Zinc supplementation in critically ill patients: a key pharmaconutrient?

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CRD summary
The potential use of zinc supplementation in critically ill patients was investigated. The authors concluded that there was inadequate evidence to recommend the routine use of high dose zinc supplementation in the critically ill. Although data was possibly pooled inappropriately, the conclusions appear appropriate due to lack of data.

Authors' objectives
To investigate the potential use of zinc supplementation in critically ill patients.

Searching
MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched without language restrictions (dates spanned 1980 to December 2007). Search terms were reported. Review articles and the authors' personal files were searched for additional studies. Unpublished manuscripts were included in the review process. Data reported in abstracts only was excluded.

Study selection
Randomised controlled trials (RCTs) of mechanically ventilated critically ill adults that investigated any form of oral, enteral or parenteral zinc supplementation were eligible for inclusion. Critically ill patients were defined as patients cared for in an intensive care unit environment who had an urgent or life-threatening complication (high baseline mortality rate). Studies had to report at least one of the following outcomes: mortality (intensive care unit, hospital, long-term); length of stay; quality of life; complications; and cost. Studies that reported surrogate outcomes only were excluded.

Included studies were of patients with severe head injuries (ventilated), patients with burns of more than 30% total body surface area (TBSA) and more than 20% TBSA and trauma patients (surgical intensive care unit). Zinc dose ranged from 6.5mg to 37.5mg. Concurrent micronutrient regimens varied (comparator groups received standard trace elements, placebo or elemental zinc followed by placebo). Duration of supplementation ranged from five days to three months.

The authors state neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
It appeared that validity was assessed in terms of concealed randomisation, intention-to-treat analysis, exclusions after randomisation and blinding. Scores were assigned to three of the four studies. The number of reviewers that performed validity assessment was unclear.

Data extraction
Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for mortality. Data were extracted independently by two reviewers and authors were contacted for further information if required.

Methods of synthesis
Risk ratios and 95% CIs were pooled in a random-effects meta analysis. Statistical heterogeneity was assessed using the $X^2$ test. Studies were also described narratively.

Results of the review
Four RCTs were included in the review (n=140). Three RCTs used intention-to-treat, three were double-blinded and two reported concealed randomisation.

Although there was a trend towards reduction in mortality, supplementation with zinc was not associated with a statistically significant effect on this outcome compared with placebo (RR 0.63, 95% CI 0.25 to -1.59, p=0.33). There...
was no evidence of statistical heterogeneity. There was no significant difference between zinc supplementation and placebo on intensive care unit stay or hospital length of stay.

**Authors' conclusions**
There was inadequate evidence to recommend the routine use of high dose zinc supplementation in the critically ill.

**CRD commentary**
The review question was supported by clear inclusion criteria for participants, intervention, outcomes and study design. Studies in any language and unpublished studies were eligible for inclusion, which decreased the possibility of language and publication biases. Data extraction was performed in duplicate, which reduced the risk of reviewer error and bias; it was unclear whether similar steps were taken for validity assessment and study selection. Details of study quality assessment were lacking (for example, scores appeared to have been awarded for most trials, but it was unclear how they were calculated) and the results of the assessment did not appear to be considered in interpreting the review results. Statistical heterogeneity was assessed; however, it was unclear how appropriate pooling using meta-analyses was due to the diversity in intervention, comparators and duration of treatment, and lack of detail about patient characteristics. Despite some methodological issues, the authors’ conclusions appear appropriate due to lack of data.

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

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

**Research:** The authors stated that research was needed to clarify the role of zinc supplementation in critically ill and other patient populations. The optimal dose with a maximal positive effect on underlying inflammatory, immunologic and metabolic processes, while being safe and well-tolerated by critically ill patients, needed to be determined. Large scale rigorously designed RCTs could then be conducted to elucidate the efficacy of these doses.

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