Does Oral Zinc Aid the Healing of Chronic Leg Ulcers?

A Systematic Literature Review

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Objective: To determine whether oral zinc sulfate is an effective treatment for promoting healing of venous or arterial leg ulcers.

Data Sources: The search strategy of the Cochrane Wounds Group was used. This includes searches of electronic databases, conference proceedings, relevant bibliographies, and hand searching of journals.

Study Selection: Studies were included if they were randomized controlled trials of oral zinc sulfate in the treatment of chronic venous or arterial ulcers with objective measures of healing. Six of the 10 studies initially identified were included in the review.

Data Extraction: The trial method, participants, interventions, outcomes, baseline comparability, adequate reporting of withdrawals, and blinding of assessment were extracted by 2 reviewers independently.

Data Synthesis: No trial showed a statistically significant benefit of zinc sulfate for healing leg ulcers. There is limited evidence to suggest that zinc might increase healing in individuals with a low serum zinc level, but more evidence is needed.

Conclusions: There is no evidence of benefit from the general use of zinc sulfate in patients with chronic leg ulcers. There is a need for further research to see if oral zinc sulfate is beneficial in the treatment of patients with leg ulcers who have a low serum zinc level. If it is demonstrated to be beneficial, further trials are required to establish dose and duration of treatment.

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LEG ULCERS are a common problem thought to affect about 1% of the population at some point in their lives and about 1.5 per 1000 people at any one time. Leg ulcers are more common in women than men, and the prevalence increases with age. Venous disease is present in the majority of cases; peripheral vascular disease may coexist or may be the main cause of an ulcer. Other disease processes may also be involved, such as diabetes or rheumatoid disease. Leg ulceration is chronic, and an ulcer may be present for months or years without healing. After healing, recurrence rates are high. There are many approaches to management, with large variations in practice at local and international levels.

Zinc is an essential trace metal. Its presence is necessary for some enzymes and hormones to function. It also has anti-inflammatory effects on phagocytic cells. Zinc-deficient individuals (determined by serum zinc levels) demonstrate slower wound healing and are more prone to infections. Zinc deficiency is treated with oral zinc sulfate, 30 to 150 mg/d.

Studies in rats have indicated that the addition of zinc sulfate to their diet promoted the healing of thermal burns and excised wounds, but it is unclear if the rats’ standard diet was zinc deficient. A randomized controlled trial in people with pilonidal sinus wounds suggested that oral zinc sulfate (220 mg 3 times daily) decreased the time to healing of pilonidal sinus wounds by 43%. The serum zinc levels of participants were not measured.

This review summarizes the evidence for the effectiveness of oral zinc sulfate in promoting healing of leg ulcers.

DATA SOURCES

The comprehensive search strategy of the Cochrane Wounds Group was used to identify randomized controlled trials and controlled clinical trials of any aspect of wound care, and trials of zinc...
in the treatment of leg ulcer were identified as part of this. An abbreviated search strategy is described herein.

**Electronic Database Searches**

MEDLINE was searched for randomized controlled trials and controlled clinical trials from January 1966 to December 1997 with the use of a mixture of free text terms and Medical Subject Headings headings (limited to humans; not limited for languages):

- decubitus ulcer/ leg ulcer/ or varicose ulcer/ skin ulcer/ (\[venous or stasis or arterial\] adj [adjective] ulcer$)$ tw (text word)
- ([decubitus or foot or ischaemic] adj ulcer$\$$).tw
- ([varicose or leg or skin] adj ulcer$\$$).tw
- (decubitus or [chronic adj wound$\$$]).tw
- ([sinus adj wound$\$$] or [cavity adj wound$\$$]).tw
- zinc/ or zinc oxide/ or ointments/ or anti-infective agents/
- random allocation/ or randomized controlled trials/
- controlled clinical trials/ or clinical trials

The following databases have also been searched from the earliest date available until December 1997:

- EMBASE
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- ISI Science Citation Index (on BIDS [Bath Information and Data System])
- BIOSIS (on Silver Platter)
- British Diabetic Association Database
- CISCOM (Complementary Medicine Database of the RCCM)
- Conference Proceedings (on BIDS)
- Cochrane Library
- Dissertation Abstracts
- Royal College of Nursing Database (CD-ROM)

**Journal Hand Searches**


**Conference Proceedings**


**Efforts to Identify Unpublished Studies**

Several databases were searched (up to December 1997) to attempt to identify unpublished studies. These include CRIB (Current Research in Britain); Department of Health and Social Security Database; SIGLE (System for Information on Grey Literature in Europe); UK National Research Register; and Smith and Nephew Wound Care Database.

A pharmaceutical company that makes zinc sulfate tablets (Thames Laboratories, Wrexham, Wales) was asked for any relevant trials it could supply. It provided only trials that had already been identified from the searches of the databases.

**STUDY SELECTION**

Full copies of all studies that appeared eligible from the search were obtained. They were read by 2 reviewers (E.A.J.W. and C.I.H.) independently to assess whether they met the inclusion criteria. These criteria were as follows: controlled trials of oral zinc sulfate against placebo or no intervention, in the treatment of venous or arterial leg ulcers; ulcers present for at least 4 weeks; participants randomly allocated to either group; an objective measure of ulcer healing reported, such as time to complete healing or number of ulcers healed at the end of the trial or rate of healing; and other treatments being the same in both treatment arms.

The populations of trials were not limited. Trials with patients of any age, with leg ulcers lasting at least 4 weeks because of venous or arterial disease, were considered. Any disagreements between the 2 reviewers were resolved by discussion.

The methodological quality of the studies was documented by each reviewer according to the following criteria: method of randomization, allocation concealment, intention-to-treat analysis, adequate reporting of withdrawals, blinding of assessment, and baseline comparability of groups.

A total of 10 studies of the use of oral zinc and the treatment of leg ulcers were identified. All of the studies were relatively small, with between 10 and 104 participants. Of these, only 6 were randomized controlled trials\(^8\)-\(^12\) and were included in this review. The other 4 studies were not randomized trials\(^13\)-\(^16\) and were therefore excluded.

Only 1 author\(^16\) was contacted for additional information. It was not considered feasible to contact the remaining authors of trials because of the length of time (up to 30 years) since the trials were carried out.

**DATA EXTRACTION**

Data extraction was performed independently by 2 reviewers (E.A.J.W. and C.I.H.). The data recorded were trial method, trial participants, adequacy of allocation concealment, interventions in both groups, outcomes recorded, trial results, adequate reporting of withdrawals, blinding of outcome assessment, and baseline comparability of groups.

The number of ulcers healed at the end of the trial or time to healing of ulcers was used if available. The rate
of healing or rate of change in ulcer area was used if necessary, but these are more open to bias, as they are affected by the size of the ulcers. Larger ulcers are likely to epithelialize more rapidly and so they appear to have a greater change in area in a given time.

Data were checked and entered into the computer by 1 reviewer (E.A.J.W.). Treatment effects were calculated with the RevMan package, version 3.1.1 (Update Software, Oxford, England). Results are expressed as relative risk ratios (RRs) and 95% confidence intervals (CIs).

DESCRIPTONS OF THE STUDIES

Five studies were comparisons of oral zinc vs placebo; the sixth did not use a placebo (Table). The duration of treatment with zinc varied from less than 4 weeks to 1 year.

Four studies,10-12 measured serum zinc levels at baseline and during the trial period. A different level for “normal” was used in each study; Haeger and Lanner10 used 13.0 µmol/L, Hallbrook and Lanner11 used 16.8 µmol/L, and Phillips et al12 used the group mean of 19.5 µmol/L. Clayton7 reported only the group mean level of 12.7 µmol/L.

DATA SYNTHESIS

The Figure shows the RRs and 95% CIs for the number of ulcers healed at the end of each study.

Chronic Venous Ulcers

In the study by Greaves and Ives,8 3 of 18 patients in the zinc group and 2 of 18 in the placebo group had healing of ulcers at 4 months (RR, 1.30; 95% CI, 0.28-7.95). Two patients withdrew and were not included in the analysis. The results for the mean healing rate were skewed and not usable.

In the study by Phillips et al,12 10 of 19 ulcers in the zinc group and 12 of 23 in the placebo group had healed at 10 months (RR, 1.01; 95% CI, 0.57-1.80).

Hallbrook and Lanner11 found that the number of ulcers healed at 18 weeks was 9 of 13 in the zinc group and 8 of 14 in the placebo group (RR, 1.25; 95% CI, 0.67-2.31). The groups were subdivided into those with serum zinc levels less than 16.8 µmol/L and greater than or equal to 16.8 µmol/L. Those below this level who were given zinc healed more often (5 of 7) than those in the
control group (1 of 7) (RR, 5.00; 95% CI, 0.77-32.5). In those with this level of serum zinc or higher, more patients taking placebo healed (7 of 7) than those given zinc (4 of 6) (RR, 0.67; 95% CI, 0.84-2.33).

In the study by Haeger et al.,9 the number of ulcers healed at 3 months was 11 of 15 in the zinc group and (4 of 6) (RR, 0.67; 95% CI, 0.84-2.33).

Little can be inferred from his results. Haeger and Lanner10 did, that the healing rate was much less in those in patients receiving placebo, but this did not achieve statistical significance. They also found that the healing rate was much less in those in the placebo group with low serum zinc level than in any of the other 3 groups: 1.4 vs 5.0 to 7.2 µmol/L. However, it is not clear if there was an appreciable difference in the time to ulcer healing in the different groups.

**Arterial Ulcers**

Haeger and Lanner10 found that all but 2 of the 30 ulcers healed within 1 year (RR, 1.40; 95% CI, 0.88-2.26), and they were both in the control group in patients with a low serum zinc level. The 2 ulcers that failed to heal were both much larger than the average size (33% and 160%), and this will have influenced the probability of healing.

### Table 1: Outcomes and Notes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean No. of days to 50%</td>
<td>Average serum zinc for all participants was 12.7 µmol/L. Average ulcer size was 47% greater at baseline in control group than treatment group.</td>
</tr>
<tr>
<td>and 90% reduction of ulcer area;</td>
<td>Rate of reepithelialization as linear mm/wk; No. of controls healed at end of trial</td>
</tr>
<tr>
<td>no range or SD given</td>
<td>Intention-to-treat analysis not used; 2 patients withdrawn and not included in analysis; serum zinc not measured; rate of reepithelialization was not used as data were skewed</td>
</tr>
<tr>
<td>No. of ulcers healed at 3 mo</td>
<td>At baseline mean ulcer size of treatment group was 50% greater than in control group; third arm of trial “allocated” to effervescent zinc sulfate; results of this group were not included in review</td>
</tr>
<tr>
<td>No. of ulcers healed within 1 y,</td>
<td>Initially 50 participants recruited but only reported results of 30 patients with ulcers between 100 and 1000 mm², as very large and small ulcers behaved irregularly in their healing; at baseline mean size of zinc group ulcers was 74% larger than in control group</td>
</tr>
<tr>
<td>by low or normal serum zinc; healing quotient (healed area in mm²/d)</td>
<td>No information is given on the length of time ulcers took to heal, so it is not clear if there was an appreciable difference in the time to ulcer healing in the different groups.</td>
</tr>
<tr>
<td>No. of ulcers healed at 18 wk by low or normal serum zinc; healing rate in mm²/d</td>
<td>Initially 50 participants recruited but only reported results of 27 patients with ulcers between 100 and 1000 mm², as very large and small ulcers behaved irregularly in their healing</td>
</tr>
<tr>
<td>No. of ulcers healed at end of study; mean linear healing rate</td>
<td>After allocation serum zinc was measured; groups were divided into high or low serum zinc levels depending on if they were above or below group average of 19.5 µmol/L</td>
</tr>
</tbody>
</table>

They reported a much higher average rate of epithelialization in the group with a low serum zinc level given oral zinc than in the group with a low serum zinc level taking placebo (6.2 vs 2.6 mm²/d), but only the mean value is given, which does not allow detailed analysis. Also, the treated group with a low zinc level had ulcers 26% larger than those in the control group, which is likely to increase the rate of epithelialization.

No information is given on the length of time ulcers took to heal, so it is not clear if there was an appreciable difference in the time to ulcer healing in the different groups.

**COMMENT**

The studies of oral zinc vary substantially in the length of treatment and follow-up and whether the level of the serum zinc was measured initially. Interpretation of these findings is therefore difficult. It was not appropriate to pool any of the results, as the initial size of ulcers and length of follow-up varied between studies.

In the treatment of chronic venous ulcers, Haeger and Lanner,10 Phillips et al,12 and Greaves and Ive8 did not find any significant difference between the number of ulcers healed with oral zinc or placebo treatment. Only Phillips et al measured the serum zinc level in patients. Clayton7 conducted a small trial over a very short period, which included a patient with an arterial ulcer. Little can be inferred from his results.

Hallbrook and Lanner11 found overall that there was no difference between treatment and control groups. When the groups were subdivided according to initial serum zinc level, ulcers in patients with low serum zinc levels who were receiving treatment healed substantially more often than those in patients receiving placebo, but this did not achieve statistical significance.

Also, they found that the healing rate was much less in those in the placebo group with low serum zinc level than in any of the other 3 groups: 1.4 vs 5.0 to 7.2 mm²/d. However, it is not clear if there was an initial hypothesis that zinc had a greater effect in those with a low serum zinc level, and this finding could be the result of “data dredging.”

In the treatment of chronic arterial ulcers, Haeger and Lanner10 found that 2 ulcers in patients with low serum zinc levels who were taking placebo did not heal after a year, but this may have been the result of the initial ulcer size. They also found, as Hallbrook and Lanner did, that the healing rate was much less in those in the placebo group with low serum zinc levels than in
any of the other 3 groups: 26 vs 4.1 to 6.6 mm²/d. This was not confirmed by Phillips et al.

CONCLUSIONS

It is not possible to draw definite conclusions for the use of zinc sulfate in the treatment of chronic venous or arterial ulcers. There is no evidence that oral zinc sulfate is generally beneficial in promoting healing of chronic venous ulcers. There is limited evidence that it may be beneficial in the treatment of leg ulcers in individuals who have a low serum zinc level. Recommendations for the dose and duration of treatment cannot be made on the basis of the available information.

There is a need for further research to see whether oral zinc sulfate is beneficial in the treatment of patients with leg ulcers who have a low serum zinc level. If it is demonstrated to be beneficial, further trials are required to assess the level of serum zinc to be used as a cutoff and the optimal dose and duration of treatment with zinc sulfate.

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REFERENCES