials have been published. It therefore seems appropriate to adjust new meta-analysis for multiple testing on accumulating data to control the over-all type 1 error risk in cumulative meta-analysis. The idea in TSA is that if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials may be needed. However, there is insufficient evidence to reach a conclusion if the Z-curve does not cross the boundary or does not surpass the required information size. To construct the trial sequential monitoring boundaries (TSMB) the required information size is needed and will be calculated as the least number of participants needed in a well-powered single trial. We will adjust the required information size for heterogeneity with the diversity adjustment factor. We will apply TSA since it prevents an increase of the risk of type 1 error (< 5%) due to potential multiple updating and testing on accumulating data whenever new trial results are included in a cumulative meta-analysis and provides us with important information in order to estimate the level of evidence of the experimental intervention. Additionally, TSA provides important information regarding the need for additional trials and the required sample size herein. We will apply trial sequential monitoring boundaries according to an information size suggested by the trials with low-risk of bias and an a priori 20% relative risk reduction (RRR) of SUP.

Analysis of subgroups or subsets

We plan to do the following subgroup analyses:

1. Comparing estimates of the pooled intervention effect in trials with low risk of bias to estimates from trials with high risk of bias (i.e., trials having at least one unclear or high risk of bias component).

2. If none of the included trials have low risk of bias we will compare the intervention effect estimate in trials with

lower risk of bias (adequate allocation sequence generation, allocation concealment, and blinding of investigators, participants, and outcome assessors) to the intervention effect in trials with high risk of bias.

3. Comparing estimates of the pooled intervention effect in trials conducted in medical ICUs, surgical ICUs and mixed ICUs.

4. Comparing estimates of the pooled intervention effect in trials comparing PPI vs. placebo or no treatment and H2RA vs. placebo or no treatment.

5. Comparing estimates of the pooled intervention effect in trials conducted in patients receiving enteral nutrition to estimates from trials in patients not receiving enteral nutrition.

Dissemination plans
Publication in international peer-review journal.

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Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes