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Oral zinc for arterial and venous leg ulcers (Review)

Wilkinson EAJ

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Oral zinc for arterial and venous leg ulcers.

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Oral zinc for arterial and venous leg ulcers (Review)

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[Intervention Review]

Oral zinc for arterial and venous leg ulcers

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ABSTRACT

Background

Leg ulcers affect up to one percent of people at some time in their life. Leg ulceration is chronic in nature and ulcers may be present for months or even years without healing. After healing there is a high risk of recurrence. Treatments include wound dressings alongside the treatment of underlying medical problems such as poor blood supply, infection and poor nutrition.

Objectives

To assess the effectiveness of oral zinc in healing arterial or venous leg ulcers.

Search methods

For this seventh update we searched The Cochrane Wounds Group Specialised Register (searched 02 September 2014) and The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 8). In the original version of the review a company manufacturing zinc sulphate tablets was asked for references to relevant trials.

Selection criteria

Randomised controlled trials comparing oral zinc sulphate with placebo or no treatment in people with arterial or venous leg ulcers were eligible for inclusion. There were no restrictions on date or language of publication. The main outcome measure used was complete healing of the ulcers. Trials were eligible for inclusion if they measured ulcer healing objectively by documenting time to complete healing, proportion of ulcers healed during the study, or healing rates of ulcers.

Data collection and analysis

All data extraction and assessment of trial quality was done by both authors independently.

Main results

Six small trials (183 participants) were eligible for inclusion. Four trials considered people with venous ulcers, one trial involved people with arterial ulcers and one people with mixed aetiology ulcers. Serum zinc was measured in four trials and four trials compared oral zinc sulphate with placebo in people with venous ulcers; pooling these trials indicated no statistically significant difference between the two groups for healing (RR 1.22, 95%CI 0.88 to 1.68). Overall, there is no evidence that oral zinc increases the healing of arterial or venous leg ulcers.

Authors' conclusions

Oral zinc sulphate does not appear to aid the healing of arterial and venous leg ulcers, however all included studies were small and at unclear risk of bias (due to poor reporting).

PLAIN LANGUAGE SUMMARY

Oral zinc supplements for treating leg ulcers

Leg ulcers (open sores, usually on the lower leg) can be slow and difficult to heal. They may take weeks or months to heal. There is a high risk of the ulcer returning. Leg ulcers often cause distress to patients and are costly for health services. Failure to heal may be due in part to poor nutrition which reduces the ability of the body to repair itself. Minerals such as zinc are necessary for good healing and so it was thought that taking zinc sulphate tablets might aid healing of ulcers. We found six trials that used zinc to treat leg ulcers but all were too small to show a benefit, even if one exists. Furthermore the methods used in the existing trials mean that their results were possibly biased. On the basis of the evidence we have so far it appears that taking zinc tablets does not improve leg ulcer healing, however better quality trials are needed.

BACKGROUND

Leg ulcers are a common problem thought to affect about 1% of the population at some point in their lives (Callam 1992), and about 1.5/1000 of the population at any one time (Callam 1985). Leg ulcers are more common in women than men and their prevalence increases with age. Venous disease is present in the majority of cases; peripheral vascular disease may co-exist or may be the main cause of an ulcer. Other diseases, such as rheumatoid arthritis and diabetes, may also contribute. Leg ulceration is chronic in nature as ulcers may be present for months or years without healing, and once they have healed recurrence rates are high. Management approaches vary considerably in practice and include care of the ulcer using dressings and treatment of underlying medical problems such as malnutrition, lack of minerals and vitamins, poor blood supply or infection.

Zinc is an essential trace metal that is necessary for some enzymes and hormones to function. It also has anti-inflammatory effects on phagocytic cells (cells that 'swallow' and digest bacteria and cell debris) (Seymour 1996). Zinc-deficient individuals (as determined by serum zinc levels) demonstrate slower wound healing and are more prone to infections. Zinc deficiency is treated with oral zinc sulphate (30 to 150 mg per day) (Seymour 1996).

Although serum zinc is used to assess the zinc status of the body as a whole, it is not necessarily a meaningful measurement, since serum zinc levels display a diurnal (daylight-related) variation. They also rise immediately after meals but fall to below baseline levels within two hours. In people with severe zinc deficiency, serum zinc levels can be maintained by zinc released from tissue (Aggett 1991). Consequently, serum zinc measurements do not necessarily reflect total body zinc (Aggett 1991).

Studies have indicated that the addition of zinc sulphate to the diet of rats promoted the healing of thermal burns and excised wounds, however, it was unclear if the rats' standard diet was zinc deficient (Strain 1954).

A randomised controlled trial (RCT) in people with pilonidal sinus wounds suggested that oral zinc sulphate (220 mg three times daily) decreased the time to healing of the wounds by 43%; serum zinc concentrations of participants were not measured (Pories 1967).

This review set out to summarise the evidence for the effectiveness of oral zinc sulphate in promoting the healing of leg ulcers.

OBJECTIVES

To determine whether oral zinc sulphate increases the rate of healing of venous or arterial leg ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials (RCTs) of oral zinc sulphate in the treatment of chronic leg ulcers due to venous or arterial disease.

Types of participants

People of any age with venous or arterial leg ulcers of at least four weeks' duration. Studies in people with isolated ulcers of the foot were excluded.

Types of interventions

Comparisons of oral zinc sulphate with placebo or no intervention.

Types of outcome measures

The following objective measures of healing were regarded as valid:

- number of ulcers healed at the end of the trial;
- time to healing of ulcers;
- rate of healing, or rate of change in the area of the ulcer.

The incidence and severity of side effects were also recorded.

Search methods for identification of studies

The search methods for the sixth update of this review can be found in [Appendix 1](#).

For this seventh update in September 2014 we searched the following electronic databases:

- Cochrane Wounds Group Specialised Register comprising references identified from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings (searched 02 September 2014);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 8);

The following search strategy was used in The Cochrane Central Register of Controlled Trials (CENTRAL):

```
#1 MeSH descriptor: [Zinc] explode all trees 1196
#2 MeSH descriptor: [Zinc Sulfate] explode all trees 151
#3 zinc next (sulphate or sulfate):ti,ab,kw 357
#4 #1 or #2 or #3 1403
#5 MeSH descriptor: [Administration, Oral] explode all trees 20175
#6 oral or systemic:ti,ab,kw 118527
#7 #5 or #6 119073
#8 MeSH descriptor: [Leg Ulcer] explode all trees 1203
#9 ((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*)
or (stasis next ulcer*) or (crural next ulcer*) or "ulcus cruris" or
"ulcer* cruris"):ti,ab,kw 1556
#10 #8 or #9 2051
#11 #4 and #7 and #10 16
```

No date or language restrictions were applied. No new studies were identified for inclusion in this update.

Data collection and analysis

Full copies of all studies which appeared eligible from the search were obtained and were checked by two review authors who jointly made decisions about inclusion. Any disagreements were resolved by discussion. The author of one of the trials was contacted for clarification of details of his trial. It was not considered feasible to contact the other authors of trials due to the length of time since the trials had been carried out. Data extraction was performed independently by two review authors. The data recorded were:

- description of trial design;
- description of trial participants;
- interventions in both groups;
- outcomes recorded;
- trial results;
- adequacy of reporting of withdrawals.

Data were checked and entered into the computer by one review author. Treatment effects were calculated using RevMan. Results were expressed as risk ratios (RR), with 95% confidence intervals (CI) for dichotomous variables and for continuous variables results were expressed as mean difference (MD).

Comparisons were made between the number of ulcers healed in patients taking oral zinc sulphate compared with placebo, for venous and arterial aetiologies (causes). Where serum zinc was measured at baseline, a subgroup analysis by zinc serum level, normal or low, was reported using the levels defined by the trial authors.

Assessment of risk of bias in included studies

Each included study was independently assessed using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance)(see Appendix 5 for details of criteria on which the judgement was based). Blinding and completeness of outcome data were assessed for each outcome separately. A risk of bias table was completed for each eligible study.

RESULTS

Description of studies

No new studies were identified in this latest review update. As a result of previous searches, a total of eighteen studies of oral zinc sulphate (440 to 660 mg per day) for the treatment of venous or arterial leg ulcers was retrieved in full. Of these twelve studies did not meet the inclusion criteria and were excluded from the review for the following reasons; eight were non-randomized studies

(Carruthers 1969; Cohen 1969; Floersheim 1980a; Floersheim 1980b; Husain 1969; Myers 1970; Rubisz-Brzezinska 1980; Tschumi 1981), two used alternate allocation (Floersheim 1980c; Gueri 1975), one did not meet inclusion criteria for minimum duration of ulcer (Larsen 1976) and one was not a trial but a review article (Gray 2003)(see Characteristics of excluded studies). Six RCTs were included (see Characteristics of included studies). All included studies were relatively small, with between 10 and 42 participants.

Four of the included trials involved hospital outpatients, the fifth trial concerned inpatients and the sixth described the participants as ambulant patients, but did not specify whether they were inpatients or outpatients. Five of the trials included patients with venous ulcers; one included patients with arterial ulcers only. Three trials were conducted in England and three in Sweden.

Five studies were comparisons of oral zinc sulphate with placebo, while the sixth trial used a control group that received no treatment. The durations of treatment with zinc sulphate varied from four weeks to a year. Results were reported as the number of ulcers healed at the end of the study and, in some cases, by the average rate of healing. No study reported the time to complete healing of ulcers.

Four studies measured serum zinc at baseline and during the trial period (Clayton 1972; Haegar 1974; Hallbook 1972; Phillips 1977). The definition of a normal serum zinc concentration varied between studies: Hallbook 1972 used 110 micrograms/100 ml; Haegar 1974 85 micrograms/100 ml; Phillips 1977 127.5 micrograms/100 ml, while Clayton 1972 only described the group mean. Only the Phillips 1977 trial mentioned the time at which samples were taken (afternoon).

Use of mean serum zinc as the cut point between low and normal serum zinc is not appropriate, as it will vary with each group and may give rise to erroneous results. Those below the group mean may be regarded as having 'low' serum zinc and yet in other studies would be well above the cut-off level.

Risk of bias in included studies

The six studies included in the review were small (median sample size 33, range 10 to 42 people) (Figure 1).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Participants – all outcomes	Blinding (performance bias and detection bias): Healthcare providers – all outcomes	Blinding (performance bias and detection bias): Outcome assessors – all outcomes	Incomplete outcome data (attrition bias): Drop out rate described and acceptable – all outcomes	Incomplete outcome data (attrition bias): ITT analysis – all outcomes	Selective reporting (reporting bias)	Other bias
Clayton 1972	?	+	+	?	?	?	?	+	-
Greaves 1972	?	+	+	+	?	+	-	+	+
Haegar 1972	?	?	?	?	?	+	-	-	-
Haegar 1974	?	?	?	?	?	?	-	-	-
Hallbook 1972	?	?	+	?	?	+	-	-	+
Phillips 1977	?	+	+	+	?	+	+	+	+

Allocation

Sequence generation:

None of the included studies report the method used to generate the randomisation sequence and they are therefore at unclear risk of bias.

Allocation concealment:

Adequate allocation concealment was reported by three studies which all used pharmacy controlled randomisation to conceal allocation and were therefore at low risk of bias (Clayton 1972; Greaves 1972; Phillips 1977). The remaining three studies did not report if allocation was concealed (Haegar 1972; Haegar 1974; Hallbook 1972).

Blinding

Blinding: (Participants - all outcomes):

Adequate blinding of participants was reported in four studies of which two clearly reported that the participants were blinded (Greaves 1972; Phillips 1977). The other two studies were judged to have adequately blinded participants because they were reported as double blind and the participants were given capsules identical in appearance (Clayton 1972; Hallbook 1972) and were therefore at low risk of bias. The remaining two studies either provided insufficient information to permit a judgement on blinding of participants (Haegar 1972) or did not report on blinding (Haegar 1974).

Blinding: (Healthcare providers - all outcomes):

Only two studies reported adequate blinding of healthcare providers and were at low risk of bias (Greaves 1972; Phillips 1977). Three studies were reported as double-blind but did not report who was blinded (Clayton 1972; Haegar 1972; Hallbook 1972). Haegar 1974 did not report on blinding.

Blinding: (Outcome assessors - all outcomes):

Three studies were reported as double-blinded but did not provide sufficient information to permit a judgement if the outcome assessors were blinded (Clayton 1972; Haegar 1972; Hallbook 1972). Blinding of outcome assessors was not reported by Greaves 1972; Haegar 1974; Phillips 1977.

Incomplete outcome data

Incomplete outcome data addressed: (Drop-out rate described and acceptable - all outcomes):

The drop-out rate was described adequately and was acceptable in four studies, two did not have any missing data (Hallbook 1972; Phillips 1977) and two studies reported a drop-out rate which was judged to be acceptable (below 10%) (Greaves 1972; Haegar 1972) and therefore were at low risk of bias for this domain. In the remaining two studies, insufficient information was provided to permit a clear judgement (Clayton 1972; Haegar 1974).

Incomplete outcome data addressed: (ITT analysis - all outcomes):

Four studies did not undertake ITT analysis as all the randomised participants were not included in the final analysis and therefore

were at high risk of bias (Greaves 1972; Haegar 1972; Haegar 1974; Hallbook 1972). Phillips 1977 included all the randomised participants in the analysis and therefore ITT was achieved (low risk of bias). The remaining study did not provide sufficient information to judge if an ITT analysis had been conducted (Clayton 1972).

Selective reporting

This domain was judged to be at low risk of bias in three studies, though the study protocol was not available, the important outcome measures stated in the methods section were reported in the results (Clayton 1972; Greaves 1972; Phillips 1977). Three studies were at high risk of bias, one study did not report the outcomes of a third arm of the trial (Haegar 1972) and in two studies there was selective reporting based on a post hoc decision to present data of ulcers of a size 100 -1000 mm² (Haegar 1974; Hallbook 1972).

Other potential sources of bias

Three studies were judged at low risk of bias for this domain because there was no imbalance in the baseline characteristics and the studies seemed to be free from other forms of bias (Greaves 1972; Hallbook 1972; Phillips 1977). The remaining three studies were judged at high risk of bias because there was baseline imbalance in the mean ulcer area and no mention was made if this was adjusted for in the analysis (Clayton 1972; Haegar 1972; Haegar 1974).

Effects of interventions

Arterial ulcers

In the Haegar 1974 study involving people with leg ulcers due to arterial disease all but two of the 30 ulcers healed within one year (RR 1.14, 95% CI 0.89 to 1.47) (Analysis 1.1). The two non-healing ulcers were both in the control group and the patients had low serum zinc levels. The two ulcers that failed to heal were also both much larger than the average initial size (by 33% and 160%), which reduced their probability of healing. The average rate of re-epithelialisation in the subgroup with low serum zinc that received oral zinc was 6.2 mm²/day compared with the subgroup with low serum zinc that received placebo (2.6 mm²/day). Mean values only were provided, which limited further analysis. Furthermore, the groups were not balanced at baseline (ulcers were 26% larger in the zinc group).

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

Chronic venous ulcers

Haegar 1972: the number of ulcers healed at 12 weeks was 11 out of 15 (73%) in the zinc group and 11 out of 21 (52%) in the placebo group (RR 1.4, 95% CI 0.84 to 2.33) (Analysis 2.1).

Greaves 1972: three out of 18 (17%) patients healed in the zinc group and two out of 18 (11%) healed in the placebo group, at four months (relative risk for healing (RR) 1.5, 95% confidence interval (CI) 0.28 to 7.93). There was no statistically significant difference in healing between the groups (Analysis 2.2).

Hallbook 1972: the number of ulcers healed at 18 weeks was nine out of 13 (69%) in the zinc treatment group, and eight out of 14 (57%) in the placebo group (RR 1.23, 95% CI 0.67 to 2.25) (Analysis

2.3). The authors then undertook a subgroup analysis to examine the effect of zinc in those with low serum zinc. It is not clear if this analysis was pre-specified. People with serum zinc below 110 micrograms per 100 ml who received zinc sulphate were not significantly more likely to heal (5/7 or 71%) than those with low serum zinc in the placebo group (1/7 or 14%), (RR 5.0, 95% CI 0.77 to 32.57). Mean zinc-serum levels were measured at baseline, 6, 12 and 18 weeks. Patients treated with placebo (in both the low and normal serum groups), had consistently lower serum zinc levels throughout the trial.

Of the people with serum zinc concentrations greater than 110 micrograms per 100ml, four out of six in the zinc group (67%) healed compared with seven out of seven (100%) of people in the placebo group. This difference was not statistically significant, (RR 0.69, 95% CI 0.38 to 1.23).

Phillips 1977: at 10 months, 10 out of 19 (53%) of ulcers had healed in the zinc group and 12 out of 23 (52%) in the placebo group (RR 1.01, 95% CI 0.57 to 1.8). No statistically significant difference in healing between the groups was therefore observed (Analysis 2.4).

Pooling the four trials that compared oral zinc sulphate with placebo in people with venous ulcers ($I^2 = 0\%$) showed no statistically significant difference between the two group (RR 1.22, 95% CI 0.88 to 1.68) (Analysis 3.1).

Clayton 1972 only reported the mean number of days to 90% healing in the two groups, with no indication of range. This did not allow full analysis. The treated group took, on average, 25.5 days to achieve 90% healing compared with 12.0 days in the untreated group. One patient had an arterial ulcer, but it was not known to which group this patient was allocated.

Side effects of zinc sulphate

Side effects did not appear to be a major problem. Phillips 1977 and Greaves 1972 reported no side effects in the trials though Clayton 1972 reported a tendency to constipation in both groups. Hallbook 1972 reported mild side effects (dry skin, perspiration) occurring in the placebo group only.

Haegar 1972 reported that three patients in the treatment group withdrew due to dizziness, itching and nausea, and two in the placebo group due to dizziness and a skin rash. Minor side effects in those taking zinc were dizziness (one person) and constipation (two people). Haegar 1974 reported that two people in the treatment group suffered nausea after a few weeks of treatment; they withdrew from the study. No other side effects were reported.

Haegar (Haegar 1972; Haegar 1974) and Hallbook 1972 reviewed the full blood count and liver enzymes initially, and at the end of treatment, and found no appreciable change in any of the parameters.

DISCUSSION

There is currently no evidence that oral zinc speeds the healing of either venous or arterial leg ulcers, though the available evidence is limited and of poor quality. Studies of oral zinc vary substantially in terms of the duration of treatment, follow up and prognostic comparability of treatment groups at baseline. All existing studies were too small to be able to detect a moderate effect of zinc.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review are based on small trials of poor quality. At present there is no evidence to support the use of oral zinc sulphate in the treatment of people with leg ulcers due to venous or arterial disease. This finding, should however, be contextualised within the generally low quality of the included studies. Patient numbers in all the trials were too small to detect any effect of zinc sulphate as statistically significant in either direction.

Implications for research

If further research is conducted to look at the effect of using oral zinc sulphate to treat people with leg ulcers, these trials should be robust in design. The following points should be taken into consideration in the design of any future studies:

- Recommendations outlined in the CONSORT Statement should be adopted as far as possible.
- Recruitment numbers should be based on an a priori sample size calculation. In many trials the sample size is too small to detect clinically important differences between treatments as statistically significant. In order to recruit sufficient patient numbers, multicentre trials should be more frequently considered. When these trials are commissioned they require a strong infrastructure to provide support and promote collaboration.
- The method of random sequence generation and treatment allocation should ensure low risk of bias (i.e., computer generated randomisation programme with allocation concealment e.g., by using a remote, telephone randomisation service).
- The primary endpoint of treatment trials should be complete ulcer healing and the primary outcome should preferably be time to healing, analysed by survival methods. In addition, the length of follow-up needs to be of sufficient duration to capture a meaningful proportion of events.
- For each patient a single reference ulcer should be selected. Multiple ulcers on a patient should not be randomised individually and considered as independent unless the trial has been specifically designed to accommodate this, and appropriate statistical analysis, that accounts for clustering, prespecified.
- Assessment of outcomes should be undertaken either by assessors masked to trial treatment or confirmed by remote, blinded adjudication from photographs.
- Analysis should be according to intention-to-treat.
- Evaluations should provide sufficiently full details of the interventions used, including descriptions of all components of compression, such that readers would be able to apply the treatments described (with training where necessary).
- Evaluations should report the skill level of staff providing care.

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Sciences, University of York. Catherine Hawke was an author of the original review but has not been involved in the updating process.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Clayton 1972

Methods	Randomised double-blind trial of oral zinc vs placebo.
Participants	Setting: dermatology ward, London, England. 10 inpatients with chronic ulcers: 8 venous, 1 traumatic and 1 arterial ulcer. Baseline comparability of groups: mean ulcer size was 47% greater at baseline in the placebo group than treatment group. Age, sex and diagnosis not compared.
Interventions	Oral zinc sulphate 220 mg or lactose placebo. Frequency and duration of treatment were not recorded. 4-week follow up.
Outcomes	Mean number of days to 50 % and 90% reduction of ulcer area. No range or standard deviation given.
Notes	Average serum zinc for all participants was 83 micrograms/100ml.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were issued according to a random schedule known only to the pharmacist." Comment: Method of generating the random schedule not reported.
Allocation concealment (selection bias)	Low risk	Quote: "All were given identical looking "ulcer capsules, which contained either 220 mg of zinc sulphate or lactose by double blind technique. They were issued according to a random schedule known only to the pharmacist." Comment: Pharmacy-controlled randomisation done.
Blinding (performance bias and detection bias) Participants - all outcomes	Low risk	Quote: "All were given identical looking "ulcer capsules, which contained either 220 mg of zinc sulphate or lactose by double blind technique" Comment: Reported as double blind and judged that participants are likely to be blinded to treatment allocation.
Blinding (performance bias and detection bias)	Unclear risk	Quote: "All were given identical looking "ulcer capsules, which contained either 220 mg of zinc sulphate or lactose by double blind technique"

Oral zinc for arterial and venous leg ulcers (Review)

Clayton 1972 (Continued)

Healthcare providers - all outcomes

Comment: Reported as double blind but information was insufficient to permit judgement if the healthcare providers were blinded.

Blinding (performance bias and detection bias) Outcome assessors - all outcomes	Unclear risk	Quote: "All were given identical looking "ulcer capsules, which contained either 220 mg of zinc sulphate or lactose by double blind technique" Comment: Reported as double blind but information was insufficient to permit judgement if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) Drop out rate described and acceptable - all outcomes	Unclear risk	Comment: The study did not state if there were any drop outs also, the study does not state if all the randomised participants were followed up.
Incomplete outcome data (attrition bias) ITT analysis - all outcomes	Unclear risk	Comment: No drop outs or withdrawals were reported. The total numbers of participants assessed were also not reported. We cannot judge if an ITT analysis was conducted.
Selective reporting (reporting bias)	Low risk	Comment: The study protocol was not available but the important outcome measures stated in the methods section are reported in the results.
Other bias	High risk	Quote: "The total mean initial ulcer area was 44.9 cm ² in the treated group and 65.8 cm ² in the untreated group" Comment: The baseline ulcer area in the placebo group was larger than in the treatment group, thus favouring the zinc group and no mention was made that this was adjusted from the analysis.

Greaves 1972

Methods	Randomised, double-blind, trial of oral zinc sulphate vs placebo.
Participants	Setting: dermatology department in the north of England. 38 patients with chronic venous leg ulcers 'their ulceration predominantly due to venous stasis', but included 3 people with diabetes and 1 with rheumatoid disease. All but 5 were ambulant. Patients were reviewed every 3-4 weeks during the trial. At baseline groups were comparable for age, sex, and mean ulcer area.
Interventions	Oral zinc sulphate 220 mg or lactose 3 times daily until ulcer healed or for a maximum of 4 months. Ulcers were treated with antiseptics, non adherent dressings and a crepe bandage.
Outcomes	Rate of re epithelialisation as linear mm/week. Number of ulcers healed at the end of the trial.
Notes	Intention-to-treat analysis not used - 2 patients withdrawn and not included in analysis. Serum zinc not measured.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to either placebo or zinc capsules" Comment: Method of generating the random schedule not reported.

Oral zinc for arterial and venous leg ulcers (Review)

Greaves 1972 (Continued)

Allocation concealment (selection bias)	Low risk	<p>Quote: “Patients were randomly allocated to either placebo or zinc capsules by the pharmacy department , Royal Victoria Infirmary, Newcastle upon Tyne ”</p> <p>Comment: Pharmacy-controlled randomisation done and this was judged to be adequate concealment.</p>
Blinding (performance bias and detection bias) Participants - all outcomes	Low risk	<p>Quote: “Neither the physician nor the patients knew which capsules have been prescribed.”</p> <p>Comment: Blinding of participants was done and unlikely that the blinding could have been broken.</p>
Blinding (performance bias and detection bias) Healthcare providers - all outcomes	Low risk	<p>Quote: “Neither the physician nor the patients knew which capsules have been prescribed.”</p> <p>Comment: Blinding of key study personal (physician) was ensured and unlikely that the blinding could have been broken.</p>
Blinding (performance bias and detection bias) Outcome assessors - all outcomes	Unclear risk	<p>Comment: Not stated.</p>
Incomplete outcome data (attrition bias) Drop out rate described and acceptable - all outcomes	Low risk	<p>Quote: “Thirty-six patients completed the trial, 2 having defaulted.”</p> <p>Comment: No reason for missing data provided. However, the dropout rate was less than 10% and judged to be acceptable.</p>
Incomplete outcome data (attrition bias) ITT analysis - all outcomes	High risk	<p>Quote: “Thirty-six patients completed the trial, 2 having defaulted.”</p> <p>Comment: ITT analysis not done, as two of the 38 patients defaulted and they were not included in the results.</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: The study protocol was not available but the important outcome measures stated in the methods section are reported in the results.</p>
Other bias	Low risk	<p>Comment: There was no imbalance in the baseline characteristics and the study seems to be free from other forms of bias.</p>

Haegar 1972

Methods	Randomised, double-blind controlled trial of oral zinc sulphate vs placebo. Method of randomisation not described.
Participants	Setting: surgical department in Malmo, Sweden. 36 ambulant patients with uncomplicated venous ulcers. Not specified whether participants were inpatients or outpatients. The groups were comparable at baseline for age and sex distribution. Mean ulcer size of the treatment group was 50% greater than the control group.
Interventions	Oral zinc sulphate 200mg 3 times daily or placebo (unspecified) for 3 months. Other interventions were the same in both groups: Katadyn silver spray, and compressive bandages with aluminium foil and rubber foam, dressed 2-3 times per week.
Outcomes	Number of ulcers healed at 3 months

Haegar 1972 (Continued)

Notes

Participants in 3rd arm of the trial were 'allocated' to effervescent zinc sulphate. The results of this group were not included in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "The patients were given alternatively zinc sulphate capsules and placebo capsules according to a randomised double blind system."</p> <p>Comment: Method of generating the random schedule not reported.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: Not stated</p>
Blinding (performance bias and detection bias) Participants - all outcomes	Unclear risk	<p>Quote: "The patients were given alternatively zinc sulphate capsules and placebo capsules according to a randomised double blind system."</p> <p>Comment: Whilst reported as double blind the information given was insufficient to permit judgement as they did not state if the participants were blinded. The capsules were identical in appearance.</p>
Blinding (performance bias and detection bias) Healthcare providers - all outcomes	Unclear risk	<p>Quote: "The patients were given alternatively zinc sulphate capsules and placebo capsules according to a randomised double blind system."</p> <p>Comment: Reported as double blind but information was insufficient to permit judgement as they did not state if the healthcare providers were blinded.</p>
Blinding (performance bias and detection bias) Outcome assessors - all outcomes	Unclear risk	<p>Quote: "The patients were given alternatively zinc sulphate capsules and placebo capsules according to a randomised double blind system."</p> <p>Comment: Reported as double blind but information was insufficient to permit judgement as they did not state if the outcome assessors were blinded.</p>
Incomplete outcome data (attrition bias) Drop out rate described and acceptable - all outcomes	Low risk	<p>Quote: "Out of 15 patients on zinc sulphate in capsules, three discontinued the treatment with reasons like dizziness, itching and nausea." Two patients withdrew from the placebo group, "The stated reasons for discontinuation after placebo were dizziness and exanthema in two patients."</p> <p>Comment: Imbalance in numbers and reasons for missing data across intervention group. But, reasons for drop out were given and the rate was less than 10% and judged to be acceptable.</p>
Incomplete outcome data (attrition bias) ITT analysis - all outcomes	High risk	<p>Comment: ITT analysis not done as all the randomised participants not included in the final results.</p>
Selective reporting (reporting bias)	High risk	<p>Quote: "A third group was treated with zinc sulphate in the pharmaceutical form of effervescent tablets."</p> <p>Comment: The study protocol was not available but the results from this group were not included in the study report.</p>
Other bias	High risk	<p>Comment: There was baseline imbalance in mean ulcer area, which was higher in the zinc sulphate capsule treatment group (557 mm²) as compared to the placebo group (370 mm²) favouring the control group. It was not clear if this was adjusted from analysis.</p>

Haegar 1974

Methods	Patients randomised to receive zinc sulphate or not. No placebo given. Patients' fasting serum zinc measured at baseline. Patients in each treatment group divided into 2 groups, normal serum zinc (> 85 micrograms/100ml) and low serum zinc (< 85 micrograms/100ml). Not clear if randomisation was stratified by serum zinc level.
Participants	Setting: vascular surgery out patients, Malmo, Sweden. 30 patients with ischaemic leg ulcers with ulcers between 100 mm ² and 1000 mm ² . At baseline little assessment of comparability: age range similar, mean size of treatment group ulcers was 74% larger than the control group.
Interventions	Oral zinc sulphate 200mg 3 times daily, or no treatment. Participants followed up for up to 14 months. Other interventions not described.
Outcomes	Number of ulcers healed within 1 year, by low or normal serum zinc. Healing quotient (healed area expressed as mm ² /day).
Notes	Initially 50 participants recruited but only reported the results of 30 patients with ulcers between 100 mm ² and 1000 mm ² , as the very large and small ulcers healed irregularly.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were divided according to serum zinc levels. In both group with normal values and that with subnormal values, approximately half of the patients were given oral zinc sulphate at random." Comment: Method of generating the random schedule not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: Not stated
Blinding (performance bias and detection bias) Participants - all outcomes	Unclear risk	Comment: Not stated
Blinding (performance bias and detection bias) Healthcare providers - all outcomes	Unclear risk	Comment: Not stated
Blinding (performance bias and detection bias) Outcome assessors - all outcomes	Unclear risk	Comment: Not stated
Incomplete outcome data (attrition bias) Drop out rate described and acceptable - all outcomes	Unclear risk	Quote: "Two patients suffered from nausea of a minor degree after a few weeks of zinc treatment and were excluded from the series." Comment: Insufficient information to permit judgement of attrition as number of randomised not stated.
Incomplete outcome data (attrition bias) ITT analysis - all outcomes	High risk	Quote: "During the course of the investigation it became clear that very large ulcers and very small ulcers, respectively, behaved irregularly in their healing patterns."

Haegar 1974 (Continued)

Quote: “we decided to include only ulcers within the range 100-1000 mm² in the statistical analysis.”

Comment: ITT analyses not done as all the randomised participants were not included in the final results. Only 30 out of 50 patients had ulcers that met the required range (100-1000 mm²) and were included in the analysis.

Selective reporting (reporting bias)	High risk	Comment: The study protocol was not available but the important outcome measures stated in the methods section are reported in the results. However there was selective reporting based on a post hoc decision to present data only with ulcers in the range 100-1000 mm ² .
Other bias	High risk	Comment: There was some baseline imbalance in mean ulcer area of two groups, normal serum zinc treatment group with initial ulcer area 521 mm ² and normal serum zinc control group with initial ulcer area 366 mm ² , favouring the control group. Also, it was not clear if this was adjusted from analysis.

Hallbook 1972

Methods	Patients were randomly allocated to receive zinc sulphate or placebo. Double blind procedure. Serum zinc measured initially and concentrations above 110 micrograms/100 ml were regarded as 'normal'.
Participants	Setting: surgical out-patients, Lund, Sweden. 27 patients with chronic venous leg ulcers 100 -1000 mm ² . Groups comparable at baseline in terms of age and sex and mean ulcer area.
Interventions	Oral zinc sulphate 200 mg or placebo (unspecified) 3 times daily for 18 weeks. All given 'same topical therapy and pressure dressings'.
Outcomes	Number of ulcers healed at 18 weeks by low or normal serum zinc. Healing rate expressed as mm ² /day.
Notes	Initially 50 participants recruited but only reported the results of 27 patients with ulcers between 100 mm ² and 1000 mm ² , as the very large and small ulcers 'healed irregularly'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “The patients were treated with zinc sulphate or placebo effervescent tablets, according to randomisation scheme.” Comment: Method of generating the random schedule not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Blinding (performance bias and detection bias) Participants - all outcomes	Low risk	Quote: “The placebo and zinc sulphate tablets were identical in appearance and taste, so the trial was strictly double blind.” Comment: Reported as double blind and judged that participants are likely to be blinded to treatment allocation.
Blinding (performance bias and detection bias) Healthcare providers - all outcomes	Unclear risk	Quote: “The placebo and zinc sulphate tablets were identical in appearance and taste, so the trial was strictly double blind.”

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Hallbook 1972 (Continued)

Comment: Reported as double blind but information was insufficient to permit judgement if the healthcare providers were blinded.		
Blinking (performance bias and detection bias) Outcome assessors - all outcomes	Unclear risk	<p>Quote: "The placebo and zinc sulphate tablets were identical in appearance and taste, so the trial was strictly double blind."</p> <p>Comment: Reported as double blind but information was insufficient to permit judgement if the outcome assessors were blinded.</p>
Incomplete outcome data (attrition bias) Drop out rate described and acceptable - all outcomes	Low risk	<p>Quote: "All patients persisted with the treatment."</p> <p>Comment: No drop outs.</p>
Incomplete outcome data (attrition bias) ITT analysis - all outcomes	High risk	<p>Quote: "Fifty patients with chronic venous ulcers were given placebo or zinc sulphate. Because great variations in the size of the ulcers would make healing difficult to evaluate, only patients with in the range 100-1000 mm² (27 patients) were included in the study."</p> <p>Comments: Out of the 50 patients randomised only 27 were followed up as they were in the range of 100-1000 mm². No details of the remaining 23 were given.</p>
Selective reporting (reporting bias)	High risk	Comment: The study protocol was not available but the important outcome measures stated in the methods section are reported in the results. However there was selective reporting based on a post hoc decision to present data only with ulcers in the range 100-1000 mm ² .
Other bias	Low risk	Comment: There was no imbalance in the baseline characteristics and the study seems to be free from other forms of bias.

Phillips 1977

Methods	Double blind randomised controlled trial of zinc sulphate vs placebo. Method of randomisation not described.
Participants	Setting: dermatology outpatient department in London, England. 42 ambulant patients with venous leg ulcers, 2 with psoriasis and 1 with rheumatoid disease. At baseline the groups were comparable for age, sex and mean ulcer area.
Interventions	Zinc sulphate 220mg twice daily, or placebo, until the ulcer healed or the end of the trial at 10 months. Other treatment in both groups was a pad of polyether foam supported with a tubular gauze bandage and a tubular elastic bandage.
Outcomes	Number of ulcers healed at the end of the study. Mean linear healing rate.
Notes	After allocation the serum zinc was measured. The groups were divided into 'high' or 'low' serum zinc levels depending on whether they were above or below the group average of 127.5 micrograms/100 ml.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to either zinc capsules or lactose capsules."

Oral zinc for arterial and venous leg ulcers (Review)

Phillips 1977 (Continued)

Comment: Method of generating the random schedule not reported.		
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated to either zinc capsules or lactose capsules by the Pharmacy department of St Bartholomew's or Hackney Hospitals." Comment: Pharmacy-controlled randomisation done.
Blinding (performance bias and detection bias) Participants - all outcomes	Low risk	Quotes: "Neither the physicians nor the patients knew which capsules had been prescribed." Comment: Blinding of participants was done and unlikely that the blinding could have been broken.
Blinding (performance bias and detection bias) Healthcare providers - all outcomes	Low risk	Quotes: "Neither the physicians nor the patients knew which capsules had been prescribed." Comment: Blinding of key study personal (physician) was ensured and unlikely that the blinding could have been broken.
Blinding (performance bias and detection bias) Outcome assessors - all outcomes	Unclear risk	Comment: Not stated
Incomplete outcome data (attrition bias) Drop out rate described and acceptable - all outcomes	Low risk	Quotes: "All 42 patients completed the trial." Comment: No missing data.
Incomplete outcome data (attrition bias) ITT analysis - all outcomes	Low risk	Comments: Participants complete no withdrawals reported.
Selective reporting (reporting bias)	Low risk	Comments: The study protocol was not available but the important outcome measures stated in the methods section are reported in the results.
Other bias	Low risk	Comment: There was no imbalance in the baseline characteristics and the study seems to be free from other forms of bias.

Abbreviations:

> = less than

< = more than

vs = versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Carruthers 1969	Not a trial, but a letter giving the authors' experience on the use of oral zinc sulphate.
Cohen 1969	Not a trial, but a letter about the treatment of pressure sores with oral zinc sulphate.
Floersheim 1980a	Allocation to treatment groups not randomised.
Floersheim 1980b	Allocation to treatment groups not randomised, and outcome was not healing.

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Study	Reason for exclusion
Floersheim 1980c	Allocation to treatment groups not randomised but alternate.
Gray 2003	Not a trial, a review article.
Gueri 1975	Alternate allocation to treatment groups.
Husain 1969	Allocation to treatment groups not randomised.
Larsen 1976	Did not meet inclusion criteria for minimum duration of ulcer.
Myers 1970	Allocation to treatment groups not randomised, and no control group.
Rubisz-Brzezinska 1980	Allocation to treatment groups not randomised.
Tschumi 1981	Allocation to treatment groups not randomised, and outcome measured was toxicity - not healing.

DATA AND ANALYSES

Comparison 1. Zinc versus placebo in arterial ulcers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 healed within one year	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.89, 1.47]
1.1 number of ulcers healed with initial serum zinc over 85 micrograms/100ml	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.80, 1.26]
1.2 number of ulcers healed with initial serum zinc under 85 micrograms/100ml	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.83, 2.25]

Analysis 1.1. Comparison 1 Zinc versus placebo in arterial ulcers, Outcome 1 healed within one year.

Comparison 2. Zinc versus placebo in venous ulcers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 number healed at 12 weeks	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.84, 2.33]
2 number healed at 16 weeks	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.28, 7.93]
3 number healed at 18 weeks	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.67, 2.25]
3.1 serum zinc less than 110 micro-grams/100 ml	1	14	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.77, 32.57]
3.2 serum zinc greater than 110 micrograms/100ml	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.38, 1.23]
4 number healed at 40 weeks	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.57, 1.80]

Analysis 2.1. Comparison 2 Zinc versus placebo in venous ulcers, Outcome 1 number healed at 12 weeks.

Analysis 2.2. Comparison 2 Zinc versus placebo in venous ulcers, Outcome 2 number healed at 16 weeks.

Analysis 2.3. Comparison 2 Zinc versus placebo in venous ulcers, Outcome 3 number healed at 18 weeks.

Analysis 2.4. Comparison 2 Zinc versus placebo in venous ulcers, Outcome 4 number healed at 40 weeks.

Comparison 3. Zinc versus placebo in venous ulcers pooled

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed at final end-point	4	141	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.88, 1.68]

Analysis 3.1. Comparison 3 Zinc versus placebo in venous ulcers pooled, Outcome 1 Number of ulcers healed at final endpoint.

Study or subgroup	Zinc n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Greaves 1972	3/18	2/18		6.73%	1.5[0.28,7.93]
Haegar 1972	11/15	11/21		30.84%	1.4[0.84,2.33]
Hallbook 1972	9/13	8/14		25.91%	1.21[0.68,2.17]
Phillips 1977	10/19	12/23		36.52%	1.01[0.57,1.8]
Total (95% CI)	65	76		100%	1.22[0.88,1.68]
Total events: 33 (Zinc), 33 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.76, df=3(P=0.86); I ² =0%					
Test for overall effect: Z=1.19(P=0.24)					

Favours experimental 0.001 0.1 1 10 1000 Favours control

APPENDICES

Appendix 1. Search methods - sixth update 2012

For this sixth update we searched the following electronic databases:

- Cochrane Wounds Group Specialised Register (searched 17 May 2012);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 5);
- Ovid MEDLINE (2010 to May Week 2 2012);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations May 16, 2012);
- Ovid EMBASE (2010 to 2012 Week 19);
- EBSCO CINAHL (2010 to May 2 2012).

The following search strategy was used in The Cochrane Central Register of Controlled Trials (CENTRAL):

```
#1MeSH descriptor Zinc explode all trees
#2MeSH descriptor Zinc Sulfate explode all trees
#3zinc NEXT (sulphate or sulfate)
#4(#1 OR #2 OR #3)
#5MeSH descriptor Administration, Oral explode all trees
#6oral or systemic
#7(#5 OR #6)
#8MeSH descriptor Leg Ulcer explode all trees
#9((varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (stasis NEXT ulcer*) or (crural NEXT ulcer*) or "ulcus cruris")
#10(#8 OR #9)
#11(#4 AND #7 AND #10)
```

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#) respectively. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in

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MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format ([Lefebvre 2011](#)). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) ([SIGN 2011](#)). No date or language restrictions were applied.

No new studies were identified for inclusion in this update.

Appendix 2. Ovid MEDLINE search strategy

```

1 exp Zinc/ (21518)
2 exp Zinc Sulfate/ (769)
3 (zinc adj (sulphate or sulfate)).tw. (785)
4 or/1-3 (22350)
5 exp Administration, Oral/ (58259)
6 (oral or systemic).tw. (370750)
7 or/5-6 (390027)
8 exp Leg Ulcer/ (9371)
9 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris).tw. (3457)
10 ((arterial or ischaemic or ischemic) adj (wound* or ulcer*)).tw. (481)
11 or/8-10 (10336)
12 4 and 7 and 11 (5)
13 randomized controlled trial.pt. (227736)
14 controlled clinical trial.pt. (38419)
15 randomized.ab. (184259)
16 placebo.ab. (87140)
17 clinical trials as topic.sh. (76548)
18 randomly.ab. (127090)
19 trial.ti. (67818)
20 or/13-19 (515952)
21 Animals/ (2356741)
22 Humans/ (6514614)
23 21 not 22 (1542419)
24 20 not 23 (470364)
25 12 and 24 (2)

```

Appendix 3. Ovid EMBASE search strategy

```

1 exp ZINC/ (45148)
2 exp Zinc Sulfate/ (2176)
3 (zinc adj (sulphate or sulfate)).tw. (1100)
4 or/1-3 (46982)
5 exp Oral Drug Administration/ (66250)
6 (oral or systemic).tw. (523987)
7 or/5-6 (562947)
8 exp Leg Ulcer/ (5682)
9 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris).tw. (5129)
10 ((arterial or ischaemic or ischemic) adj (wound* or ulcer*)).tw. (715)
11 or/8-10 (8028)
12 4 and 7 and 11 (16)
13 Clinical trial/ (703132)
14 Randomized controlled trials/ (15676)
15 Random Allocation/ (47956)
16 Single-Blind Method/ (14398)
17 Double-Blind Method/ (81450)
18 Cross-Over Studies/ (29415)
19 Placebos/ (150233)
20 Randomi?ed controlled trial$.tw. (70884)
21 RCT.tw. (8759)
22 Random allocation.tw. (833)
23 Randomly allocated.tw. (12959)
24 Allocated randomly.tw. (1145)
25 (allocated adj2 random).tw. (253)
26 Single blind$.tw. (8733)
27 Double blind$.tw. (83338)

```


28 ((treble or triple) adj blind\$.tw. (201)
29 Placebo\$.tw. (126093)
30 Prospective Studies/ (177762)
31 or/13-30 (993657)
32 Case study/ (12822)
33 Case report.tw. (151906)
34 Abstract report/ or letter/ (483634)
35 or/32-34 (644533)
36 31 not 35 (966471)
37 animal/ (685714)
38 human/ (7946975)
39 37 not 38 (456790)
40 36 not 39 (945531)
41 12 and 40 (8)

Appendix 4. EBSCO CINAHL search strategy

S10 S3 and S6 and S9
S9 S7 or S8
S8 T1 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer*) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer*)
S7 (MH "Leg Ulcer+")
S6 S4 or S5
S5 T1 (oral or systemic) or AB (oral or systemic)
S4 (MH "Administration, Oral+")
S3 S1 or S2
S2 T1 (zinc sulphate or zinc sulfate) or AB (zinc sulphate or zinc sulfate)
S1 (MH "Zinc")

Appendix 5. Risk of bias assessment criteria

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process to permit judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?***Low risk of bias***

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Any one of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?***Low risk of bias***

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Any one of the following.

- Insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Any of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

High risk of bias

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

FEEDBACK

Methodological qualities of included studies

Summary

The reviewers appear to have scored quality of allocation concealment according to what the trial investigators reported about double blinding. In order to see the quality scores for concealment of allocation the reader has to display 'Quality' in MetaView. The review authors report that the method of random allocation was not described in any of the included trials. We would, therefore, expect all the trials to score 'B' (Unclear) for quality of allocation concealment. However, trials reported as double blind have been scored 'A', and the one trial reported as not blinded has been assigned category 'D' (which means that a quality score was not used). The Cochrane Handbook Section 6.3, and Schulz KF et al. JAMA 1995; 273(5):408-12 and 274(18):1456-8, explain the difference between allocation concealment and treatment blinding. The guide to using Review Manager software advises on the use of the category 'D'.

Reply

We have modified the scores as per these comments.

Contributors

The authors of the review.

Results

Summary

Odds ratios are misleading when event rates are high. The relative risk should be used instead. For example, in the study Hallbrook (1972), 9/13 versus 8/14 for 'number healed at 18 weeks', which intuitively are rather similar rates, is reported by the reviewers as Peto odds ratio 1.95, but the relative risk is only 1.25.

The overall picture tends to get lost in detailed description of results from each individual study. For example: "Haegar (1974) found all but two of the 30 ulcers healed within one year OR 8.73 (0.49, 156.29), the two that did not heal were both in the control group and had a low serum zinc. The two ulcers that failed to heal were both much larger than the average...". Overall, the event rate was 16/16 versus 12/14. The reported Peto odds ratio is 8.73, but the more appropriate relative risk is only 1.40.

The review authors should do a pooled analysis of the trials in venous ulcer, regardless of the fact that the length of follow-up varied between trials. This is permissible, since the results are so consistent across the four trials. The total number of healed ulcers is 33/65 versus 33/76, which corresponds to a relative risk of 1.22 (95% CI 0.88 to 1.68). Over all trials, therefore, there is no evidence of effect.

Reply

We have now used the relative risk to summarise the outcomes.

Contributors

The authors of the review.

Discussion

Summary

"There is some evidence to suggest that zinc might promote healing in individuals who have low serum zinc. This needs further evaluation". This statement seems to be unwarranted. The reviewers correctly point out that the study that suggested this (Hallbrook 1972) may be flawed in design, conduct and analysis. Hallbrook found no difference overall (9/13 versus 8/14 ulcers healed), the investigators then did a subgroup analysis, probably post hoc, of patients with low serum zinc which showed 5/7 versus 1/7 ulcers healed. Subgroup analyses must always be interpreted with caution, but they are particularly inappropriate when there is no overall effect.

Reply

We have moderated our statement thus:

One small study suggested a benefit of zinc in patients with low serum zinc, however this needs further evaluation as the finding arises from a sub-group analysis of only 14 patients.

Contributors

The authors of the review.

Implications for research

Summary

"There is limited evidence that zinc may be beneficial in the treatment of venous leg ulcers when there is a low serum zinc, but recommendations for the dose and duration of treatment cannot be made on the available information." The reviewers should not accept this implication, which is based only on the study by Hallbrook.

Reply

We have reflected this comment in the 'Implications for practice.'

Contributors

The authors of the review.

Minor criticisms

Summary

1. Text: The review contains many spelling and grammatical errors. It needs to be copy edited.

2. Criteria for considering studies for this review: Types of outcome measures: Adverse effects are not mentioned, yet they are reported in the Results section.

3. Search strategy for the identification of studies: The dates of the latest search should be included as well as the sources searched.
4. Description of studies: The text is duplicated. When studies are quoted the full study identifier, including date, should be used. "The trial in arterial ulcers..."; since this trial has not been mentioned before the description of it should begin: "One trial was in patients with arterial ulcers". Ten studies were identified. After, "only six were randomised controlled trials", it is redundant to add, "The remaining four were not randomised controlled trials".
5. Implications for research: The reviewers state that "Future trials need to be of an adequate size and duration of follow up". What might an adequate trial size and duration of follow up be, to answer the outstanding clinical questions?

Reply

1. We have copy edited the review.
2. Side effects have been added to the outcome measures.
3. Date of search has been added.
4. Study identifiers are limited by the number of characters permitted in RevMan.
5. The purpose of this review is not to design a trial. The sample size and follow up period will depend on the setting, desired effect size and population.

Contributors

The authors of the review.

Query re statement in the Plain Language Summary regarding leg wound healing, 16 October 2017

Summary

Email received from Joel Steinberg as follows: 'I note an opening comment to the effect that most leg wounds will heal with good local wound care even though this could take weeks to months. Really? My experience beyond training in vascular medicine and many years of practice, is that stasis ulcers usually require a compression gradient bandaging and/or reduction of underlying venous hypertension in order to heal, and ischemic wounds usually require revascularization. I am concerned that to state otherwise is misleading. Are there strong studies to support the comment of concern? Of additional concern is the phrase 'may be due to poor nutrition'. Indeed there are likely cases where nutrition may be a factor leading to slow healing. But my experience is that it would be quite unusual to find a case where nutrition is the sole factor to explain delayed healing. Rather, usually other factors that accompany poor nutrition are at play, such as poor hygiene and poor compliance. Permit me to suggest that the above phrase be slightly revised, to read in part, 'may in part be due to poor nutrition.' I think adding that small caveat will provide the reader with a more accurate picture of the issues at work in trying to get a wound to heal. Again I applaud the author for a fine and helpful review. The work will provide the medical community with important information.'

Declaration of interest:

'I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment.'

Reply

Author, Ewan Wilkinson: 'Thank you for your feedback. This section has been revised in accordance with your comments.'

Contributors

Joel Steinberg, Cooper University Hospital, NJ, USA

Ewan Wilkinson - Author.

WHAT'S NEW

Date	Event	Description
23 November 2017	Feedback has been incorporated	Minor amendments made to the Plain Language Summary in response to feedback. Feedback included in the review with review author response.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 3, 1999

Date	Event	Description
2 September 2014	New search has been performed	Seventh update, new search no new studies included.
2 September 2014	New citation required but conclusions have not changed	This conclusions of the review remain unchanged.
31 July 2012	Amended	Minor text edits
28 June 2012	New citation required but conclusions have not changed	Sixth update, no change to conclusions, Catherine Hawke moved to acknowledgements as no longer involved in the review.
28 June 2012	New search has been performed	New search, no new studies identified
9 November 2010	New search has been performed	Risk of bias assessment completed and table added. No change to conclusions.
1 September 2010	New search has been performed	New search, no new trials identified, one reference added to the table of excluded studies. The conclusions of the review remain unchanged.
26 November 2008	New search has been performed	New search; no new studies identified.
8 August 2008	Amended	Converted to new review format.
8 May 2007	New search has been performed	For the third update, new searches were carried out in May 2007. No new studies were found.
2 June 2005	New search has been performed	For the second update, new searches were carried out in June 2005. No new studies were found. After translation, the study by Larsen (1976) was excluded from the review.
22 February 2002	New search has been performed	The first update was published in The Cochrane Library, Issue 1, 2002, with one study (Larsen 1976) added to Studies awaiting assessment, pending translation from Danish.
14 August 1998	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

EW and CH independently assessed the studies for the original review. EW wrote the review which was checked by CH.

EW prepared the update and checked all versions of the updated review.

CH was not involved in the updating process for this review.

Contributions of editorial base:

Nicky Cullum: edited and approved the early updates of the review.

Sally Bell-Syer: co-ordinated the editorial process, edited the updated review, actioned the feedback from the copy editor and checked the risk of bias assessment.

Amanda Briant: ran the searches, edited the search methods section for the updated review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Public Health, University of Oxford, UK.
- Department of Public Health, Oxfordshire Health Authority, UK.
- Liverpool Health Authority, UK.
- NIHR/Department of Health (England), (Cochrane Wounds Group), UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Astringents [*administration & dosage]; Leg Ulcer [blood] [*drug therapy]; Randomized Controlled Trials as Topic; Wound Healing; Zinc [blood]; Zinc Sulfate [*administration & dosage]

MeSH check words

Humans