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Reinar LM, Forsetlund L, Bjørndal A, Lockwood DNJ

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[Intervention Review]

Interventions for skin changes caused by nerve damage in leprosy

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ABSTRACT

Background

More than three million persons are disabled by leprosy worldwide. The main complication of sensory nerve damage is neuropathic ulceration, particularly of the feet. In this review we explored interventions that can prevent and treat secondary damage to skin and limbs.

Objectives

To assess the effects of self-care, dressings and footwear in preventing and healing secondary damage to the skin in persons affected by leprosy.

Search methods

We searched the Cochrane Skin Group Specialised Register (April 2008), the Cochrane Central Register of Controlled Trials (The *Cochrane Library* Issue 1, 2008), MEDLINE (from 2003 to April 2008), EMBASE (from 2005 to April 2008), CINAHL (1982-2006) and LILACS (1982- April 2008) as well as online registers of ongoing trials (April 2008).

Selection criteria

Randomised controlled trials involving anyone with leprosy and damage to peripheral nerves treated with any measures designed to prevent damage with the aim of healing existing ulcers and preventing development of new ulcers.

Data collection and analysis

Two authors assessed trial quality and extracted data.

Main results

Eight trials with a total of 557 participants were included. The quality of the trials was generally poor. The interventions and outcome measures were diverse. Although three studies that compared zinc tape to more traditional dressings found some benefit, none of these showed a statistically significant effect. One trial indicated that topical ketanserin had a better effect on wound healing than clioquinol cream or zinc paste, RR was 6.00 (95% CI 1.45 to 24.75). We did not combine the results of the two studies that compared topical

phenytoin to saline dressing, but both studies found statistically significant effects in favour of phenytoin for healing of ulcer (SMD -2.34; 95% CI -3.30 to -1.39; and SMD -0.79; 95% CI -1.20 to 0.39). Canvas shoes were not much better than PVC-boots, and double rocker shoes did not promote healing much more than below-knee plasters.

Authors' conclusions

One study suggested that topical ketanserin is more effective than clioquinol cream or zinc paste. Topical phenytoin (two studies) may be more effective than saline dressing regarding ulcer healing. For the other dressings the results were equivocal. Canvas shoes were a little better than PVC-boots, but not significantly, and the effect of double rocker shoes compared to below-knee plasters was no different in promoting the healing of ulcers. No side effects were documented.

There is a lack of high quality research in the field of ulcer prevention and treatment in leprosy. New trials should follow the current standards for design and reporting of randomised controlled trials.

PLAIN LANGUAGE SUMMARY

Interventions for skin changes caused by nerve damage in leprosy

Three million persons are affected by nerve damage caused by leprosy (Hansen's disease) worldwide. Leprosy is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*. About 30% of people with leprosy develop nerve damage that can lead to loss of normal sensation and skin damage. The skin can crack and become infected and ulcerated. Impairment of the affected limb, caused by nerve damage, can result in severe joint deformity and injuries. The major areas affected by sensory loss are the hands (especially the palms), feet (especially the soles) and eyes. The drug therapy offered to those with leprosy is efficacious and has low relapse rates. However, even with treatment, many with leprosy will go on to develop secondary damage to skin and limbs as the nerve damage sustained cannot be reversed. In some, treatment leads to inflammatory reactions in the nerves, sometimes resulting in further damage.

Many interventions may help the healing of such ulcers. The rationale behind the use of, for example, appropriate footwear is to protect feet from damage that can lead to superficial sores on the soles of the feet, and later ulcers and secondary infections. Self-care includes daily management to reduce the effects of nerve function impairment. Education, information and empowerment of those affected by leprosy (and their carers) is part of some leprosy programmes and might prevent ulcers developing. Dressings might enhance the healing of ulcers.

We included eight trials with a total of 557 participants. Based on weak evidence we suggest that dressings with topical ketanserin may be more effective than clioquinol cream or zinc paste and topical phenytoin may be more effective than saline dressings regarding ulcer healing. Canvas shoes seem to be a little better than PVC-boots, but not significantly. Double rocker shoes do not show statistically significant benefit compared to below-knee plaster in promoting healing of ulcers. Whether the interventions reduce social stigma and lead to better quality of life were not investigated in any of the eight trials in this review. No side effects were documented.

There is a lack of high quality research in the field of ulcer prevention and treatment in leprosy. New trials should follow the current standards for design and reporting of randomised controlled trials.

BACKGROUND

Description of the condition

More than three million individuals are currently disabled by leprosy (Hansen's disease) worldwide (WHO 2006). Despite intensive efforts to control the disease, the total incidence is reported to be about 700,000 new cases per year (738,00 and 634,376 new cases detected in 1999 and 2000 respectively), in affected countries (Lockwood 2002b; WHO 2002b). The proportion of new cases of leprosy in children under 15 years of age was 18% in 2000 (WHO 2002). Hence person-to-person transmission remains a problem; there are significant numbers of childhood cases and many people suffer from the consequences of leprosy (McDougall 2002). At

the beginning of 2003 the number of people currently on drug treatment for leprosy was around 524,000 (WHO 2003). There were 407,791 new cases diagnosed and reported to WHO in 2004 (WHO 2006b). Although the incidence rate is declining slowly worldwide it is rising in a few places (WHO 2006).

South East Asia has the highest prevalence of leprosy followed by the Americas, Africa, the Western Pacific, Eastern Mediterranean and Europe (WHO 2002). The seven most affected countries are India, Brazil, the Democratic Republic of Congo, Tanzania, Nepal, Madagascar and Mozambique. Of all those identified as having the disease, 64% live in India .

Causes

Leprosy is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*.

Clinical manifestations and complications

The principal manifestations are skin lesions (flat or raised patches on the skin, sometimes a few and sometimes numerous, depending on host immunity). In those with a large number of bacteria the skin may become diffusely thickened. Thickened or cracked skin, or skin ulcers, may be later complications and peripheral neuropathy, (inflammation of nerves in the limbs, which become thickened and damaged) is common. Complications result from nerve damage, through immune reactions and also through direct invasion by the *M. leprae* bacteria. When the small sensory and autonomic nerve fibres in the skin are damaged this initially causes local loss of sensation and loss of the skin's ability to sweat. Damage to peripheral nerves eventually leads to more widespread loss of sensation, skin dryness and reduced function of the muscles supplied by the affected nerve. The dry skin can crack and become infected and ulcerated, and misuse of the affected limb can ultimately result in severe joint deformity and injuries.
The major areas affected by nerve damage in leprosy are the hands (especially the palms), feet (especially the soles) and eyes. The main complication of sensory nerve damage is ulceration secondary to sensory loss, particularly of the feet. The drug therapy offered to people infected with *M. leprae* is efficacious if given for sufficient length of time (WHO 2006). However, even with treatment, many persons with leprosy will go on to develop secondary damage to skin and limbs as the nerve damage sustained cannot be reversed.

Diagnosis

Leprosy is diagnosed clinically by two principal signs:

- anaesthetic skin lesions i.e. parts of the skin that are numb and not able to detect painful stimuli such as a pin prick;
- thickened peripheral nerves that can easily be felt through the skin;

and by:

- positive smear i.e. evidence of the causative bacterium, *M. leprae,* using microscopic examination of a sample of tissue (skin smear).

Classification

There are two main forms of classification (Lockwood 2002a). They are the Ridley-Jopling scheme and the World Health Organization (WHO) PB/MB (paucibacillary/multi bacillary) classification .

Ridley-Jopling scheme

This classifies leprosy on a scale from 'tuberculoid' to 'lepromatous' based on the clinical appearance and bacterial index of lesions (Lockwood 2002a). 'Tuberculoid' indicates that the body's immunity is good and there are few skin lesions. 'Lepromatous' means that the body has a poor immune response to the mycobacteria and there is uncontrolled bacterial multiplication, many skin lesions and also lesions in the mucosa of the nose and mouth. Peripheral nerve damage can occur at any point on the scale. Between the extremes of ' tuberculoid' and 'lepromatous' are the 'unstable borderline tuberculoid' and 'borderline lepromatous' forms.

WHO classification

This classification is based on the number of skin lesions:
1. paucibacillary (PB) - up to five lesions
2. multi bacillary (MB) - greater than five lesions (and/or positive smear at any site).
This is a simple classification scheme that makes treatment simpler for field workers, but it is less specific than the Ridley-Jopling scheme. The WHO classification system is the most widely used.

Description of the intervention

Chemotherapy with a combination of drugs (multidrug treatment (MDT)), is used to treat leprosy. The drugs used are rifampicin, dapsone and clofazimine - they are effective in killing bacilli, but do not prevent further nerve damage. Virtually all people affected by leprosy, and registered with their local health services, are treated with MDT. Other interventions in leprosy care are aimed at prevention and treatment of secondary damage to skin and limbs.

How the intervention might work

The rationale behind the use of, for example, appropriate footwear is to protect feet from damage that can lead to superficial sores on the soles of the feet, and later ulcers and secondary infections (McDougall 2002). Many interventions may help the healing of

such ulcers (Srinivasan 1989). Self-care includes daily management to reduce the effects of nerve function impairment. Education, information and empowerment of those affected by leprosy (and their carers) is part of some leprosy programmes (McDougall 2002). Ketanserin is thought to decrease peripheral vascular resistance. This vasodilation might have beneficial effects on capillary haemodynamics and cause increase in the blood flow and enhance healing of ulcers (Salazar 2001). Phenytoin is another topical dressing thought to enhance healing. The rationale behind this is that it accelerates the formation and maturation of collagen fibres, stimulates fibroblast proliferation, and inhibits collagenase activity (Bansal 1993).

Impact

Nerve damage can happen before, during and after chemotherapy treatment. It affects approximately 30% of people diagnosed with leprosy (2.6% with PB, 37% with MB, 2 years after detection and MDT treatment) (Lockwood 2001). Approximately 6% to 9% of people with newly diagnosed leprosy present with grade 2 disabilities (visible deformity or damage present) and as many as 20% to 56% of people have established nerve damage at diagnosis (Lockwood 2002b). These figures vary from country to country and between disease types.

Why it is important to do this review

The key to effective management of leprosy is early diagnosis and treatment, and early recognition and management of nerve damage, combined with effective health education to prevent limb damage. A successful treatment of the nerve damage itself can be effective for preventing ulcer development. Corticosteroids have been used for this purpose. However, a systematic review of three randomised controlled trials comparing prednisolone with placebo or comparing different doses of corticosteroids did not show a significant long-term effect (Van Veen 2007). Also, corticosteroids are not well tolerated by everybody and may cause harmful effects. It is, therefore, still of importance to find the best way of prevention or treatment of skin damage.

People with leprosy are, after a few days on chemotherapy, no longer infectious and can lead a normal social life. This has contributed in recent years to the management of leprosy programmes worldwide moving away from clinics dedicated to the treatment of leprosy to primary health care services in general. However, despite the opportunity to lead a normal social life, long-term nerve and muscle damage can lead to great psychosocial and financial difficulties, social stigmatisation and decreased quality of life. Care and awareness of limb use will in all circumstances be necessary and education of those with leprosy is considered a central element to achieve a satisfactory level of self-care (Lockwood 2002c). In this review we want to explore the effect of several types of potential interventions that can prevent and treat secondary damage to skin and limbs, such as education, information, self-care programmes, dressings (i.e. zinc tape, saline, iodine, gauze soaked in different ointments, dry dressings), skin care, footwear or other measures designed to prevent damage.

OBJECTIVES

To find out if any interventions can prevent secondary damage to the skin in people with leprosy, for example:

- self-care;
- dressings;
- appropriate footwear.

Which of the interventions are the most effective?

Do these interventions reduce social stigma and lead to better quality of life?

Are any interventions harmful?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Anyone with leprosy and damage to peripheral nerves who are on multi-drug treatment or are post treatment.

Types of interventions

Education, information, self-care programmes, dressings (i.e. zinc tape, saline, iodine, gauze soaked in different ointments, dry dressings), skin care, footwear or other measures designed to prevent damage.

Types of outcome measures

Participants with no skin/limb damage at trial entry

Primary outcomes

(a) Prevention of skin ulcers, measured at six months and at one year
(b) Prevention of limb deformity, measured at six months and at one year

Secondary outcomes

(a) Prevention of cracked, thick skin
(b) Quality of life measures or other psychological or functional measures, acceptability of intervention
(c) Cost of intervention (i.e. footwear, dressings, self-care programme)
(d) Adverse events, either those sufficiently serious to stop intervention, or minor ones reported by the participant
All of these secondary outcomes to be measured at six months and one year.

Tertiary outcomes

(a) Quality of life measures or other psychosocial or functional measures, acceptability of intervention
(b) Days off work, school, or other tasks
(c) Cost of interventions
(d) Adverse events, either those sufficiently serious to stop intervention, or minor ones reported by the participant

Participants with existing skin ulceration at trial entry

Primary outcome

Healing of existing ulcer (measured as percentage healed at six weeks, six months and at one year)

Secondary outcomes

(a) Prevention of recurrence of the same ulcer
(b) Prevention of other, new ulcers
(c) Prevention of limb deformity
All of these secondary outcomes to be measured at six months and one year.

Tertiary outcomes

(a) Quality of life measures or other psychosocial or functional measures, acceptability of intervention
(b) Days off work, school, or other tasks
(c) Cost of interventions
(d) Adverse events, either those sufficiently serious to stop intervention, or minor ones reported by the participant

Search methods for identification of studies

Electronic searches

We searched the Cochrane Skin Group Specialised Register (April 2008) using the following terms:
lepros* or hansen* or leprae or leprotic
We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2008) using the following strategy:
#1(leprosy):ti,ab,kw
#2(hansen's disease):ti,ab,kw
#3MeSH descriptor Leprosy explode all trees
#4(#1 OR #2 OR #3)
#5(SR-SKIN)
#6(#4 AND NOT #5)
The UK Cochrane Centre has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. Further searching has been undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.
We searched MEDLINE (OVID) from 2003 to April 2008 using the search strategy in Appendix 1
We searched EMBASE from 2005 to April 2008 using the search strategy in Appendix 2
We searched CINAHL (Cumulative Index to Nursing & Allied Health Literature) from 1982 to October 2006 using the search strategy in Appendix 3. This search could not be run in 2008 as the Skin Group and the Norwegian Knowledge Centre for the Health Services no longer have access to CINAHL.
We searched AMED (Allied and Complementary Medicine) from 1985 - to April 2008 using the following strategy:
1. exp leprosy/
2. leprosy.tw.
3. hansen's disease.tw.
4. 1 or 2 or 3
We searched LILACS (Latin American & Caribbean Health Sciences Literature) from 1982 to April 2008 using the search strategy in Appendix 4

Ongoing Trials

We searched the following ongoing trials registers on 10 th April 2008 using the terms 'lepro%', 'leprosy' and 'leprous'.
The metaRegister of Controlled Trials www.controlled-trials.com
The U.S. National Institutes of Health ongoing trials register www.clinicaltrials.gov
The Australian and New Zealand Clinical Trials Registry www.anzctr.org.au
The Ongoing Skin Trials register on www.nottingham.ac.uk/ongoingskintrials

Searching other resources

References from published studies

We checked references from identified reviews and included studies.

Unpublished literature

We made an effort to identify unpublished and ongoing trials by correspondence with authors and field experts. We had planned in our protocol to search grey literature by searching SIGLE (System for Information on Grey Literature in Europe) but neither we nor the Skin Group had access to the system.
We contacted experts on tropical medicine and/or leprosy to check our list of studies identified in the above searches and to ask if they knew of any studies we had not found.
We searched the CD produced of all the papers published in the main leprosy journals back to the 1920s (Leprosy Research Foundation) "Compact disc of leprosy literature, 1913-1991". Loma Linda, California, USA, 1993.

Conference proceedings

Abstracts from conferences found in the International Journal of Leprosy (1934 to 2005) were checked for further RCTs.

Hand searching

We handsearched the International Journal of Leprosy for reports of trials from 1934 to 2005.

Language

We imposed no language restrictions when searching for publications.

Adverse events

We did not carry out a specific search for adverse events. Adverse events bodies were not contacted. However, we screened for reporting of adverse events in the included randomised trials. In future updates of this review we plan to screen other studies with other designs for adverse events.

Data collection and analysis

Selection of studies

In the protocol we had stated that studies which were clearly not randomised trials should be excluded. At least three of the studies that we found stated that they had used alternation when allocating participants to groups. Studies using such methods are considered to be quasi-randomised and are excluded from reviews whenever randomised controlled trials are stated as the inclusion criterion for type of design. However, treatments allocated alternately "are in principle unbiased being unrelated to patient characteristics", under the assumptions that the underlying sequence in which participants present to the study is random and that the procedure is concealed to the persons that assign participants (Altman 1999). Although such methods are possible to conceal, they are according to the Cochrane Handbook usually not concealed. If the allocation procedure is open it is easy to manipulate by the person in charge. This may result in a selection bias which in turn will threaten the validity of the study. However, the same requirement of concealment of the allocation schedule relates to the use of random numbers tables (Chalmers 1999). Actually, failure to conceal is found to be more important in predicting bias than other components of allocation, such as the generation of the allocation sequence, for instance by computer, random numbers table or alternation (Higgins 2006).
The use of random numbers table makes it easier to conceal the allocation, but the Cochrane Handbook says nothing about whether use of such tables usually is blinded when concealment is not reported on. However, Pildal and colleagues who compared articles that were unclear in their reporting of allocation concealment with their protocols, revealed that only 16% of 96 studies in reality had adequate concealment in their protocol (Pildal 2005). Except for one study protocol that was rated as inadequate, all the others were unclear also in their protocols. Consequently, in cases where it is only stated that a random numbers table or alteration have been used, we will not be sure whether it was concealed or not and hence resulted in a "true" randomisation. Therefore, we included those studies that had used alternate allocation as well as those studies that had used a possibly open random numbers table. We rated the studies as unclear or inadequate with regard to concealment accordingly.
We based inclusion or exclusion on the full article. Studies that were clearly not randomised trials were excluded, others were as-

sessed for eligibility by two authors (LMR, LF). Consensus with persisting disagreement was to be adjudicated (by AB), but this was not necessary. We kept a log of excluded studies with reasons for exclusions. We wrote to two trial authors for missing data about study designs in March 2005 and March 2006, but received no replies by March 2008.

Data extraction and management

Two authors performed the data extraction (LMR, LF), and independently entered data onto a data extraction form. We resolved discrepancies by consensus. One author (LMR) checked data extraction forms and entered data into Review Manager (RevMan). We were not blinded to the names of trial authors, journal or institutions.

Assessment of risk of bias in included studies

We assessed the quality by evaluating the following components for each included study. We categorised each component as adequate, unclear, or inadequate. The quality components criteria were those suggested by Juni 2001 since there is some evidence that these are associated with biased estimates of treatment effect:
(a) the method of generation of the randomisation sequence;
(b) the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen;
(c) who was blinded/not blinded (participants, clinicians, outcome assessors);
(d) how many participants were lost to follow up in each arm (split into post-randomisation exclusion and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat).
In addition the quality assessment also included:
(e) degree of certainty that the participants have leprosy or complications of leprosy;
(f) baseline assessment of the participants for age, sex, duration and severity of complications;
(g) aims, interventions (with details of how it was done) and outcome measures clearly defined;
(h) use and appropriateness of statistical analyses.
Two authors performed the quality assessment and independently judged the components on the quality assessment form (LMR, LF). We resolved disagreements with a third author (AB). We described the quality of each study based on a summary of these components. We also assessed the overall quality of the included studies. Note that the nature of interventions made it impossible to meet all criteria adequately, i.e. blinding of providers. Two authors (LMR,LF) recorded the information in Table 1

Measures of treatment effect

Two authors (LMR, LF) analysed the data with input from a statistician. We calculated standardised mean differences for continuous outcomes (with 95% confidence interval). We expressed the results as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes.

Assessment of heterogeneity

We assessed clinical heterogeneity by looking at the populations, concurrent treatment, settings and outcome measures. We used the I^2 test to assess statistical heterogeneity. I^2 values of 25% or less were considered to indicate low heterogeneity, and values of 75% or greater were considered high heterogeneity (Higgins 2006), and the Chi-square test where we considered a significance level of $p < 0.1$ to indicate heterogeneity.

Data synthesis

We presented the results of the trials with presence of clinical heterogeneity in a narrative. In future updates, when trials are regarded to be sufficiently clinically or methodologically similar, but statistical heterogeneity is present, we will pool the results by using a random effects model.

Subgroup analysis and investigation of heterogeneity

We did no sub-group analyses. As no trials were combined, it was irrelevant to investigate reasons for heterogeneity. In future updates of this review we will look for sources of heterogeneity if appropriate (i.e. country of origin, leprosy classification, intervention, compliance, outcome assessment).

Sensitivity analysis

We did no sensitivity analyses. If, in future updates of this review, we pool trials, we will re-analyse the data using fixed or random effects model as appropriate. We will also do sensitivity analyses if appropriate to examine the effects of including or excluding subgroups based on participant factors, treatment factors or study factors.

RESULTS

Description of studies

Results of the search

In total, the search found 854 citations to potentially relevant trials. Thirty-five citations were retrieved in full text and eight were included. The search did not reveal any ongoing trials.

Included studies

We included 8 trials with a total of 557 participants. All included trials were small and had included between 43 and 110 people affected by leprosy. The age range of participants in four studies was 18 to 70 years, two studies reported an average age of 42 and 46, while two studies did not report information on the age of the participants. All included studies were published between 1982 and 2004. One study had three arms and one study reported on two separately conducted trials (multicenter study). The initial assessment and baseline reporting of leprosy and damage to peripheral nerves was recorded in varying details, as was the reporting of outcome measurements and the results. The follow-up period varied from one month to one year.

All trials reported the primary outcome of healing of existing ulcers, measured either as percentage healed or number of ulcers healed. The other primary outcome, prevention of limb deformity was not reported in any of the included trials. All participants had skin damage at trial entry. Typical outcome measures were:

- number of ulcers healed;
- size of ulcers or reduction of ulcer size;
- number of new ulcers;
- ulcer free at one year;
- ulcers not healed;
- ulcers fully healed.

None of the included trials measured the outcomes we had listed as secondary or tertiary outcomes for our review.

The studies took place in India, Indonesia, Mexico and Ethiopia. All studies included participants affected by leprosy with plantar ulcers (simple ulcers, trophic leprosy ulcers or with anaesthetic feet), and two studies also included people with ulcers on hand and elbow (Salazar 2001) and ulcers on palm and gluteal ulcers (Bansal 1993). Most participants had simple plantar ulcers, but some studies also included participants with infected ulcers i.e. treated with antibiotics. Three studies were hospital (in-patient) based (Bansal 1993; Bhatia 2004; Söderberg 1982), while five were based at out-patient clinics (Overbeek 1991; Pring 1982; Salazar 2001; Seboka 1998; Walton 1986).

Three trials evaluated zinc tape, two trials topical phenytoin, and one trial topical ketanserin. One trial evaluated canvas shoe and another plaster of Paris double-rocker plaster shoe. Co-interventions varied and included bed-rest, ulcer care, education, ulcers cleaned with benzalkonium chloride, soaking and drying of feet. Two trials (Söderberg 1982; Walton 1986) had statements on the social acceptability of the intervention but reported no actual findings in this regard. One trial had asked the participants which of the interventions they preferred and had also made a simple cost analysis. Two studies reported on whether there were harmful effects (Bhatia 2004; Salazar 2001). We have included details of all the studies in the Characteristics of included studies.

There was great diversity (or heterogeneity) between interventions and methods used to measure outcomes in the trials. Two studies (Bansal 1993; Bhatia 2004) used similar interventions and outcome measures. Bansal and Bhatia also restricted the participants to bed rest. The rest of the studies used different interventions and comparisons and could therefore not be pooled. We were unable to extract data from the study comparing adhesive zinc tape with gauze soaked in Eusol, so we described the results from the study (Söderberg 1982).

Excluded studies

We excluded 32 studies, the main reason for exclusion being that they were not randomised trials. The table of the Characteristics of excluded studies lists the studies that did not meet the inclusion criteria.

Risk of bias in included studies

In the included trials it was often difficult to make out whether the participants had one or several ulcers. When the allocation is done on an individual level and the participants have several ulcers, it means that one person will contribute several times in the analysis. This represents a unit of analysis error if not corrected for. In turn, this might lead to an over-estimate of the effect because the intra-variance between healing of ulcers on the same person may be smaller than the inter-variance of healing of ulcers between individuals. In three studies the number of participants were the same as the number of ulcers, four studies may have had a unit of analysis error (but they all had results that were insignificant statistically), while the fifth used two treatments for each participant, one for each ulcer, but it is unclear how this was analysed (Bhatia 2004).

The methodological quality of the trials was generally poor; only three of the trials were scored as having moderate overall quality while all the others were rated as low. How each trial scored on each quality component can be found in Table 1. Most of the trials were characterised by inadequate and unclear reporting. Only the interventions were reasonably well described; it seemed like both intervention and control groups were treated equally in all other respects. None of the studies reported on sample size calculations. Sample sizes ranged from 38 to 110, with a mean of 67 and a median of 57. Four studies most probably did do analysis by intention-to-treat, one study lost one participant in the experiment group, one study was unclear as to who was included in which analysis (Bhatia 2004) and two studies clearly did not use intention-to-treat analysis (excluded lost participants from analysis).

Allocation

All studies gave inadequate description of the randomisation procedure. Three studies stated only that the participants had been randomly assigned (Pring 1982; Salazar 2001; Seboka 1998), and four studies had used alternate assignment (Bansal 1993; Overbeek 1991; Söderberg 1982; Walton 1986). One study had used a table of random numbers for the assignment procedure (Bhatia 2004), but the authors are unclear as to whether the randomisation itself was concealed or whether it applies to the providers throughout the study: "After breaking the code at the end of the study, it was found that each group had 15 patients". None of the others specified whether the procedure had been concealed. Consequently, the trials very likely suffer from a lack of control of selection bias. We assessed base-line measurements as indications of similarity of the groups and judged them as adequate in three of the eight studies (Bansal 1993; Bhatia 2004; Salazar 2001). In Walton 1986 it is stated that base-line measurements were comparable but only the age of participants in the two groups is provided (which differed by about eight years), so we rated this component as unclear accordingly. In the other studies base-line values were either not provided and therefore rated as unclear or deemed as showing diversity between groups and therefore rated as inadequate.

Blinding

Two studies reported blinding of outcome assessors explicitly (Bansal 1993; Bhatia 2004). None of the other study reports mentioned blinding of assessors, so for lack of sufficient details we rated these studies as unclear regarding this component.

Other potential sources of bias

Follow-up and exclusions

It was not easy to deduce follow-up rates but if accepting no mention in the text and no signs of attrition in tables, as a 100% follow-up, the follow-up rates ranged from 47% (Overbeek 1991) - 100% (Bansal 1993; Bhatia 2004; Pring 1982; Salazar 2001; Seboka 1998). The follow-up in Söderberg 1982 was unclear.

Effects of interventions

Of the 8 studies included, with a total of 557 participants, only 2 compared the same interventions and also had comparable outcomes. We present the results with reference to the original questions posed by the review. All trials reported on the first of the primary outcomes we had stated for the review, that of 'healing of existing ulcers'.

Can any intervention prevent/heal secondary damage to the skin in persons with leprosy, for example self-care, dressings or appropriate footwear?

Comparisons between dressings

We included three studies on zinc tape, but they all had different comparisons and had reported differently on the outcome measures for wound healing, so pooling of results was not meaningful (Overbeek 1991; Söderberg 1982; Walton 1986).

Zinc tape versus magnesium sulphate/glycerin

Walton et al reported a small trial conducted in India (Walton 1986). Forty-three people affected by leprosy with plantar ulcers were allocated to either zinc tape (22 participants) or gauze soaked in magnesium sulphate ointment (21 participants). The participants had one ulcer each. Outcome measures were number of ulcers healed and mean reduction of ulcer area (not reported here). There was only 65% follow-up for both groups (14 participants returned to clinic in each group after 1 month). Four ulcers treated with adhesive zinc tape and two in the control group healed completely. The RR for ulcers healed at one month for zinc tape compared with magnesium sulphate was RR 2.00 (95% CI 0.43 to 9.21 Analysis 1.1), although this is a clinical effect the study failed to demonstrate a statistical significant difference between zinc tape and gauze soaked in magnesium/glycerin regarding the promotion of ulcer healing.

Zinc tape versus gauze soaked in Eusol (Edinburgh University solution of lime)

Söderberg et al conducted a multi-centre trial in India (Söderberg 1982). Ninety people affected by leprosy with 128 plantar ulcers in 2 hospitals were separately alternately allocated to either adhesive zinc tape or ordinary gauze dressings soaked in Eusol. One centre, Mangalore, had 30 participants; 15 in each group The other centre, Polambakkam, had 60 participants; 33 in the zinc tape group and 27 in the Eusol group. The outcome measure was time to heal in days and the follow-up time was one to two months. In Mangalore it took about 20 (CI 18 to 23) days on average for superficial ulcers to heal in the zinc tape group versus about 30 days (CI 27 to 33) to heal in the gauze group. For deep ulcers it took 35 (CI 30 to 40) days to heal in the zinc-tape group, while in the gauze group about 44 (CI 22 to 61) days were needed for healing. In Polambakkam the average number of days to heal in the zinc tape group for superficial wounds were about 13 (CI 9 to15) days and 23 (CI 15 to 28) days in the gauze group. For deep ulcers it took 17 days (CI 12 to 20) in the zinc tape group and 30 (CI 12 to 63) days in the gauze group. The authors of the trial state that all the participants in Mangalore wore shoes, while eighteen of the participants in Polambakkam wore shoes. We do not know if this explains the heterogeneity in the results.

The average healing time was shorter for ulcers treated with zinc tape compared to gauze treated ulcers, but according to the authors, this difference was only statistically significant in Polambakkam, which was the larger group. The authors state further that zinc tape has the following advantages: low cost, easy application and convenience, also it can be worn under shoes without causing pressure and is socially more acceptable as no bandages are needed. However, the authors had not asked any of the users about their preferences.

Zinc oxide tape versus povidone iodine

In Indonesia, Overbeek et al conducted a trial where they compared zinc oxide tape with gauze soaked in 10% povidone iodine (Overbeek 1991). A total of 56 people were recruited and alternately allocated into 2 groups, (in 10 different clinics); the preliminary size of groups is unknown. During the investigation 18 participants were lost to follow-up and 38 people were included in the analysis; 26 in the zinc oxide tape and 12 in the iodine group. The primary outcome measure was the mean difference between groups in the reduction of the ulcer area.
The secondary outcome was mean surface area reduction of the ulcers between subgroups of high (walking > 2.2 km per day or > 4.07 hours work per day) and low (< 2.2 km per day or < 4.07 hours work per day) activity level of the participants in both groups. There was no information on whether numbers of ulcers were the same as numbers of persons. The follow-up was six weeks. The authors found no statistical significant difference between the groups, although the ulcer healing was in favour of zinc oxide tape: SMD 0.29 (95% CI -0.40, 0.97 Analysis 3.1). Also regarding the difference in healing, depending on high and low activity, the healing was slightly better for the zinc tape participants with low activity compared to those with high activity, and slightly better for iodine participants with low activity compared to those with high activity (not analysed here because of the very small numbers).

Comparison between topical agents

One study of moderate quality compared the use of topical ketaserin (Salazar 2001) with clioquinol cream or zinc paste.

Topical ketanserin versus clioquinol cream or zinc paste

In Mexico, Salazar conducted a trial where the intervention group (n=33) was treated with topically applied ketanserin gel (2%) and the controls (n=33) were treated with topically applied clioquinol cream or zinc oxide paste (Salazar 2001). The outcome measure was the number of completely healed ulcers. All persons had one ulcer each and there was no loss to follow-up. At three months follow-up, 37% of the ulcers in the intervention group had healed compared with 6% for the controls; the RR was 6.00 (95% CI 1.45 to 24.75 Analysis 4.1), i.e. the study demonstrated a statistical significant difference between the two groups as to promoting ulcer healing.

Comparison between topical agent versus dressing

Two studies compared phenytoin versus saline dressing. These two studies were not pooled because of statistical heterogeneity (Bansal 1993; Bhatia 2004).

Topical phenytoin versus saline dressing

Two Indian studies with a total of 145 participants reported the effect of topical phenytoin compared with normal saline on trophic ulcers (Bansal 1993; Bhatia 2004). Bhatia et al used 3 comparison groups, with 15 participants in each. The total number of fully healed ulcers were the same for both intervention groups in this study, but measured as the mean percentage reduction of ulcer size, there were nevertheless some differences between the 2% and 4% phenytoin groups, but they were not statistically significant. In Bansal et al ten participants had two ulcers each, in which case one ulcer was treated with phenytoin and the other with normal saline. It is unclear if the trialists adjusted for this in the analyses. The ulcers in the Bansal study were of "varying chronicity", while in Bhatia they had "less than three months duration", i.e. acute ulcers. All participants in the Bhatia and Bansal studies had bedrest. The outcome measure was the mean percentage of ulcer volume reduction. Follow-up was done at four weeks for all participants. In the Bhatia study it is unclear whether all participants were included at the end of the study. Bhatia's study gave an estimate of SMD -2.34 (95% CI -3.30 to -1.39 Analysis 5.1). Bansal's study gave an estimate of SMD -0.79 (95% CI -1.20 to 0.39 Analysis 5.1). Both studies demonstrated a statistically significant difference between the effect of topical phenytoin versus saline dressing, favouring phenytoin.

Trials of footwear

The two studies comparing footwear were too clinically heterogeneous to be pooled. One study compared canvas shoe with PVC-boot (Seboka 1998) and the other study compared double rocker plaster shoe with padded below-knee plaster (Pring 1982). The studies varied in time of follow-up from six weeks to a year.

Canvas shoe versus PVC-boot

In rural Ethiopia, Seboka et al conducted a study involving 110 farmers affected by leprosy (Seboka 1998). The participants had either one or more plantar ulcers or had a scar of a healed ulcer. They were allocated to either canvas shoe group (52) or PVC boot ("Wellington boot") group (58). The outcomes were the number of participants being ulcer free and number of particpants having ulcers not healed, acceptability of the footwear and footwear condition. The study had a one-year follow-up and one person

in the canvas shoe group was lost to follow-up. There was no statistically significant difference between the two groups when it came to participants being ulcer free at one year; (RR 1.16; 95% CI 0.77 to 1.74 Analysis 6.1). The authors reported that no new ulcers developed during study period in either group. The RR for those having ulcers not healed at one year was 0.52 (95% CI 0.15 to 1.75 Analysis 6.2), favouring the canvas shoe group, although this result was not statistically significant. They also reported that PVC boots were much more durable than the canvas shoes, but they could become very hot. Eighty percent of the farmers rated PVC boots as "excellent" for social acceptability and suitability for work. The canvas shoes were rated as socially acceptable, but not rated as highly suitable for work.

Double-rocker plaster shoe versus below-knee plaster

Pring's Indian study reported a comparison of a traditional below-knee plaster with a padded, moulded double-rocker plaster shoe (Pring 1982). Forty-seven people affected by leprosy with a total of 55 plantar ulcers were randomly allocated to both groups. In addition dressings with magnesium sulphate, glycerine and acriflavine were applied to all ulcers and removed after six weeks, at follow-up. Also, at the time of application and removal of plasters all participants were given health education on foot care (daily foot inspection, foot soaking and scraping, and the importance of the regular wearing of soft-lined chappals. Outcome measures were ulcers fully healed, ulcers nearly healed and ulcers failed to heal. The authors found that of the 31 ulcers treated with plaster shoe, 18 were fully healed after 6 weeks; 8 were nearly healed and 5 failed to heal. Of the 24 ulcers treated by below-knee plaster, 18 were fully healed, 3 nearly healed and 3 had failed to heal after 6 weeks. The authors state that the plaster shoe was more acceptable to the person affected by leprosy and cheaper to apply. The statistical analysis of ulcers fully healed showed (RR 1.29; 95% CI 0.89 to 1.88 Analysis 6.1) in favour of the below-knee plaster group; nearly healed (RR 2.06; 95% CI 0.61 to 6.96 Analysis 6.2) in favour of the double rocker plaster shoe group; and for ulcers not healed (RR 0.78; 95% CI 0.21 to 2.93 Analysis 6.3) favouring the plaster shoe group, i.e. no statistical significant differences between groups were demonstrated.

We did not find any randomised trials that evaluated the effect of self-care, other educational interventions or rest versus activity. No trials reported prevention of limb deformity as an outcome.

Which of the interventions are the most effective?

We did not find any studies that directly compared different treatments, except for the comparisons reported above, so we cannot say whether for instance zinc tape is more effective than topical phenytoin.

Do these interventions reduce social stigma and lead to better quality of life?

Only one study reported that canvas shoes were seen as socially acceptable to their users, although PVC boots were perceived as more suitable for work (Seboka 1998). Plaster shoe is more acceptable than below-knee plaster (Pring 1982). We did not find any studies that reported on quality of life.

Are any interventions harmful?

Three studies, one on topical ketanserin versus clioquinol cream or zinc paste (Salazar 2001), one on topical phenytoin versus saline dressing (Bhatia 2004) and the third study comparing zinc tape to gauze with Eusol (Söderberg 1982) reported that no adverse effects of the treatment were observed, while the trialists did not report adverse effects in the other studies.

DISCUSSION

Summary of main results

We found and included eight studies with a kind of randomisation procedure for allocating participants to groups. Although the three studies that compared zinc tape to more traditional dressings found some benefit, none of these had a statistically significant effect. Topical ketanserin had a better clinical effect on wound healing than clioquinol cream or zinc paste. The two studies that compared topical phenytoin to saline dressing demonstrated a statistically significant effect in both studies. Canvas shoes were not much better than PVC-boots and double rocker shoes did not promote healing more than below-knee plasters. None of the studies reported any harms caused by the treatment, except for a general statement by the trial authors of the plaster study that plasters in general may result in osteoporosis of bones in the foot caused by lack of use, which in turn may result in fractures when plaster is removed.

Overall completeness and applicability of evidence

The studies we identified were not sufficient to address all of the objectives of the review. Our objective was to investigate whether there were interventions that could prevent or treat secondary damage to the skin in people with leprosy, for example self-care, dressings or appropriate footwear. We found eight studies altogether of seven different interventions, so the lack of replication of studies in itself limits the reliability and applicability of results. As none of the comparisons were done crosswise we can draw no conclusions as to which of the interventions were the most effective.

Likewise, none of the studies investigated whether the interventions had the potential to reduce social stigma and lead to better quality of life. We did not find any trials that evaluated the effect of self-care or educational interventions.

Quality of the evidence

The studies that we included did not allow any robust conclusion regarding the objectives they addressed. There were several reasons for this. Overall, it was difficult to assess the validity of the results of the studies, due to the lack of clear reporting of methods and data in general and of the allocation process in particular. We do recognise that these studies were reported at a time when the importance of a full description of the allocation process had not been much focused on in contemporary literature. In fact, only one of the studies (Bhatia 2004) would have had a chance to report according to previous (Begg 1996) or current guidelines for reporting clinical trials (Moher 2001).

The empirical evidence for whether one can suppose that the allocation procedure has been concealed or not in the real setting, when not reported on, is conflicting (Pildal 2005). For example, in one study, authors of 40 rheumatology articles published in 1997/1998, in which the statement regarding allocation concealment was unclear, were asked by means of a questionnaire whether they in fact had concealed the allocation procedure and in 78% of 32 trials, the allocation process was reported by their trialists to have been concealed (Hill 2002). In a study by Deveraux 2004, 98 articles reporting trials in 29 journals in the period 1997 to 1998, were assessed for reports of concealment of allocation. They found 54 out of 56 (96%) trials with an unclear allocation procedure in the published documents were reported by the researchers in a telephone interview to actually have used concealment when allocation to groups had been done. However, a third study collected 102 authorised protocols of randomised controlled trials for the years 1994 and 1995 from two districts in Denmark (Pildal 2005). They were used for verification of whether concealment had been done or not when the statement in their corresponding publications was unclear. The authors found that only 16% (15/96) of the publications not reporting concealment had stated in the protocol that this would be done. Compared to using the authors' self-report to determine the real occurrence of concealment, using the protocols for verification of actual use, seems more credible.

Accordingly, we consider that the studies included in our review that did not report on allocation concealment, most likely did not conceal the allocation process, which in consequence may have led to selection bias.

One included study clearly used blinded assessors to assess degree of ulcer healing and one study most likely used blinded assessors. Due to the small sample sizes, the conclusions in all trials may be subjected to the possibility of both erroneously seeing a difference when there is none (type I error) and erroneously not seeing a difference when there is one (type II error), as the risk of both errors increases with small samples. Moreover, only one comparison was replicated so the other comparisons were all only done in one study.

As demonstrated in two of the studies (Bansal 1993;Bhatia 2004) there seems to be a lack of consensus of how to measure wound surface area. This may result in less reliable, imprecise and non-comparable measures. A complete healing of wounds would be easier to measure objectively than surface area and also would be the outcome of greatest interest to people with leprosy as well as to healthcare providers. Others have recommended that investigators measure time to healing, analysed as a life table or by survival analysis (Palfreyman 2006). For some of the trials the follow-up time was only four weeks and this might be somewhat short - results from one of the included trials indicate that ulcers may need a longer healing period.

Shaw and colleagues conducted a systematic review on the clinical effect of topical phenytoin on wound healing (Shaw 2007). They too found that most papers failed to describe randomisation, treatment allocation and blinding techniques adequately. The authors included prospective controlled trials or RCTs and carefully concluded that topical phenytoin might have a positive effect on wound healing in a variety of wounds (including leprosy).

Potential biases in the review process

Overall, the inadequate reporting of the trials is the most important threat to the validity of the review process. This may have led to misunderstandings during the critical appraisal of the studies and of our descriptions and evaluations. We have not assessed potential publication bias. Since several studies with no significant effect and also with very few participants, have been published, this is an indicator that suggests that publication bias in this case is not very likely. However, we cannot know if we have identified all relevant studies. The trials we found were small, so similar sized trials may have been done and not been reported. The authors of the included trials may have done additional trials. Also, the countries in which the trials were done, are not well represented in the databases we searched (except for LILACS). For example, Indian literature may have escaped our searches.

AUTHORS' CONCLUSIONS

Implications for practice

Which of the interventions are the most effective?

Topical ketanserin may be more effective than clioquinol cream or zinc paste and topical phenytoin may be more effective than saline dressing in ulcer healing. However, this is based on very weak evidence, for topical ketanserin only one study tested the

comparison and for phenytoin the summary analysis of two studies did not show a very clear effect. For the other comparisons the results were equivocal. Whether the interventions reduce social stigma and lead to better quality of life were not investigated in any of the trials. Three studies reported that no side effects of treatment were observed.

Implications for research

The disabilities resulting from sensory nerve damage in leprosy, have a serious impact on the quality of life of the persons affected. Not only is it potentially disabling, but since leprosy still carries social stigma, visible signs of the presence of the disease in the person concerned may cause distress and prejudice. Research should not be neglected, as there is a need for high quality research in the field of ulcer prevention and treatment in people with leprosy. However, research projects in the management of skin changes and ulcers in leprosy need to be improved regarding methodological quality, including setting a standard in identifying suitable outcome measures. An important tool to attain improved quality is to follow the current standards for design and reporting of randomised controlled trials.

In particular this research should aim to compare:

(a) different types of dressings, including dry dressings;

(b) different types of topical agents;

(c) topical agents versus dressings;

(d) different types of footwear;

(e) different self-care and educational programmes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bansal 1993

Methods	Type of trial: Quasi-randomised controlled trial Study duration: Four weeks Allocation procedure: Participants assigned alternately. Blinding of participants and clinicians not applicable. Outcome assessor was independent to study groups
Participants	Country and setting where study took place: In-patients (hospital) in India Participants: 100 people (14 females) affected by leprosy having difficult ulcers of varying chronicities. Inclusion criteria: Trophic leprosy ulcers Exclusion criteria: People affected by leprosy with other systemic diseases or gross cellulitis
Interventions	Intervention in experimental group (n=50): topical phenytoin powder (daily) Intervention in control group (n=): saline (daily) Co-interventions both groups: All necrotic tissue and slough was removed by meticulous debridement, and the ulcers were cleansed with sterile swab. All participants continued their anti leprosy treatment and appropriate antibiotics. A strict bed-rest regimen and a uniform dietary regimen were followed for all participants
Outcomes	Healing of ulcer.
Notes	In the cases where the participants had two ulcers one ulcer was treated with phenytoin and the other with normal saline. Unclear if ten participants with two ulcers were included in the overall outcome measurement

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Bhatia 2004

Methods	Type of trial: Randomised controlled trial Study duration: Four weeks Allocation procedure: Table of random numbers. Double-blind. Outcome assessor was blinded to study groups.
Participants	Country and setting where study took place: Hospital (in-patients) in India. Participants: 45 people (14 females) affected by leprosy aged 18 to 60 years with acute leprosy trophic ulcers (i.e. less than three months duration). BL and LL type of leprosy (Ridley Jopling classification). Inclusion criteria: Simple ulcers

Bhatia 2004 (*Continued*)

	Exclusion criteria: Anemia, hypoproteinaemia, chronic use of immunosuppressant medication, immobility, folate deficiency, those receiving oral phenytoin, a history of adverse effects caused by phenytoin, any other systemic disease and pregnant or lactating females
Interventions	Intervention in experimental group 1 (n=15): Topical 2% phenytoin sodium suspension (Daily up to four weeks) Intervention in experimental group 2 (n=15): Topical 4 % phenytoin sodium suspension (Daily up to four weeks) Intervention in control group (n=15): Saline dressing (Daily up to four weeks) Co-interventions all groups: All necrotic tissue and slough was removed. The ulcers were cleansed with sterile swab. All participants continued to receive their anti leprosy treatment and appropriate antibiotics. Strict bed rest and uniform dietary regimen
Outcomes	Healing of ulcer. Local and systemic adverse effects (monitored by clinical assessment and interrogation of the participant)
Notes	Simple ulcers were defined as one involving only skin and subcutaneous tissue and having no bone involvement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Overbeek 1991

Methods	Type of trial: Quasi-randomised controlled trial Study duration: Six weeks Allocation procedure: Alternation per out-patients clinic. Information on blinding of participants, clinicians and outcome assessor not given. 32% of the participants were lost to follow up. Groups were not similar at baseline
Participants	Country and setting where study took place: Out-patients clinics in Indonesia. Participants: 56 people affected by leprosy with plantar ulcers. Divided in groups by high or low activity level (walking > 2.2 km per day or > 4.07 hours work per day was defined as high activity). Of the 38 participants that were followed through the study 32 were men (6 females) and the average age was 42 years. Inclusion criteria: People affected by leprosy with simple plantar ulcers. Exclusion criteria: People affected by leprosy with ulcers that were infected, were necrotic or if there were signs of osteomyelitis
Interventions	Intervention in experimental group (n=26): Zinc oxide tape Intervention in control group (n=12): Povidone-iodine 10% Co-intervention in experimental group: Povidone-iodine10%
Outcomes	Healing of ulcer.

Overbeek 1991 (*Continued*)

Notes	Published in Dutch. We had data-collection and quality-assessment checked by Dutch native	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Pring 1982

Methods	Type of trial: Randomised controlled trial Study duration: Six weeks Allocation procedure: Information not given in paper. Blinding of participants and clinicians not possible. Outcome assessor was probably not blinded to study groups	
Participants	Country and setting where study took place: Outpatients (majority) in India (or Nepal). Not clear information in paper. Participants: 47 people (gender not given) affected by leprosy, 55 ulcers. Inclusion criteria: Simple plantar ulcers. Informed consent.	
Interventions	Intervention in experimental group (n=31 ulcers): Padded moulded double-rocker plaster shoe Intervention in control group (n=24 ulcers): Padded below-knee plaster Co-interventions both groups: Intensive health education on foot care (daily foot inspection, foot soaking and scraping and the importance of regular wearing of soft-lined chappals)	
Outcomes	Healing of ulcers.	
Notes	Participants were randomised, but results given only for ulcers (not equally distributed between groups). Simple plantar ulcers were defined as ulcer on the plantar surface of the anaesthetic foot which did not involve either the underlying bone, joint or tendon	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Salazar 2001

Methods	Type of trial: Randomised, controlled trial Study duration: Three months No information given on allocation procedure. No information on blinding of participants, clinicians or outcome assessor. Baseline and outcome measures documented by the use of photographs
Participants	Country where study took place: Mexico (probably). Outpatients examined every two weeks. 66 people (30 females) affected by leprosy with skin ulcers. Ulcers were secondary to vascular, bony, infectious, neurological or traumatic causes. Inclusion criteria: Participants should have had supervised anti leprosy treatment for at least one year, negative bacilloscopy last 12 months, aged between 18 and 70 years and grade II and III ulcers according to Wagner's classification, present for more than 6 months. Exclusion criteria: Participants with ulcers with additional infections, positive bacilloscopy, erythema nodosum leprosum, a leprosy reaction, previous thrombotic episodes or lumbar sympathectomy, treatment with diuretics, those with obvious edema of the lower limbs, arterial hypertension, cardiac disease, renal or liver failure
Interventions	Intervention in experimental group (n=33): Topically applied 2% ketanserin gel every 12 hours. Control group intervention (n=33): clioquinol 3% or zinc oxide paste every 12 hours. Co-intervention both groups: Ulcers cleaned with benzalkonium chloride
Outcomes	Healing of ulcers. Side effects classified as minimum, moderate and severe.
Notes	Insufficient reporting. The Wagner classification system of wounds: grade 0 = no open lesion; grade 1 = superficial ulcer without penetration to deeper layers; grade 2 = ulcer penetrates to tendon, bone, or joint; grade 3 = lesion has penetrated deeper than grade 2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths; grade 4 = wet or dry gangrene in the toes or forefoot; grade 5 = gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at the below the knee level) is indicated. 57 of ulcers were located on foot/foot soles.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Seboka 1998

Methods	Type of trial: Randomised controlled trial Study duration: One year Allocation procedure not given in the paper. Blinding of participants and clinicians not possible. Unclear if outcome assessor was blinded to study groups. One person lost to follow up in experimental group
Participants	Country and setting where study took place: Rural area in Ethiopia. Participants: 110 male farmers. Inclusion criteria: One or more plantar ulcer(s), or had scar of a healed ulcer. Loss of sensation as tested by a 10 g monofilament
Interventions	Intervention in experimental group (n=52): Canvas shoe Intervention in control group (n=58): PVC boot
Outcomes	New ulcer(s) Healing of ulcers. Acceptability of the footwear determined by a standard set of questions
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Söderberg 1982

Methods	Type of trial: Quasi-randomised controlled trial Study duration: Two months Allocation procedure: Selection on a random alternate basis. Blinding of participants and clinicians not possible. Unclear if outcome assessor was blinded to study groups
Participants	Country and setting where study took place: Two hospitals (Mangalore and Polambakkam) in India (in-patients). Participants: 90 people, 18 females, (with a total of 128 ulcers, 86 ulcers in Mangalore and 42 in Polambakkam) affected by leprosy with non-complicated ulcers on the soles of the feet. Disability grade 1 and 2 (WHO classification)
Interventions	Intervention in experimental group (n=48): Adhesive zinc tape (zinc oxide 30%), tape changed daily when wound secretion was excessive, then less frequently. Intervention in control group (n= 42): Gauze sponge soaked with Eusol and covered with bandage, new dressings as for experimental group. Co-interventions both groups: Soaking and drying of feet. All participants in Mangalore (n=60) used shoes. Eighteen of the 30 participants in Polambakkam used shoes

Söderberg 1982 (*Continued*)

Outcomes	Healing of existing ulcer, reported separately for deep and superficial wounds. Cost, application, convenience, socially acceptability (but no information on how this was measured)	
Notes	Results were inaccurately reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Walton 1986

Methods	Type of trial: Randomised, controlled trial (possibly quasi-randomised) Study duration: One month Allocation procedure: Consecutive cases were randomly allocated to intervention and control group Blinding of participants and clinicians not possible. Unclear if outcome assessor was blinded to study groups. 35% loss to follow up	
Participants	Country and setting where study took place: Outpatient clinic in India. Rural area, farmers working in the fields and sugar plantations. 43 participants aged 25 to 58 years, gender not given. Included in study were people affected by leprosy who were both lepromatous or non-lepromatous with "simple" plantar ulcers. The study groups were comparable in terms of distance walked each day, duration of the ulcer, sex and classification of leprosy. The zinc tape group was rather younger. Information about the wearing of shoes is not given in the paper	
Interventions	Intervention in experimental group (n=22 ulcers): zinc tape 2 cm wide strips Intervention in control group (n=21 ulcers): dressings with gauze soaked in a paste of magnesium sulphate and glycerin with proflavin and benzalkonium chloride (MGSA). Co-interventions both groups: all ulcers were cleaned with antiseptic solution of cetrimide followed by ethanol. Routine debridement of the edges of ulcers. Each participant was supplied with sandals made with micro-cellular rubber soles and individually tailored arch support	
Outcomes	Change in area of wound. Healing of ulcer. Fourteen participants from each group returned to clinic after one month (65%)	
Notes	Simple ulcers were defined as: those involving only skin and subcutaneous tissue, not infected, and containing no necrotic bone or fibrous tissue	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Walton 1986 (*Continued*)

Allocation concealment (selection bias)	High risk	C - Inadequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abera 2003	Study design criteria not met. Survey.
Abera 2003b	Study design criteria not met. Survey.
Balkin 1997	Study design criteria not met. Case report.
Benbow 2001	Study design criteria not met. Descriptive study.
Bogaert 1990	Study design criteria not met. Controlled before and after study
Chauhan 2003	Particiapants diagnosed diabetes, leprosy and other conditions in a mix
Cross 1995	Probably not randomised trial. We wrote to the author in March 2005, but have not received any reply by March 2008
Cross 1996	Probably not randomised trial. We wrote to the author in March 2005, but have not received any reply by March 2008
Cross 2001	Not randomised trial
Dowlati 2002	Intervention criteria not met. Randomised trial of BCG vaccination
Ethiraj 1995	Study design criteria not met. Prospective cohort with concurrent controls
Fritschi 1959	Study intervention criteria not met. Quasi-randomised trial with intervention oral Hydergine
Jha 2002	Study intervention criteria not met. Randomised trial of punch grafting which is a surgical procedure
Kaada 1988	Study design criteria not met. Before and after study.
Kumar 1985	Study design criteria not met. Prospective cohort with concurrent controls
Kumar 1986	Study design criteria not met. Before and after study.
Laxmi 1992	Study design criteria not met. Survey.
Liangbin 2003	Study design criteria not met. Before and after study.

(*Continued*)

Maney 1958	Study intervention criteria not met. Intervention was Hydergine (0.3 mgm) injected intra-arterially. Controlled clinical trial
Mathew 1999	Study design criteria not met. Before and after study.
Matthews 1978	Study design criteria not met. Survey.
Menezes 1993	Probably not randomised trial. We wrote to the author in March 2006, but have not received any reply by March 2008
Nicholls 2002	Study design criteria not met. Descriptive case-study.
Pedrazzani 1985	Study design criteria not met. Not a controlled study with an intervention
Pedrazzani 1995	Study design criteria not met. Descriptive study.
Premkumar 1990	Study design criteria not met. Controlled before and after study where people with leprosy act as their own control
Ramanujam 1953	Study design criteria not met. Controlled before and after study
Sarma 1997	Study intervention criteria not met.
Seboka 1996	Quasi-randomisied trial (day by attendance).
Smith 1995	Study design criteria not met. Cohort study.
Stenstrom 1979	
Tuck 1971	Study design criteria not met. Case reports.
Wiseman 1990	Study design criteria not met. Before and after study.

DATA AND ANALYSES

Comparison 1. Zinc tape versus magnesium sulphate/glycerin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed after one month	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Zinc tape versus povidone iodine (10%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction of ulcer area at six weeks	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 3. Topical ketanserin (2%) versus clioquinol cream (3%) or zinc paste

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing of ulcer after three months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. Topical phenytoin versus saline dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage reduction of ulcer size at four weeks	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 5. Footwear canvas shoe versus footwear PVC boot

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of persons being ulcer free at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number of persons having ulcers not healed at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 6. Padded moulded double-rocker plaster shoe versus padded below-knee plaster

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ulcers fully healed	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Ulcers nearly healed	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Ulcers not healed	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Zinc tape versus magnesium sulphate/glycerin, Outcome 1 Number of ulcers healed after one month.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 1 Zinc tape versus magnesium sulphate/glycerin

Outcome: 1 Number of ulcers healed after one month

Study or subgroup	Zinc tape n/N	Magnesium sulph/glyc n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Walton 1986	4/14	2/14		2.00 [0.43, 9.21]

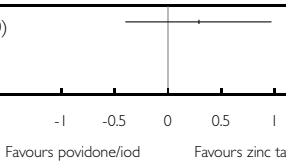
Analysis 2.1. Comparison 2 Zinc tape versus povidone iodine (10%), Outcome 1 Mean reduction of ulcer area at six weeks.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 2 Zinc tape versus povidone iodine (10%)

Outcome: 1 Mean reduction of ulcer area at six weeks

Study or subgroup	Zinc tape N	Mean(SD)	Povidone iodine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Overbeek 1991	26	388 (498)	12	260 (250)		0.29 [-0.40, 0.97]



Analysis 3.1. Comparison 3 Topical ketanserin (2%) versus clioquinol cream (3%) or zinc paste, Outcome 1 Healing of ulcer after three months.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 3 Topical ketanserin (2%) versus clioquinol cream (3%) or zinc paste

Outcome: 1 Healing of ulcer after three months

Study or subgroup	Ketanserin (2%) n/N	clioquinol or zinc n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Salazar 2001	12/33	2/33		6.00 [1.45, 24.75]

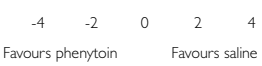
Analysis 4.1. Comparison 4 Topical phenytoin versus saline dressing, Outcome 1 Mean percentage reduction of ulcer size at four weeks.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 4 Topical phenytoin versus saline dressing

Outcome: 1 Mean percentage reduction of ulcer size at four weeks

Study or subgroup	Phenytoin N	Mean(SD)	Saline dressing N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Bansal 1993	50	55.5 (21.6)	50	72.1 (19.9)		-0.79 [-1.20, -0.39]
Bhatia 2004	15	49.1 (18.2)	15	88.4 (14.2)		-2.34 [-3.30, -1.39]



Analysis 5.1. Comparison 5 Footwear canvas shoe versus footwear PVC boot, Outcome 1 Number of persons being ulcer free at one year.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 5 Footwear canvas shoe versus footwear PVC boot

Outcome: 1 Number of persons being ulcer free at one year

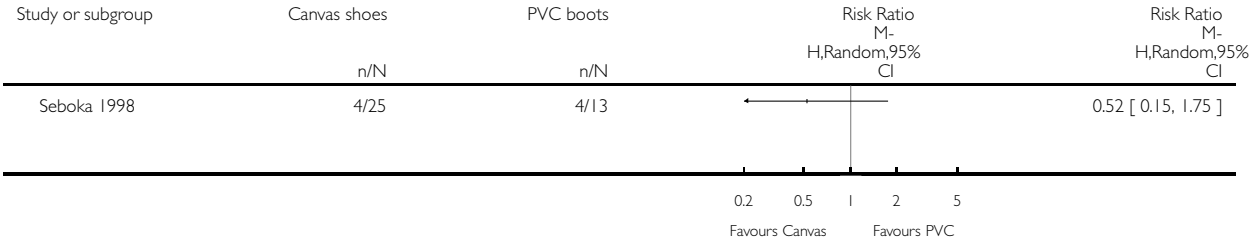
Study or subgroup	Canvas shoes n/N	PVC boots n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Seboka 1998	20/25	9/13		1.16 [0.77, 1.74]

Analysis 5.2. Comparison 5 Footwear canvas shoe versus footwear PVC boot, Outcome 2 Number of persons having ulcers not healed at one year.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 5 Footwear canvas shoe versus footwear PVC boot

Outcome: 2 Number of persons having ulcers not healed at one year

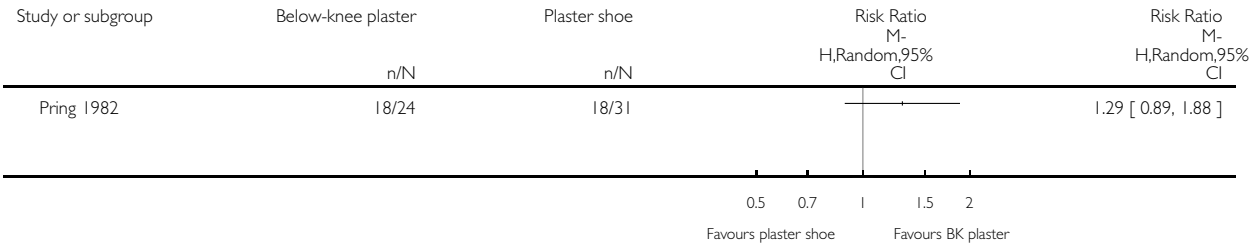


Analysis 6.1. Comparison 6 Padded moulded double-rocker plaster shoe versus padded below-knee plaster, Outcome 1 Ulcers fully healed.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 6 Padded moulded double-rocker plaster shoe versus padded below-knee plaster

Outcome: 1 Ulcers fully healed

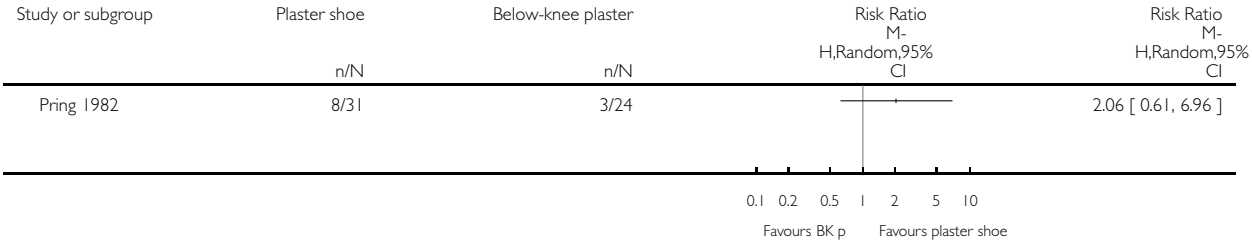


Analysis 6.2. Comparison 6 Padded moulded double-rocker plaster shoe versus padded below-knee plaster, Outcome 2 Ulcers nearly healed.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 6 Padded moulded double-rocker plaster shoe versus padded below-knee plaster

Outcome: 2 Ulcers nearly healed

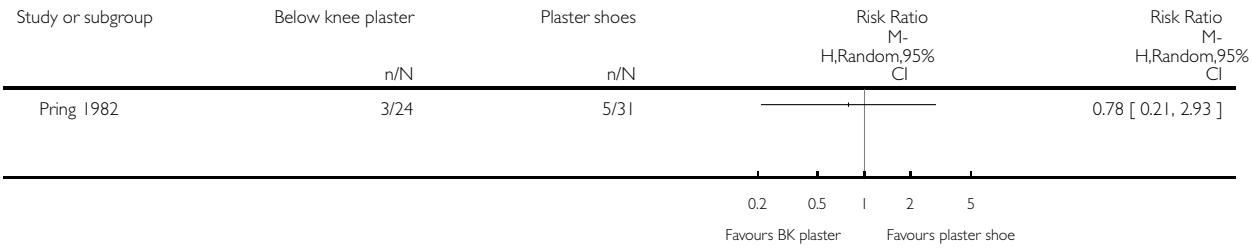


Analysis 6.3. Comparison 6 Padded moulded double-rocker plaster shoe versus padded below-knee plaster, Outcome 3 Ulcers not healed.

Review: Interventions for skin changes caused by nerve damage in leprosy

Comparison: 6 Padded moulded double-rocker plaster shoe versus padded below-knee plaster

Outcome: 3 Ulcers not healed



ADDITIONAL TABLES

Table 1. Quality components

Study	Allocation concealment	Masking outcome asse	Loss to follow up	Similar baseline	Reliable outcome mea	Intervention describ	Appropriate analysis	Overall quality	Method of random.
Bansal 1993	Inadequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Moderate	Alternately
Bhatia 2004	Unclear	Adequate	Adequate	Adequate	Adequate	Adequate	Unclear	Moderate	Table
Overbeek 1991	Inadequate	Unclear	Inadequate	Inadequate	Unclear	Adequate	Unclear	Low	Alternately
Pring 1982	Unclear	Unclear	Adequate	Inadequate	Inadequate	Unclear	Inadequate	Low	Randomly divided
Salazar 2001	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate	Adequate	Moderate	Randomly allocated
Seboka 1998	Unclear	Unclear	Adequate	Inadequate	Unclear	Adequate	Inadequate	Low	Randomly assigned
Söderberg 1982	Inadequate	Unclear	Adequate	Unclear	Unclear	Adequate	Inadequate	Low	Alternately
Walton 1986	Unclear	Unclear	Inadequate	Unclear	Adequate	Unclear	Unclear	Low	Consecutive cases randomly allocated

APPENDICES

Appendix 1. MEDLINE (OVID) Search Strategy

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.sh.
4. RANDOM ALLOCATION.mp.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. animal/ not human/
9. 7 not 8
10. CLINICAL TRIAL.pt.

11. CLINICAL TRIALS.mp
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. PLACEBOS.sh.
15. placebo$.ti,ab.
16. random$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. EVALUATION STUDIES.mp
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. leprosy.mp. or exp Leprosy/
31. hansens disease.mp.
32. 30 or 31
33. 29 and 32

Appendix 2. EMBASE (OVID) Search Strategy

1. random$.mp.
2. factorial$.mp.
3. crossover$.mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign$.mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. leprosy.mp. or exp LEPROSY/
15. hansen's disease.mp.
16. 14 or 15
17. 13 and 16

Appendix 3. CINAHL Search Strategy

1. exp Leprosy/
2. leprosy.tw.
3. hansen's disease.tw.
4. 1 or 2 or 3
5. exp Clinical trials/
6. clinical trial.pt.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
9. Randomi?ed control$ trial$.tw.
10. Random assignment/
11. Random$ allocat$.tw.
12. Placebo$.tw.
13. Placebos/
14. Quantitative studies/
15. Allocat$ random$.tw.
16. or/5-15
17. 16 and 4

Appendix 4. LILACS Search Strategy

((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Palavras]and(leprosy or lepra or hansen) [Palavras]and(nerve or nerves or nervio or nervioso) [Palavras]

WHAT'S NEW

Last assessed as up-to-date: 19 March 2008.

Date	Event	Description
8 June 2016	Amended	Edited the published note about the updating of the review.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2008

Date	Event	Description
17 February 2015	Amended	This review is going to be updated. We have written a published note to say that because the inclusion criteria has changed considerably, a new protocol and then a new review will be written
12 August 2013	Amended	Author information (affiliation) updated.
27 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Link with editorial base and coordinate contributions from co-reviewers (LMR)

Draft protocol (LMR with contributions from all)

Run search (LF)

Identify relevant titles and abstracts from searches i.e. broad screen (LMR, LF)

Obtain copies of trials (LMR, LF)

Select which trials to include (LMR, LF with AB as arbitrator when necessary)

Extract data from trials (LMR, LF)

Enter data into RevMan (LMR)

Carry out analysis (LF,LMR)

Interpret analysis (LF,LMR,)

Draft final review (LMR, LF with contribution from all)

Update review (LMR, LF,AB)

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Norwegian Knowledge Centre for the Health Services, Norway.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made some changes to the Background to update it.

In Methods, in the section 'Criteria for considering studies for this review' under 'Types of studies' we included trials that used an alternating allocation.

Under 'Types of outcome measures' we added tertiary outcomes for 'Participants with no skin/limb damage at entry'. We explained our reasons for doing this in the section 'Data collection and analysis' under 'Selection of studies'.

In the same section under 'Measures of treatment effect' we changed the effect estimate from Odds Ratio stated in the protocol to Relative Risk. This was because ulcers are quite common in people with nerve damage caused by leprosy.

Also in Methods, in the section 'Search methods for identification of studies' under 'Searching other resources' we were unable to handsearch the Indian Journal of Leprosy as it was not available, and we did not contact adverse events bodies for information.

NOTES

This review is being updated by way of a new protocol and then a review, because the inclusion criteria has changed considerably. The citation for the new protocol is as follows: Reinar LM, Forsetlund L, Brurberg KG, Lehman LF. Interventions for ulceration and other skin changes caused by nerve damage in leprosy (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD012235. DOI: 10.1002/14651858.CD012235.

INDEX TERMS

Medical Subject Headings (MeSH)

Bandages; Leg Ulcer [etiology; therapy]; Leprosy [*complications]; Peripheral Nervous System Diseases [*complications]; Randomized Controlled Trials as Topic; Skin Ulcer [etiology; *therapy]; Wound Healing

MeSH check words

Humans