The effectiveness of trace element supplementation following severe burn injury: A systematic review protocol

Rochelle Kurmis BND APD, CF JBI¹,²
Edoardo Aromataris BSc(Hons), PhD¹
John Greenwood AM, BSc(Hons), MBChB, MD, FRCS(Eng), FRCS(Plast), FRACS²

1. The Joanna Briggs Institute, School of Translational Health Science, The University of Adelaide
2. Adult Burns Center, Royal Adelaide Hospital

Corresponding author:
Rochelle Kurmis
Rochelle.Kurmis@health.sa.gov.au

Review question/objective
The objective of this review is to assess the effectiveness of trace element supplementation on clinically meaningful outcomes following severe burn injury in children and adults.

More specifically, the objectives are to assess the effectiveness of selenium, copper and zinc supplementation on mortality, length of intensive care unit (ICU) hospital stay, wound healing and infection rates (wound and nosocomial) in patients who have sustained a severe burn injury.

Background
In the United States (US) it has been estimated that each year around 450,000 people seek medical treatment for burn injuries and 3,400 people die as a direct result of fire and burns.¹ According to the 2013 American Burn Association National Burn Repository Report, fire/flame and scalds are the most commonly documented cause of burn injury (43.2% of reported hospital burn injury admissions).² Pneumonia is the most commonly reported clinical complication related to burn injury with an incidence of 5.9% in fire/flame injury admissions, with an increased frequency of patients who require mechanical ventilation for four or more days.² The average length of hospital stay for patients who survive a burn injury requiring hospital admission, is just over one day per percent of the total body surface area burned.² The mortality rate for patients admitted from fire/flame injury is reported as 6.2%, with three weeks being the average length of stay for patients with less than 70% burns who do not survive. For this patient group there is an average daily hospital charge of US$13,000 more than patients who did survive their admission.² Longer term economic costs of burn injury are also important factors to recognize, with reportedly only 50-67% of people who are actively employed at their time of burn injury returning to paid employment.³ Physical rehabilitation from burn injury is often more prolonged than that of other types of injury, however similar physical outcomes and functioning can be expected following burn injury.³ Psychological rehabilitation is not as ‘clear cut’ as physical rehabilitation, with a 39% prevalence in psychiatric disorders, major depression, anxiety disorders, and post-traumatic stress
disorder (PTSD) predominantly, one to four years post-injury. The development of PTSD appears to be related to pain scores shortly after burn injury rather than the severity of the burn injury. This is important as negative burn perceptions, as a result emotional distress and concerns with appearance, are associated with a lengthened time to healing.

Nutrition support following severe burns injury is recognized as an essential part of burn injury management. Pronounced inflammatory responses, endocrine, metabolic and immune system disturbances are observed following a severe burn injury. It is recognized that nutritional deficiencies exacerbate complications of severe burns injury such as infections, delayed wound healing and muscle catabolism, with infective complications such as wound sepsis and pneumonia remaining a major cause of mortality following hospitalization due to burn injury. Trace element deficiencies are part of the sequelae following severe burn injuries, with a recent survey of American Burn Association Burn Centers indicating that 92% of responding centers routinely supplement patients with vitamins and/or minerals. Despite this prevalence of vitamin and mineral supplementation following burns injury, variation exists in the supplements administered between centers. Trace elements, such as copper, selenium and zinc play an important physiological role in immune function as well as wound healing; however they are acutely depleted following severe burn injury. The mechanism of trace element deficiency following burn injury appears to be multi-modal. Trace elements are thought to be primarily lost through extensive exudative losses following injury and repeated surgeries. It has been reported that 5-10% of total body zinc stores and 20-40% of total body copper stores are lost within seven days of a severe burn injury, with concomitant increases in urinary excretion of these metals following burn injury contributing significantly. Trace element losses also occur through thermal destruction of skin and removal of burn eschar. The reported antagonistic relationship between endogenous selenium and the silver used in burn dressings may also contribute to observable losses of selenium.

Selenium performs it’s antioxidant role as an essential component of the active site of the enzyme glutathione peroxidase (GSH-Px), which contributes to the first line antioxidant defenses in both the intra- and extra-cellular milieus. Depleted endogenous stores of antioxidants have been associated with an increase in free radical generation and heightened systemic inflammatory responses. In the critically ill population, this is associated with increased morbidity and mortality. As the rate limiting step in the biosynthesis of GSH-Px, selenium deficiency directly influences these responses. Selenium also has identified roles in tissue oxygenation, protection against lipid per-oxidation, phagocytic activity of neutrophils, activation and regulation of thyroid hormones, DNA synthesis and cell viability and proliferation.

Similarly, the trace elements copper and zinc also promote wound healing as a component of several metalloenzymes. Copper is a component of lysyl oxidase, which is necessary for cross linking of collagen fibres; this is important for wound healing rates and healed wound integrity. Copper is also a component of superoxide dismutase when copper levels are low, synthesis of superoxide dismutase is decreased. This process is associated with oxidative damage as a result of inflammation. Zinc is required for the function of over 200 metalloenzymes, as well as for normal cell replication and growth. Immune function is also influenced by zinc status, with deficiency leading to thymic atrophy, loss of T-helper cell function and alterations to the normal profiles of serum immunoglobulins.

Currently, many international evidence-based nutrition support guidelines available for clinicians provide global recommendations for the ICU setting. These guidelines are commonly adopted for
burn injury patients as specific guidance for this sub-population may or may not be available. More often, recommendations for burns injury patients are extrapolated from critical care data. The critical care population is recognized as a heterogeneous group. Burn injury however, is a specific sub-group, characterized by the severe hypermetabolic, inflammation, endocrine and immune responses. These combine to have a pronounced effect on nutritional requirements and therefore evidence-based recommendations for nutritional supplementation in burn injury should be separated from the ‘general’ critical care population. A recently published set of recommendations for nutritional therapy in major burns stated that micronutrient substitution, including zinc, copper and selenium, be included for both adults and children. This was provided as Grade C evidence (based on the GRADE methodology [Grade of Recommendation, Assessment, Development and Evaluation\(^{13}\)]) with strong agreement between experts. Details on duration for this supplementation were provided, however recommended dosages were lacking. A search for systematic reviews on this topic of MEDLINE and the Cochrane and JBI Libraries failed to identify any existing publications. As a result, this review will examine the current evidence regarding the effectiveness of trace element supplementation in burn injury patients, with an aim to elucidate ideal trace element dosages, route of administration and timing for administration.

**Keywords**

Selenium, copper, zinc, burn injury, burn, burns, thermal injury, antioxidant, trace element, nutrition support

**Inclusion criteria**

**Types of participants**

This review will consider studies that include children (2-18 years of age) and adults (≥ 18 years of age) who have sustained a severe burn injury (defined as burn injury ≥ 10% Total Body Surface Area (TBSA) in children and ≥ 15% TBSA in adults) and been admitted to an ICU, Burns ICU (BICU), or burns unit for surgical management of their injury. Studies that include patients with significant multi-trauma in addition to burn injury will be excluded.

**Types of intervention(s)/phenomena of interest**

This review will consider studies that evaluate enteral or parenteral supplementation of selenium, copper and zinc, either alone or combined and compared to placebo or regular treatment. Intervention and comparison groups will have received standard nutrition intervention including enteral or parenteral nutrition and multi-vitamin supplements. Studies that include trace element supplementation in combination with other predefined nutrient supplementations will be considered for inclusion.

**Types of outcomes**

This review will consider studies that include the following outcome measures: mortality; length of ICU/hospital stay; rate of wound healing (time to first donor site healing or time to wound closure); complications (e.g. wound infection, hospital acquired pneumonia).

Secondary outcome measures: tissue (measured from skin biopsies) and plasma (measured via blood sampling) selenium, copper and zinc levels.
**Types of studies**

This review will primarily consider experimental study designs including randomized controlled trials. Where randomized controlled trials are not available, this review will consider both experimental and epidemiological study designs including non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies and case control studies for inclusion.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken, followed by analysis of the text words contained in the title and abstract and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. The search will target studies published from 1980 to the present date. Publications prior to 1980 will be excluded due to the significant differences in surgical techniques and standard nutrition interventions for burns patients available since this time.

The databases to be searched include:

- PubMed, CINAHL, EMBASE, Web of Science

The search for unpublished studies will include:


Initial keywords to be used will be:

Selenium, copper, zinc, burn injury, burn, burns, thermal injury, antioxidant, trace element, nutrition support

**Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

**Data collection**

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Authors will be contacted for complete data in the event relevant data appears missing from the included studies.
Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratios (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square test and also explored using subgroup analyses based on the different study designs or defining features of the population groups (including age and severity of injury) included in this review where and if appropriate. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

The authors have no known conflicts of interest to declare.
References


Appendix I: Appraisal instruments

MAStARI appraisal instrument

**JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Were participants blinded to treatment allocation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Was allocation to treatment groups concealed from the allocator?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Were the control and treatment groups comparable at entry?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Were groups treated identically other than for the named interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Were outcomes measured in the same way for all groups?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Were outcomes measured in a reliable way?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Was appropriate statistical analysis used?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall appraisal: Include □ Exclude □ Seek further info. □

Comments (Including reason for exclusion)
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer __________________________ Date __________________________

Author __________________________ Year _______ Record Number _______

1. Was study based on a random or pseudo-random sample? ☐ ☐ ☐ ☐
2. Were the criteria for inclusion in the sample clearly defined? ☐ ☐ ☐ ☐
3. Were confounding factors identified and strategies to deal with them stated? ☐ ☐ ☐ ☐
4. Were outcomes assessed using objective criteria? ☐ ☐ ☐ ☐
5. If comparisons are being made, was there sufficient descriptions of the groups? ☐ ☐ ☐ ☐
6. Was follow up carried out over a sufficient time period? ☐ ☐ ☐ ☐
7. Were the outcomes of people who withdrew described and included in the analysis? ☐ ☐ ☐ ☐
8. Were outcomes measured in a reliable way? ☐ ☐ ☐ ☐
9. Was appropriate statistical analysis used? ☐ ☐ ☐ ☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

__________________________________________

doi: 10.11124/jbisrir-2013-1134
Appendix II: Data extraction instruments

MAStARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

Reviewer ........................................ Date ........................................

Author ........................................ Year ........................................

Journal ........................................ Record Number ........................

**Study Method**

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

**Participants**

Setting

Population

**Sample size**

Group A ____________________ Group B ______________

**Interventions**

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:
Study results

Dichotomous data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (1) number / total number</th>
<th>Intervention (2) number / total number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (1) number / total number</th>
<th>Intervention (2) number / total number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>