Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient

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CRD summary

This well-conducted review concluded that antioxidants, particularly selenium, are safe and may be associated with a reduction in mortality in critically ill patients. The conclusions concerning mortality appear reliable. However, the results presented for mortality and infectious complications may not represent adequate evidence of safety.

Authors' objectives

To review randomised trials of antioxidant strategies for their effects on mortality and infectious complications in critically ill patients.

Searching

MEDLINE, EMBASE, CINAHL, the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched from 1980 to December 2003; the search terms were partially reported. Personal files, meeting abstracts and review articles were also checked, and manufacturers were contacted. Reports written in any language were eligible.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion; pseudo-randomised trials were excluded.

Specific interventions included in the review

Trace elements with or without vitamins, compared with placebo, were eligible interventions. Studies of multiple nutrients given in addition to vitamins and trace elements were excluded. Most of the included studies assessed selenium alone or combined with other antioxidants; other studies assessed zinc, tocopheroland vitamins A, C and E. The majority of studies delivered the interventions intravenously; some studies used intravenous and enteral routes, and one study used intravenous administration followed by oral administration.

Participants included in the review

Studies of critically ill adults in an intensive care unit who were receiving treatment, rather than prophylaxis, with micronutrients were eligible for inclusion. The patients included trauma and surgical patients, and patients with burns (up to 30% of total body surface area), acute pancreatic necrosis, severe head injuries and systemic inflammatory response syndrome.

Outcomes assessed in the review

Mortality, infectious complications and length of stay were eligible outcomes. Infectious complications were those defined by the studies and included pneumonia and line-related sepsis. The reviewers assumed that mortality referred to hospital mortality unless specified otherwise.

How were decisions on the relevance of primary studies made?

The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality

Two reviewers independently assessed study validity using a scoring system. This assessed allocation concealment, blinding, intention-to-treat analysis, patient selection, baseline group comparability, the percentage of patients followed up, description of the treatment protocol, the comparability of cointerventions between groups, and definition of the

outcomes (see Other Publications of Related Interest). The maximum possible validity score was 14.

Data extraction

Two reviewers independently extracted the data, with any disagreements resolved by consensus. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for mortality and complications. Length of stay data were reported as in the original trials; no further calculations were performed as the data were sparse.

Methods of synthesis

How were the studies combined?

The studies were pooled in a meta-analysis using a random-effects model. The data were analysed on an intention-to-treat basis where possible. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?

Statistical heterogeneity was assessed using a chi-squared test and the I-squared statistic. Subgroup analyses were used to assess differences between: single and combined antioxidants; parenteral and enteral administration; selenium versus non-selenium antioxidants; low- and high-dose selenium (less than or greater than 500 microg/day). A post hoc sensitivity analysis was also performed by removing one study of particularly poor quality that reported a large treatment effect. In the analyses one study with two active treatment arms was treated as two separate studies.

Results of the review

Eleven RCTs (n=886) were included.

The median quality score was 8.5 (range: 5 to 12). Of the 11 studies included in the review, five had adequate allocation concealment, six were blinded and nine used an intention-to-treat analysis. There was no evidence of publication bias for the mortality outcome.

Mortality. Antioxidants (either alone or in combination) were associated with a statistically significant reduction in overall mortality compared with placebo (RR 0.65, 95% CI: 0.44, 0.97; based on 866 patients from 11 trials). There was no evidence of heterogeneity between the study results (I-squared 0%). Subgroup analyses showed similar significant reductions in risk for single antioxidants (RR 0.52, 95% CI: 0.27, 0.98; based on 188 patients from 5 trials) and antioxidants given parenterally (RR 0.56, 95% CI: 0.34, 0.92; based on 236 patients from 7 trials), but no evidence of any significant effect for combined antioxidants, enteral administration, selenium, non-selenium antioxidants, or different doses of selenium.

Infectious complications.

There was no evidence of a difference between antioxidants and placebo for infectious complications (RR 0.90, 95% CI: 0.65, 1.21; based on 728 patients from 5 trials). There was a small amount of heterogeneity (I-squared 23.4%). Subgroup analyses showed no evidence of a difference between treatment and placebo for combined antioxidants, enteral or parenteral administration, selenium or non-selenium antioxidants.

There were insufficient data to pool for length of stay.

Authors' conclusions

Antioxidant trace elements and vitamins, particularly selenium given alone or in combination, are safe and may be associated with a reduction in mortality in critically ill patients. Parenteral administration may have more effect on clinical outcomes than the enteral route, but this was supported by only a small number of trials.

CRD commentary

This review had clearly stated study inclusion criteria. The search was comprehensive and the authors attempted to locate studies from additional sources as well as electronic databases, and did not restrict by language. Publication bias

was investigated for the main outcome and there did not appear to be any evidence of it. Study quality was assessed and the authors discussed the limitations of the studies in relation to the review findings. Most of the review processes were performed by two reviewers in duplicate, thereby reducing the risk of introducing errors and bias.

The methods used to pool the data were appropriate and the pre-specified subgroup analyses were kept to a minimum and seemed appropriate. The authors considered the limitations in their conclusions from the small number of studies overall and from some of the subgroups. This was a well-conducted systematic review and its results are likely to be reliable. Conclusions about the effects of antioxidants on mortality appear reliable. However, the conclusion that antioxidants are safe appeared to be based on the significant reduction in hospital mortality with the interventions, and this may not represent adequate evidence of safety.

Implications of the review for practice and research

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

Research: The authors stated the need for a large multicentre RCT confirming the benefits of antioxidant supplementation. Further research is also needed to assess the optimal combination of trace elements and the optimal dose of each micronutrient.

Bibliographic details

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Other publications of related interest

Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient. JAMA 1998;280:2013-9.

Indexing Status

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MeSH

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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.