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Dressings and topical agents for arterial leg ulcers (Review)

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[Intervention Review]

Dressings and topical agents for arterial leg ulcers

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ABSTRACT

Background

It is estimated that up to 1% of people in high-income countries suffer from a leg ulcer at some time in their life. The majority of leg ulcers are associated with circulation problems; poor blood return in the veins causes venous ulcers (around 70% of ulcers) and poor blood supply to the legs causes arterial ulcers (around 22% of ulcers). Treatment of arterial leg ulcers is directed towards correcting poor arterial blood supply, for example by correcting arterial blockages (either surgically or pharmaceutically). If the blood supply has been restored, these arterial ulcers can heal following principles of good wound-care. Dressings and topical agents make up a part of good wound-care for arterial ulcers, but there are many products available, and it is unclear what impact these have on ulcer healing. This is the third update of a review first published in 2003.

Objectives

To determine whether topical agents and wound dressings affect healing in arterial ulcers. To compare healing rates and patient-centred outcomes between wound dressings and topical agents.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature and Allied and Complementary Medicine databases, the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials register to 28 January 2019.

Selection criteria

Randomised controlled trials (RCTs), or controlled clinical trials (CCTs) evaluating dressings and topical agents in the treatment of arterial leg ulcers were eligible for inclusion. We included participants with arterial leg ulcers irrespective of method of diagnosis. Trials that included participants with mixed arterio-venous disease and diabetes were eligible for inclusion if they presented results separately for the different groups. All wound dressings and topical agents were eligible for inclusion in this review. We excluded trials which did not report on at least one of the primary outcomes (time to healing, proportion completely healed, or change in ulcer area).

Data collection and analysis

Two review authors independently extracted information on the participants' characteristics, the interventions, and outcomes using a standardised data extraction form. Review authors resolved any disagreements through discussion. We presented the data narratively due to differences in the included trials. We used GRADE to assess the certainty of the evidence.

Main results

Two trials met the inclusion criteria. One compared 2% ketanserin ointment in polyethylene glycol (PEG) with PEG alone, used twice a day by 40 participants with arterial leg ulcers, for eight weeks or until healing, whichever was sooner. One compared topical application of blood-derived concentrated growth factor (CGF) with standard dressing (polyurethane film or foam); both applied weekly for six weeks by 61 participants with non-healing ulcers (venous, diabetic arterial, neuropathic, traumatic, or vasculitic). Both trials were small, reported results inadequately, and were of low methodological quality. Short follow-up times (six and eight weeks) meant it would be difficult to capture sufficient healing events to allow us to make comparisons between treatments.

One trial demonstrated accelerated wound healing in the ketanserin group compared with the control group. In the trial that compared CGF with standard dressings, the number of participants with diabetic arterial ulcers were only reported in the CGF group (9/31), and the number of participants with diabetic arterial ulcers and their data were not reported separately for the standard dressing group. In the CGF group, 66.6% (6/9) of diabetic arterial ulcers showed more than a 50% decrease in ulcer size compared to 6.7% (2/30) of non-healing ulcers treated with standard dressing. We assessed this as very-low certainty evidence due to the small number of studies and arterial ulcer participants, inadequate reporting of methodology and data, and short follow-up period.

Only one trial reported side effects (complications), stating that no participant experienced these during follow-up (six weeks, low-certainty evidence). It should also be noted that ketanserin is not licensed in all countries for use in humans. Neither study reported time to ulcer healing, patient satisfaction or quality of life.

Authors' conclusions

There is insufficient evidence to determine whether the choice of topical agent or dressing affects the healing of arterial leg ulcers.

PLAIN LANGUAGE SUMMARY

Dressings and topical agents for arterial leg ulcers

What is the research question?

Does the choice of topical agents (creams or ointments) or wound dressings affect the healing of arterial leg ulcers?

Background

People with blood circulation problems in their legs can develop leg ulcers, with adults having around a 1% chance of suffering from a leg ulcer at some time in their life. The majority of ulcers (around 70%), result from poor blood flow in the veins and are called venous leg ulcers. These are generally treated by compression. Arterial leg ulcers (around 22% of ulcers) occur because of poor blood supply to the legs, when there is a block in a leg artery or narrowing of the arteries (atherosclerosis). Without treatment of the underlying poor arterial blood supply, ulcers take a long time to heal or may even never heal. These ulcers are treated to promote healing and protect from infection, by covering them with dressings or using topical agents, or both. A variety of types of dressings can be used, depending on whether the main intention is to treat infection, reduce ulcer pain, or manage the fluid that can leak from these ulcers (exudate), and so promote healing.

Study characteristics and key results

We found two small studies that presented data for 49 participants with arterial leg ulcers (search conducted January 2019). The studies also included participants with other kinds of ulcers, and it is not clear what proportion of participants were diabetic. Neither study described the methods fully, both presented limited results for the arterial ulcer participants, and one study did not provide information on the number of participants with an arterial ulcer in the control group. The follow-up periods (six and eight weeks) were too short to measure healing. Therefore, the data that were available were incomplete and cannot be generalised to the greater population of people who suffer from arterial leg ulcers.

One study randomised participants to either 2% ketanserin ointment in polyethylene glycol (PEG) or PEG alone, administered twice a day over eight weeks. This study reported increased wound healing in the ketanserin group, when compared with the control group. It should be noted that ketanserin is not licensed for use in humans in all countries.

The second study randomised participants to either topically-applied growth factors isolated from the participant's own blood (concentrated growth factors (CGF)), or standard dressing; both applied weekly for six weeks. This study reported that 66.6% of CGF-treated diabetic arterial ulcers showed more than a 50% decrease in ulcer size, compared to 6.7% of non-healing ulcers treated with standard dressing.

Only one study mentioned side effects, and reported that no participant experienced side effects during follow-up (six weeks). Neither of the two studies reported time to ulcer healing, patient satisfaction or quality of life measures.

Certainty of the evidence

There is insufficient evidence to determine whether the choice of topical agent or dressing affects the healing of arterial leg ulcers. We downgraded the overall certainty of the available evidence to 'very low' and 'low', because the studies reported their methods poorly, there were only two studies and few participants with arterial disease, and because the studies were short and reported few results. This made it impossible to determine whether there was any real difference in the number of ulcers healed between the groups.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Topical agents compared with control or standard dressing for arterial ulcers

Patient or population: participants with arterial ulcers[a]

Settings: not indicated

Intervention: topical agent[b]

Comparison: control or standard dressing

Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control or standard dressing	Risk with topical agent				
Time to ulcer healing	Neither study reported on time to ulcer healing.			-	-	-
Change in ulcer area over time (6 - 8 weeks)	Rooman 1991 reported that participants receiving ketanserin would reach 50% healing at 3.5 weeks and the control group at 6.3 weeks. Santoro 2018 reported wound reduction of at least 50% of surface and volume of lesion in 6/9 (66.6%) of the CGF group. Only all-patient data is presented for the standard dressing group 2/30 (6.7%)			49 (2 studies)[a]	⊕⊖⊖⊖ **very low**[c]	-
Complications and morbidity (6 - 8 weeks)	Not reported by Rooman 1991. Santoro 2018 reported that no participant presented with side effects during follow-up.			49 (2 studies)[a]	⊕⊕⊖⊖ **low**[d]	-
Patient satisfaction and quality of life data	Neither study reported patient satisfaction and quality of life.			-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CGF: concentrated growth factor; **CI:** confidence intervals; **PEG:** polyethylene glycol

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Rooman 1991 involved 299 participants, of which, 40 had ulcers due to arterial disease. Santoro 2018 involved 61 participants. 9/31 participants in the CGF group had diabetic arterial ulcers, but it is not clear how many arterial ulcers were in the standard dressing group.
[b] Rooman 1991 evaluated the use of 2% ketanserin ointment in PEG compared with a PEG alone control group. Santoro 2018 evaluated the use of topical application of CGF compared with standard dressing.
[c] We downgraded from high to very low due to imprecision (very small numbers of participants with arterial ulcers); short follow up period; and concerns over risk of bias (inadequate methods reporting and details on participants, inadequate reporting of subgroup data).
[d] We downgraded from high to low due to imprecision (very small numbers of participants with arterial ulcers) and concerns over risk of bias (inadequate methods reporting).

BACKGROUND

Description of the condition

Leg ulceration is a common, chronic condition that is painful and reduces health-related quality of life. A systematic review estimated that 0.12% to 1.1% of the adult population suffers from lower-limb ulcers (Graham 2003). The major causes of ulceration include venous insufficiency (poor blood flow in the veins), arterial disease, and diabetes. Although the majority of leg ulcers are due to venous disease, a significant number (around 22%) of people with leg ulcers have arterial insufficiency. 10% to 20% of leg ulcers can be of mixed aetiology, for example due to arterial and venous disease, or diabetes with arterial disease (Harding 2015; SIGN 2010). Arterial leg ulcers develop due to inadequate blood supply to the skin. This may be caused by narrowing of the arteries to the legs (atherosclerosis). It is essential to differentiate between arterial and venous ulcers, as the mainstay of treatment for venous leg ulcers is compression therapy (SIGN 2010; O'Meara 2012), which may lead to skin necrosis (or potentially even to amputation) if applied to arterial leg ulcers (Callam 1987).

Diagnosis of arterial insufficiency, or peripheral arterial disease (PAD), is made by taking a medical history. The most common accompanying complaint is pain, which may occur when walking or during exercise. When cramping pain occurs in the leg after exercise, and resolves on resting, it is called intermittent claudication. This complaint can progress until the person is eventually in pain even at rest.

In order to assess how much blood flow there is in a leg, tests are often undertaken to confirm the presence or absence of arterial disease. Generally, the first evaluation is the ankle brachial index (ABPI, ABI). If this test results in an ABI ratio of less than 0.7, compression treatment is inadvisable and the person will be referred to a vascular specialist who can order further tests, such as duplex ultrasound or arteriography (Grey 2006). The ABI threshold generally ranges between a ratio of 0.6 and 0.7, with some variation in the literature. The diagnosis of PAD is complicated in people with diabetes, as neuropathy can mask symptoms and non-compressible vessels can result in inaccurate ABI readings (Brownrigg 2016).

The key to treatment of arterial insufficiency is to improve the blood supply, Therefore, surgery is often required in order to bypass or clear the blockage. For a number of people this may not be possible, due to their preference, age and general health, or due to diffuse distal arterial disease, where the vessels to be reconstructed are very small. Non-surgical options include good wound-care, exercise to increase blood supply to the leg, pharmaceutical interventions, or physical therapies such as hyperbaric oxygen. This review only considers the use of wound dressings and topical agents in the treatment of arterial ulcers.

Description of the intervention

Dressings are usually placed over the ulcer. Ever since Winter 1962 observed that, in pigs, an acute wound covered by an occlusive dressing healed more rapidly than one exposed to air, clinicians have tried to create the ideal wound-healing environment by applying dressings that limit the loss of water vapour from the wound. However, it is not clear whether a moist wound environment is best for all wounds, regardless of aetiology (their cause). For some arterial leg ulcers accompanied by dry black toes or dry black heels, best practice recommends keeping the ulcers dry, until the dead tissue separates naturally from the healthy tissue. According to the British National Formulary (BNF), the main requirements of a dressing are to keep the wound moist with exudate (but not macerated), free of infection and excessive slough, free of toxic chemicals or fibres, at the optimal healing temperature, undisturbed, and at an optimal pH level (BNF 2013). In the UK, the BNF has classified dressings into categories to aid clinicians in selecting appropriate products. Different countries may use different systems for classifying dressings and topical agents (ointments and creams). In addition, there are a number of topical agents which aim to change the wound environment, for example cadexomer iodine, honey, phenytoin, silver and ketanserin. Topical agents are often used in combination with dressings, and provide an antimicrobial and antibacterial environment (SIGN 2010). Other therapies that have been used to treat arterial ulcers include hyperbaric oxygen, vacuum therapy and skin grafting. These are not considered in this review.

How the intervention might work

Dressings have the ability to allow excess exudate to be removed from the wound surface, provide a moist micro-environment, reduce ulcer pain, act as a semipermeable membrane, be impermeable to micro-organisms and provide thermal insulation (BNF 2013; SIGN 2010). There is a large array of dressings, and not all will have all of the above abilities. However, dressings should be sterile and contaminant-free (i.e. leave no dressing material in the wound), should not cause an allergic reaction and should not cause trauma when removed. Different topical agents also have different modes of action, and can act to reduce or prevent infection, facilitate cleansing and debridement, or reduce platelet aggregation in the capillaries and improve blood flow (Rooman 1991; Vanhoutte 1988).

Why it is important to do this review

Although there are many types of dressings and topical agents available, there is currently little evidence for their effect on the rate of healing in arterial ulcers.

OBJECTIVES

To determine whether topical agents and wound dressings affect healing in arterial ulcers. To compare healing rates and patient-centred outcomes between wound dressings and topical agents.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) or controlled clinical trials (CCTs) that evaluated dressings and topical agents in the treatment of arterial leg ulcers. Trials that used allocation processes which are transparent before assignment, such as an open list of random numbers, case record, day of the week, surname and so forth, were eligible for inclusion in the review.

Types of participants

We included men and women of any age with an arterial leg ulcer, irrespective of the method of diagnosis used. Trials that included

participants with mixed arterio-venous disease and diabetes were eligible for inclusion if they presented results separately for participants with uncomplicated arterial disease (sometimes called pure arterial disease).

Types of interventions

Interventions of interest included any dressing or topical agent applied to arterial leg ulcers. Comparisons were against either no dressing/topical agent, or against other dressings or local agents. We also accepted placebo comparators, but it was not possible to describe any comparator as a true placebo, as every local agent will have an effect on the rate of moisture loss from the surface of the ulcer, and thus may potentially have an impact on healing. We excluded studies that gave compression treatment to all participants, as this treatment is specific to venous ulcers and can be harmful when applied to arterial ulcers. Compression treatments can be used safely in people with an ABI ≥ 0.8, but people with moderate to severe arterial disease will generally have an ABI < 0.7, and should be referred to an appropriate specialist (SIGN 2010). We therefore excluded these kinds of trials, as they were most likely to be studies treating primarily venous ulcers.

Trials which used concurrent interventions, for example drug treatment or advice on exercise, were also eligible for inclusion in the review. We recorded any concurrent interventions used.

Types of outcome measures

In order to be included in the review, a trial report had to provide at least one of the primary outcomes (i.e. healing data).

Primary outcomes

- Time to complete ulcer healing/proportion of ulcers completely healed in trial period: the complete healing of an ulcer is a definitive endpoint which can be measured, and is likely to be the outcome of greatest interest to participants and, therefore, should be the primary outcome measure of any treatment.
- Change in ulcer area over time: although the primary outcome of interest is the complete ulcer healing rate (defined as the number of participants achieving complete healing), some trials report changes in ulcer area over time. These are less valid indicators of effectiveness, as the rate of decrease of ulcer area may vary during the healing process without resulting in complete ulcer healing. In addition, expressing outcomes as either a percentage of initial ulcer area healed, or absolute area healed, may lead to bias, favouring either the small or large-ulcer group where there are different ulcer sizes in the treatment groups at baseline. We used both percentage and absolute healing rates where reported, and attempted to describe the direction of any potential bias due to poor baseline comparability.

Secondary outcomes

- Complications and morbidity: some of the treatments have the potential to affect the participant adversely. We noted complications (e.g. discomfort, skin damage, pain, clinical infection and amputation) wherever the trials reported these, and compared them between interventions.
- Patient satisfaction and quality of life data: generic or specific measures of quality of life.

We excluded studies that reported only interim outcome measures of ulcer improvement, such as 'appearance of granulation tissue', as the relationship between the appearance of healthy tissues (or disappearance of unhealthy tissue) and ulcer healing is unclear.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for RCTs and CCTs, without language, publication year or publication status restrictions:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web; searched on 28 January 2019);
- the Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Register of Studies Online (CRSO; 2019, Issue 1);
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE; searched from 1 January 2017 to 28 January 2019);
- Embase Ovid (searched from 1 January 2017 to 28 January 2019);
- CINAHL Ebsco (Cumulative Index to Nursing and Allied Health Literature; searched from 1 January 2017 to 28 January 2019);
- AMED Ovid (Allied and Complementary Medicine; searched from 1 January 2017 to 28 January 2019).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. Where appropriate, the Information Specialist combined these with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6, Lefebvre 2011). Appendix 1 shows the search strategies for major databases.

The Information Specialist searched the following trials registries on 28 January 2019:

- the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch);
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We reviewed references of relevant studies for other studies of interest that could be included.

Data collection and analysis

Selection of studies

For the update of this review, two authors (CB and MS) initially screened abstracts and titles using Covidence software. They then carried out an independent assessment of potentially relevant abstracts and full-text articles, in terms of their relevance and design according to the selection criteria. We obtained full versions of articles if, from their initial assessment, they appeared to be relevant, and then checked these to verify whether they met the inclusion criteria. We resolved any disagreement by discussion.

Data extraction and management

Two review authors (CB and FP) independently extracted details of the studies. The review authors attempted to contact the study authors to obtain any data that were missing from reports. If we had identified any studies published in duplicate, we would have included them only once. For each included study, we collected the following data:

- trial setting (country, and whether primary or secondary care);
- length of follow-up;
- number of participants (or limbs or ulcers) randomised;
- inclusion criteria;
- exclusion criteria;
- description of interventions and co-interventions;
- baseline characteristics of groups for important variables (e.g. ulcer size, duration);
- trial results;
- intention-to-treat analysis;
- number and reason for withdrawals;
- source of funding;
- use of an a priori sample size/power calculation.

Assessment of risk of bias in included studies

Two review authors (CB and FP) independently evaluated the included studies for quality, using the Cochrane tool for assessing risk of bias (Higgins 2011a). This tool provides judgments made on seven domains, which include randomisation sequence generation, allocation concealment methods, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other relevant biases. We evaluated each included study as low risk, unclear risk, or high risk for each domain. We resolved any disagreements between review authors through discussion.

Measures of treatment effect

We planned to conduct analysis on an intention-to-treat basis, and therefore planned to include all randomised participants of interest in the analysis. We planned to compile the outcomes that were dichotomous into a meta-analysis and calculate odds ratios (ORs) with 95% confidence intervals (CIs). For continuous data, we planned a meta-analysis using mean differences (MDs) with standard deviations (SDs) and 95% CIs.

Unit of analysis issues

The unit of analysis for this review was the individual participant. For studies that included participants with more than one ulcer, we planned to perform a sensitivity analysis to determine if such studies had a large impact on the effect size.

Dealing with missing data

Where data were missing from the included study, we attempted to contact study authors.

Assessment of heterogeneity

A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect. We planned to obtain P values comparing the test statistic with a Chi^2 statistic distribution. To help readers assess the consistency of results of studies in a meta-analysis, Review Manager 2014 includes the I^2 statistic that describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.

Assessment of reporting biases

To assess reporting bias, we planned to create funnel plots for meta-analyses containing 10 or more included studies (Sterne 2011). As only two studies were included in this review, we could not undertake an assessment of reporting bias.

Data synthesis

We intended to make the following comparisons:

- all dressings versus no dressing;
- all occlusive or semiocclusive dressings versus traditional dressings (such as gauze);
- occlusive or semiocclusive dressings versus other occlusive or semiocclusive dressings (e.g. foam dressing versus film dressing; hydrocolloid dressing versus hydrogel dressing etc.);
- topical agents versus no topical application;
- topical agents versus placebo or control;
- topical agents versus other topical agents;
- topical agents versus dressings.

We planned to combine data for these comparisons in meta-analyses, and to use a systematic narrative overview where synthesis in this manner was inappropriate. We planned to use fixed-effect models where heterogeneity was low, but if the I^2 statistic was more than 50%, we planned to use a random-effects model.

Subgroup analysis and investigation of heterogeneity

Trials using allocation processes which are transparent before assignment, such as an open list of random numbers, case record, day of the week, surname and so forth, were eligible for inclusion in the review. We planned to undertake subgroup analysis to compare such trials with trials that had adequate allocation concealment.

Sensitivity analysis

We planned to undertake sensitivity analysis to exclude studies that used allocation processes which are transparent before assignment (open list of random numbers, case record, day of the week, surname). We planned a sensitivity analysis to remove studies that involved participants with more than one ulcer being treated within the study, to determine whether these studies had a large impact on the overall effect size. We also planned a sensitivity analysis to exclude low-quality studies, as judged by the level of risk of bias, to determine their impact on the overall results. Due to the limited number of included studies, we did not carry out any sensitivity analyses.

Summary of findings and assessment of certainty of the evidence

We created a 'Summary of findings' table to present the main results using the Review Manager 'Summary of findings table wizard' (Review Manager 2014), based on methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of*

Interventions (Higgins 2011b). We included the outcomes: time to complete healing, change in ulcer area over time; complications and comorbidity; and patient satisfaction or quality of life data. We included a narrative summary of the findings as we were not able to carry out any data synthesis. We used the GRADE approach to assess the certainty of the evidence for each outcome as high, moderate, low, or very low, based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias (Atkins 2004; Higgins 2011b). See Summary of findings for the main comparison.

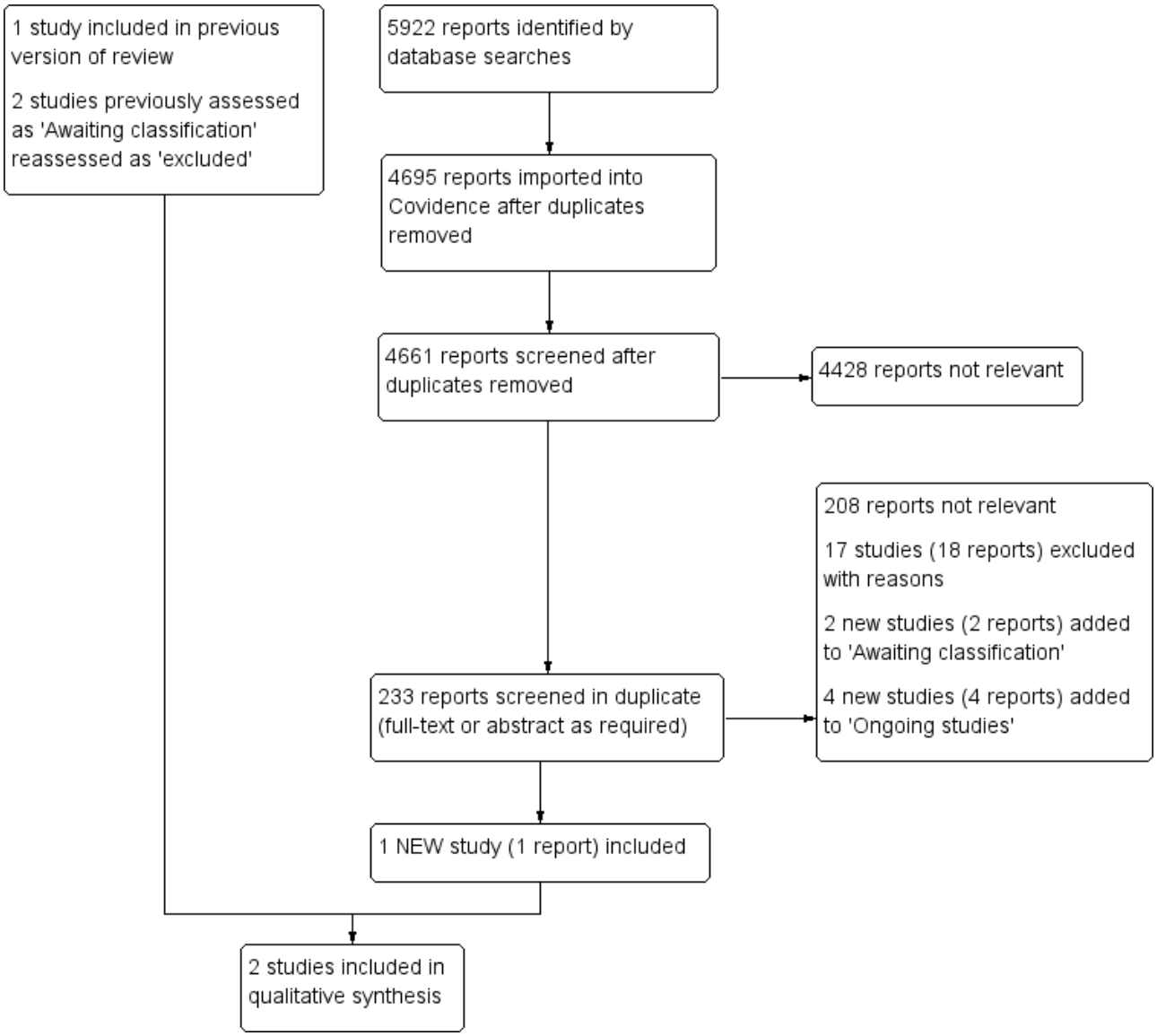
RESULTS

Description of studies

Results of the search

See Figure 1 for the PRISMA flow-chart.

Figure 1. Study flow diagram.



For this update, we included one new study (Santoro 2018). We assessed four new studies as ongoing (NCT02583958; NCT02839226; NCT03275831; NCT03468816), and two as 'awaiting classification' (Capoano 2017; NCT00658983). We assessed and excluded two studies which were previously 'awaiting classification' (Gibson 1995; Morely de Benzaquen 1990). We excluded a further 17 studies (Augustin 2016; Barouti 2015; Castell 2016; Hanumanthappa 2012; JPRN-UMIN000033048; Meaume 2014; Meaume 2017; Mo 2015; Moffatt 2014; Morimoto 2013; NCT01036438; NCT01449422; NCT02046226; Purcell 2017; Raposio 2015; Romanelli 2016; Woo 2012).

Included studies

Summary details of the included studies are given in the Characteristics of included studies table.

The trial by Rooman and Janssen compared 2% ketanserin ointment in PEG with a control group that received PEG alone,

applied twice daily, for eight weeks (Rooman 1991). For participants with purely arterial disease, 19 people were in the ketanserin group and 21 people in the control (PEG alone) group. This multicentre study recruited 299 participants with decubitus ulcers: 80 had pressure ulcers; 134 had venous ulcers; 45 had diabetic ulcers; and 40 had arterial ulcers. The publication did not describe the method of identifying the participants. This can have an impact on the transferability of the results to other settings, as the characteristics of participants recruited from a tertiary referral centre or a primary care setting may well be different, e.g. duration of ulceration, severity of underlying pathology. The trial did not report its inclusion or exclusion criteria, or the degree of arterial impairment for either group. The only outcome that the trial reported for the arterial leg ulcers subgroup was wound area as a function of time, and we could not determine time to 50% healing from the graph of results.

Santoro 2018 included 61 participants with non-healing ulcers (31 in CGF group and 30 in the standard dressing group). These were of mixed aetiology, including venous ulcers, arterial diabetic ulcers, neuropathic ulcers, traumatic ulcers and vasculitic ulcers. The trial compared topical application of concentrated growth factors CGF with application of a standard dressing of polyurethane film or foam, both applied weekly for six weeks. The trial reported numbers of participants with arterial diabetic ulcers in the CGF group, but we could not determine the number of arterial diabetic ulcers in the standard dressing group. CGF was an autologous preparation obtained from the participants' own blood, believed to be rich in platelet-derived growth factors, such as transforming growth factor beta1 and 2, fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor and stem cells. The trialists used MOWA graphics software (MObile Wound Analyzer) to calculate ulcer size.

Excluded studies

Summary details of excluded studies are given in the Characteristics of excluded studies table.

For this update, we excluded an additional 19 studies (20 reports) (Augustin 2016; Barouti 2015; Castell 2016; Gibson 1995; Hanumanthappa 2012; JPRN-UMIN000033048; Meaume 2014; Meaume 2017; Mo 2015; Moffatt 2014; Morely de Benzaquen 1990; Morimoto 2013; NCT01036438; NCT01449422; NCT02046226; Purcell 2017; Raposio 2015; Romanelli 2016; Woo 2012). This includes two studies which were previously 'awaiting classification', but which we have now excluded as we were unable to obtain the full texts for these (Gibson 1995; Morely de Benzaquen 1990).

This made a total of 82 excluded studies. The main reason for exclusion (32 studies) was a lack of outcome data presented by ulcer aetiology (Armstrong 1996; Augustin 2016; Bale 1998; Barouti 2015; Castell 2016; Daltrey 1981; Fumal 2002; Harding 2001; Janssen 1989; Kalis 1993; Krupski 1991; Meaume 2014; Meaume 2017; Mian 1991; Milward 1991; Mo 2015; Morimoto 2013; Motta 2004; Purcell 2017; Raposio 2015; Romanelli 2016; Sibbald 2011; Steed 1991; Svedman 1983; Tarvainen 1988; Thomas 1989; Vin 1997; Vuerstaek 2006; Woo 2012; Wagner 1990; Weed 2004; Zykova 2014). We could have included the majority of these studies if the authors had given subgroup data by ulcer aetiology. We excluded 23 studies because the publications did not provide enough information for us to determine whether arterial ulcers were included (Bassetti 1970; Casoni 2001; Chaloner 1992; Falabella 1998; Gago Fornells 2002; Hanumanthappa 2012; Ishibashi 1990; Jorgensen 2003; Kordestani 2008; Larsen 1997; Leaper 1986; Luongo 2003; Moffatt 2014; Moss 1984; Munter 2006; NCT01036438; NCT01449422; Nyfors 1982; Pendse 1993; Polignano 2001; Quatresooz 2006; Serra 2005; Wollina 1997). Seventeen studies did not report outcomes that were within the scope of the review, i.e. healing data (Altman 1976; Armstrong 1997; Banks 1997; Boxer 1969; Da Costa 1997; Gibson 1986; Holm 1990; Holst 1998; Jansen 2009; Johnson 1992; Jørgensen 2009; JPRN-UMIN000033048; Knighton 1988; Knighton 1991; Stromberg 1984; Varelias 2006; Wu 1996. The remaining 10 studies were excluded for other reasons: Hartman 2002 was not an RCT; one study included identical interventions in the comparison groups (Gamborg Nielson 1989); one study included only a single participant with an arterial ulcer, who did not have a comparator (Huber 1991); one study included a treatment that is no longer available (Leaper 1991); one study applied the treatment to the skin around the ulcer and not the ulcer directly (Neander 2004); and one study excluded participants with "deep arterial disease" (Senet 2011). We could not obtain a copy of the study by Schmutz 1997, but a previous Cochrane Review 'Dressings for healing venous leg ulcers' excluded it for the following reason: "Report of design of trial no results given. Author contacted but no reply" (Palfreyman 2006). We were also unable to obtain full copies of Gibson 1995 or Morely de Benzaquen 1990. Finally, although NCT02046226 met the inclusion criteria, the study was terminated due to lack of recruitment.

Ongoing studies

Four new ongoing studies were identified (NCT02583958; NCT02839226; NCT03275831; NCT03468816). See Characteristics of ongoing studies for further details.

Studies awaiting classification

We assessed two studies as 'awaiting classification' (Capoano 2017; NCT00658983). See Characteristics of studies awaiting classification for further details.

Risk of bias in included studies

A graphical description of the included studies' risk of bias can be seen in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

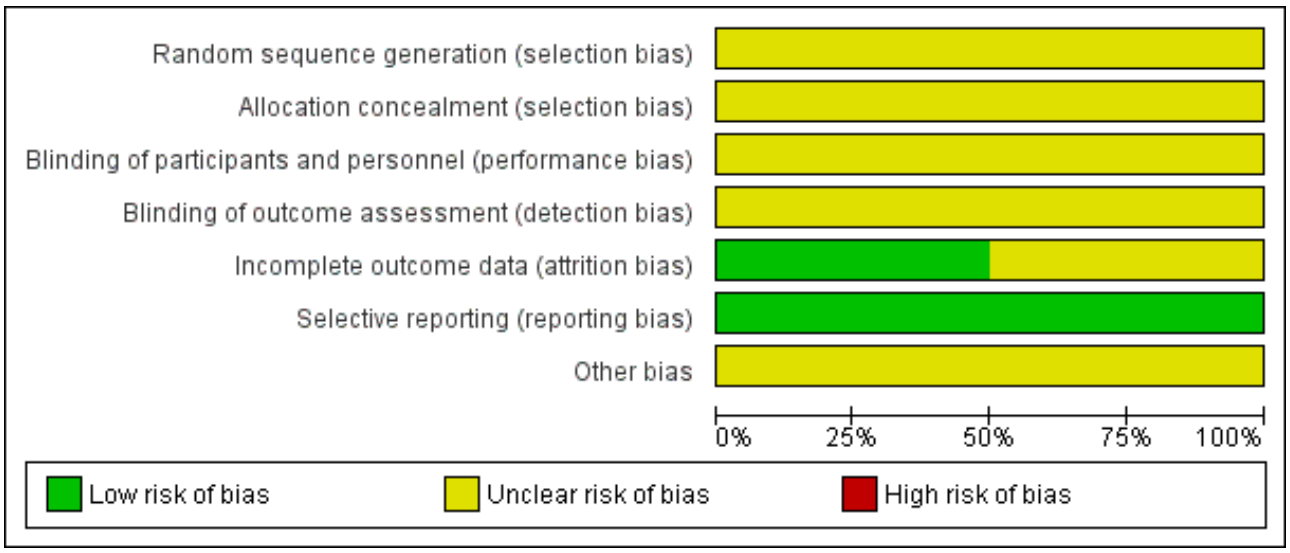
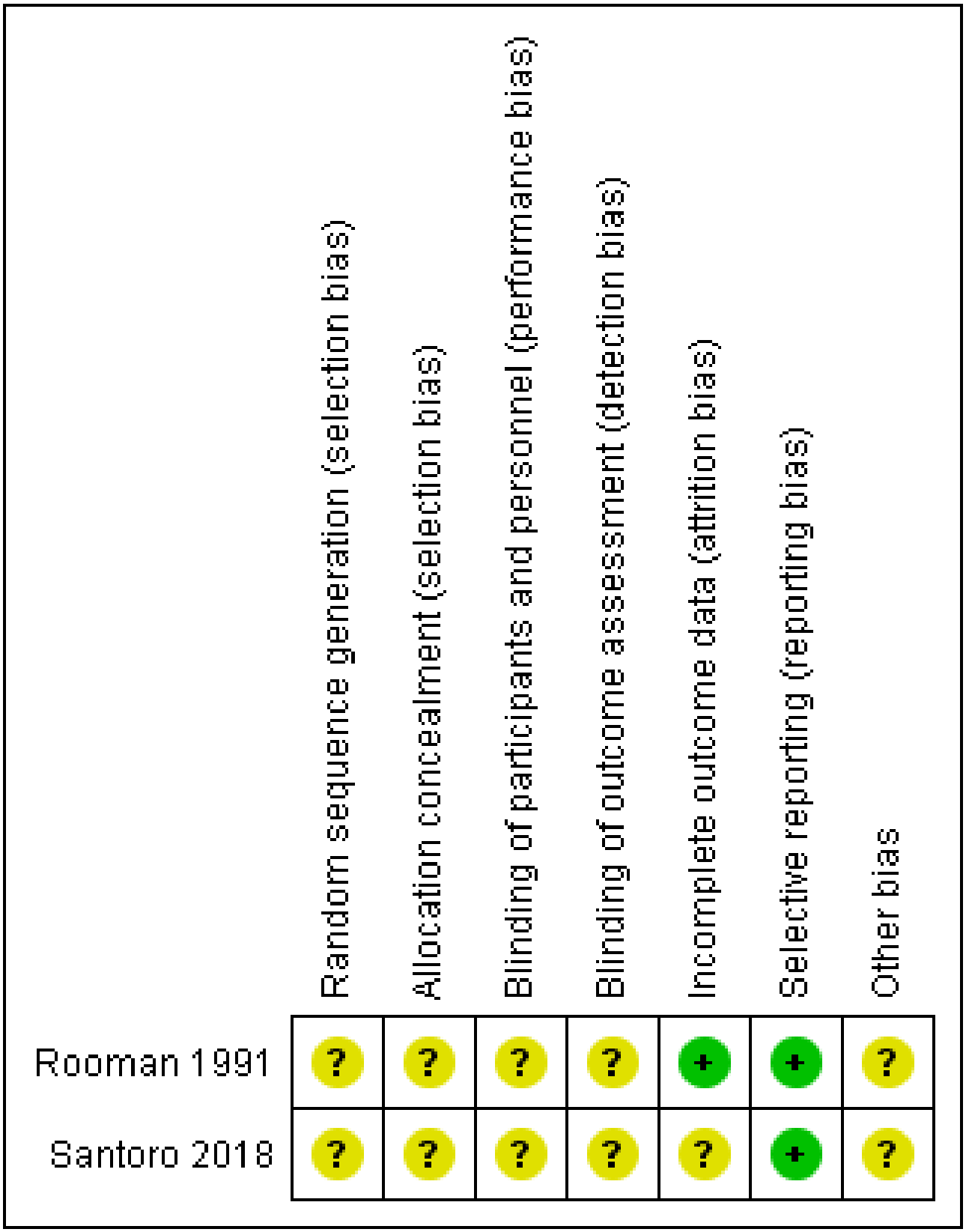


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Neither Rooman 1991 nor Santoro 2018 described the randomisation method within the text. It is unclear how people were allocated to the two groups, whether allocation sequence was randomly generated or if allocation was concealed, leading to a rating of 'unclear' for selection bias.

Blinding

Rooman 1991 described their trial as double-blind, using a placebo control, but did not describe the steps taken to ensure that clinicians and participants were unaware of the treatment (ketanserin or control). Rooman 1991 did not report how successful this blinding was, nor whether the people assessing the wound, by taking wound tracings, were blinded. Santoro 2018 did not mention blinding of participants, personnel or outcome assessors. We therefore rated both performance and detection bias for both studies as 'unclear'.

Incomplete outcome data

We rated attrition bias as 'low' in the Rooman 1991 study, as all participants appeared in the analyses. The trialists did not discuss any dropouts or loss-to-follow-up. As Santoro 2018 only reported the arterial ulcer data for the intervention group and not the control group, we rated attrition bias as 'unclear' for this study.

Selective reporting

The studies reported on all outcomes that were discussed in the publications' methods sections, so we gave both studies a 'low' rating for reporting bias. These outcomes included granulation tissue, degree of re-epithelialisation, wound surface area and a global assessment of the evolution of the ulcer in Rooman 1991. Santoro 2018 reported wound size and side effects.

Other potential sources of bias

We gave Rooman 1991 an 'unclear' rating for other sources of bias, as the trial did not perform an a priori power calculation, and with low numbers of participants with arterial ulcers (40 participants in total; 19 people receiving treatment and 21 people receiving control), the results may not be powered to answer the study questions of this review. We also gave Santoro 2018 a rating of 'unclear' risk of other bias, as it was a conference abstract (not peer reviewed), it is not clear if the use of the MOWA graphics software is validated, and the study included a small number of arterial ulcer participants (exact number unclear).

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

Time to complete ulcer healing/proportion of ulcers completely healed in trial period

Not reported.

Change in ulcer area over time

The only outcome that the Rooman 1991 study reported by ulcer aetiology was wound area as a function of time, and they presented this data in a graph. Rooman 1991 predicted that participants receiving ketanserin would reach 50% healing at 3.5 weeks and those in the control group at 6.3 weeks, meaning that the ketanserin-treated participants healed nearly twice as fast as the control-treated participants ("1.8 fold"; Rooman 1991), reported by Rooman 1991 to be statistically significant at $P < 0.01$. It should be noted that the average ulcer size at the start of the trial was larger in the control group compared with the ketanserin group, which could bias the results, even though the wound area was a percentage of the initial size (ketanserin 9.41 cm^2; control 11.03 cm^2).

Santoro 2018 used the primary outcome of wound reduction of at least 50% surface and volume of lesion after six-weeks' treatment. They reported that this was achieved in 19/31 (61.3%) of the CGF group, compared to 2/30 (6.7%) of the standard dressing control group. In the CGF group, nine participants had arterial diabetic ulcers, and six of the nine (66.6%) showed at least a 50% reduction in ulcer size. The study did not report subgroup data for diabetic arterial ulcers within the standard dressing group, so it was not possible to make a direct comparison with the appropriate control group.

We used the GRADE approach to assess the certainty of evidence for this outcome, and rated it as very low-certainty evidence (see Summary of findings for the main comparison).

Secondary outcomes

Complications and morbidity

Not reported by Rooman 1991. Santoro 2018 reported that no participant presented with side effects during follow-up.

We used the GRADE approach to assess the certainty of evidence of this outcome, and rated it as low-certainty evidence (see Summary of findings for the main comparison).

Patient satisfaction and quality of life data

Not reported.

DISCUSSION

Summary of main results

Rooman 1991 evaluated the use of a 2% ketanserin ointment in polyethylene glycol (PEG), compared with a PEG alone control group. There were a total of 299 participants in the trial, of whom only 40 people had ulcers due to arterial disease. We were able to evaluate outcomes from the study as it gave a subgroup analysis of the 40 arterial ulcer participants separately. The only outcome that the trial reported by ulcer aetiology was wound area as a function of time, which demonstrated that ketanserin ointment accelerated the healing of arterial ulcers (nearly twice as fast as the PEG alone control group). Santoro 2018 evaluated the use of an autologous preparation from the participants' own blood, which contained concentrated growth factors (CGF), compared with standard dressing (polyurethane film or foam), both applied weekly for six weeks. The trialists presented data separately for diabetic arterial ulcers, but only for the treatment group, so we were unable to compare with the appropriate control group. Rooman 1991 did not report adverse effects, and Santoro 2018 reported that no participants presented with side effects.

Whilst the results of the included trials might appear positive, the inadequate reporting of results, in combination with the lack of reporting of methods used in the trial (e.g. method of

allocation), means that we cannot confidently conclude that there is accelerated healing due to either ketanserin 2% ointment when compared with PEG alone, or due to CGF compared with standard dressing. In addition, the follow-up times were too short (at six and eight weeks) to be able to capture sufficient healing events to allow us to make comparisons. The lack of clearly stated inclusion and exclusion criteria in the included trials means that the method of identifying arterial ulcers was unclear, which reduces the generalisability of the results. Also, it should be noted that ketanserin is not licensed in all countries for use in humans. We assessed the certainty of the evidence to be very low for ulcer healing, and low for complications and morbidity. Neither of the trials reported time to ulcer healing, patient satisfaction or quality of life.

Overall completeness and applicability of evidence

Both included studies were of relatively low methodological quality, gave limited explanation of methods, and offered very little outcome data for the arterial ulcer subgroup. There were few participants, and the follow-up time was inadequate. In addition, we were unable to extract data specific to the diabetic arterial ulcer standard dressing (control) group. Therefore, the data that were available were incomplete, and cannot be generalised to the greater population of people who suffer from arterial leg ulcers.

There are many underlying reasons why such limited high-quality evidence is available for this topic. Venous ulcers are far more prevalent than arterial ulcers, so gaining enough participants for a trial of only arterial ulcers is much more difficult. Trials in wound care will always be faced with participants who vary in a large number of respects, for example the size and duration of the ulcer, the degree of arterial impairment, and concurrent treatments such as wound cleansing, exercise, nutrition and other self-care activities. This variability in participant characteristics means that an investigation examining which treatment option to use needs to employ a study design that takes into account the differences between participants. A randomised controlled trial (RCT) is the most powerful study design, but designing a double-blind RCT in dressing efficacy is challenging due to various issues. These challenges include: the difficulty of controlling the variables associated with comorbidities; calculating sample sizes to achieve statistical significance; recruiting enough participants; challenges with validating infection, inflammation and wound sizes; and challenges with validating subjective assessments, such as comfort and user-friendliness. In the UK, dressings are considered 'medical devices'; they are CE marked (Conformité Européenne or European Conformity), therefore safe to be used in the context for which they have been designed, but they are not submitted to rigorous trial processes like pharmaceutical products (i.e. drugs). There is therefore little incentive to fund large trials. This lack of research is hindered by limited legislation, as manufacturers are not required by law to provide evidence of efficacy (Madden 2012). Therefore, simply recommending further RCTs or controlled clinical trials (CCTs) may not be helpful. We suggest instead that alternative methodologies are explored to provide some guidance to clinicians on the best way to care for arterial leg ulcers.

Quality of the evidence

Using GRADE criteria, we rated the certainty of evidence as low to very low, due to small numbers of relevant studies, inadequate reporting of the results, and too short a follow-up time (six or eight weeks) to be able to capture sufficient healing events to make comparisons. As discussed above, the trials presented very limited outcome data for the arterial ulcer subgroup. We deemed the methodological quality to be low, because we gave the majority of bias domains an 'unclear' rating due to inadequate reporting. We only rated two of the seven domains as low risk for the Rooman 1991 study: attrition bias and reporting bias. We only rated one domain as low risk in the Santoro 2018 study (reporting bias). The study did not discuss randomisation methods and allocation concealment, or give any indication of blinding methods. The trials did not identify outcome assessors as blinded, and the low number of participants could bias the results. The trials did not report essential information about how and where the participants were recruited, neither did they present full inclusion and exclusion criteria.

Potential biases in the review process

The authors took precautions to prevent reviewer biases in the review process, including independent, duplicate inclusion and exclusion of identified studies, risk of bias assessments and data extraction. For this particular review, a concern with bias lies in the fact that many studies did not indicate whether their included participants had arterial disease, or did not indicate any diagnostic criteria that would allow the readers to determine arterial disease. This could have led us to exclude studies that did, in fact, meet the inclusion criteria. To combat this issue, the review authors assessed studies carefully and discussed any uncertainties amongst themselves.

Agreements and disagreements with other studies or reviews

We have not identified any other systematic reviews that evaluated the effect of different dressings or topical agents on the healing of arterial leg ulcers.

A Cochrane Review, published in 2006, evaluated the effects of different dressings on venous leg ulcers when applied under compression bandages (Palfreyman 2006). Although the review included a total of 42 studies, the authors could not conclude that any one type of dressing was superior to another. This review has since been split into four separate reviews of specific dressing types, to determine any effect of alginate dressings (O'Meara 2013a), foam dressings (O'Meara 2013b), hydrocolloid dressings (Ribeiro 2014), and hydrogel dressings (Ribeiro 2013). The foam and alginate-dressing reviews still found no difference between the effectiveness of different dressing type on ulcer healing.The hydrocolloid and hydrogel reviews are still in preparation, and are currently only published as protocols. While we cannot draw any conclusions about arterial ulcers from these reviews, they provide relevant information on the topic of dressings for ulcers, as well as the current state of knowledge and research.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine whether the choice of topical agent or dressing affects the healing of arterial leg ulcers.

Implications for research

This review has identified a lack of evidence to support or reject the use of dressings or topical agents in the healing of arterial leg ulcers. As indicated in the Overall completeness and applicability of evidence section, there are many issues that inhibit the design and conduct of RCTs for the investigation of dressings and topical agents for ulcers. To ensure future RCTs or CCTs are applicable to the variety of people with arterial leg ulcers, and therefore useful to clinicians, they must balance the variables arising from comorbidities, and address the challenges relating to recruitment and validation of outcome measurements.

Nevertheless, there is a requirement for the following studies in the healing of arterial leg ulcers:

- comparison between various modern dressings;
- comparison between wound dressings alone versus topical agents applied underneath wound dressings.

These studies should have clear inclusion and exclusion criteria, and sufficiently long follow-up to determine dressing effectiveness.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Rooman 1991

Methods	Trial design: "double-blind, placebo controlled study" Setting: Belgium Primary or secondary care: not indicated Intention-to-treat: not indicated Funding source: not indicated A priori sample size calculation: not indicated
Participants	Number of participants: a total of 299 participants with decubitus ulcers in study, but only 40 with arterial disease (n = 19 ketanserin; n = 21 control); only the 40 with arterial disease are of interest in this review. Age (entire study population): ketanserin 70.2 years; control 96.6 years Gender (entire study population): 89 males, 208 females, 2 not specified (ketanserin 44 males,106 females; control 45 males,102 females, 2 not specified) Ulcer size (entire study population): ketanserin 9.41 cm^2; control 11.03 cm^2 Ulcer age (entire study population): ketanserin 412 days; control 480 days Inclusion criteria: not indicated, it was not clear how the diagnosis of 'arterial ulceration' was made Exclusion criteria: not indicated Withdrawals: not indicated
Interventions	Treatment: 2% ketanserin ointment in PEG, applied twice daily Control: PEG ointment (unclear how many times applied daily) Follow-up: 8 weeks or until healing, whichever was sooner
Outcomes	Relative wound area as a function of time Other outcomes were reported, but trial authors did not differentiate the results by ulcer aetiology
Notes	No additional surgical interventions were mentioned Both of the study authors were employed by Janssen Research Foundation; Janssen was a manufacturer/supplier of ketanserin
Risk of bias	

Rooman 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as a randomised study, but randomisation sequence generation not discussed.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind, placebo controlled", but no description of methods used to ensure blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appeared in analyses; no discussion of dropouts.
Selective reporting (reporting bias)	Low risk	All identified outcomes reported on.
Other bias	Unclear risk	Low number of participants with arterial ulcers, a total of 40 (19 treatment group; 21 control).

Santoro 2018

Methods	Trial design: randomised Setting: Italy Primary or secondary care: not indicated Intention-to-treat: not indicated Funding source: not indicated A priori sample size calculation: not indicated
Participants	Number of participants: 61 participants with non-healing ulcers (31 in CGF group and 30 in the standard dressing group) Age (entire study population): mean age 69.3 years Gender (entire study population): 50.8% male Ulcer size (entire study population): not indicated Ulcer age (entire study population): not indicated Inclusion criteria: participants with non-healing ulcers (venous, arterial diabetic, neuropathic, traumatic, vasculitic) Exclusion criteria: not indicated Withdrawals: not indicated
Interventions	Treatment: topical application of CGF weekly

Santoro 2018 *(Continued)*

	Control: application of polyurethane film or foam weekly (standard dressing) Follow-up: 6 weeks
Outcomes	Primary endpoint: reduction of at least 50% of surface and volume of lesions after 6 weeks treatment Side effects
Notes	No additional surgical interventions were mentioned Data taken from conference abstract which indicates that a larger study is underway, although no details of this detected Low number of participants with arterial ulcers (9 in treatment group; unclear number in control) Authors contacted to request further details 31 May 2019 (no response received) No details on funding provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on randomisation methods provided in abstract.
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment provided in abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details on blinding participants or personnel mentioned in abstract.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on blinding of outcome assessors mentioned in abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Arterial ulcer data available for CGF group only not standard dressing group. Overall CGF and standard dressing data presented.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Wound size measured by Mobile Wound Analyser. It is not clear if this is validated. Data presented as conference abstract only. Low number of participants with arterial ulcers (9 in treatment group; unclear number in control).

CGF: concentrated growth factor
PEG: polyethylene glycol

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

Study	Reason for exclusion
Altman 1976	Healing data not reported.
Armstrong 1996	Outcome data not presented by ulcer aetiology.
Armstrong 1997	Healing data not reported for the two people with arterial ulcers.
Augustin 2016	Outcome data not presented by ulcer aetiology.
Bale 1998	Outcome data not presented by ulcer aetiology.
Banks 1997	Healing data not reported for the two people with arterial ulcers.
Barouti 2015	Outcome data not presented by ulcer aetiology.
Bassetti 1970	Not enough information given to determine ulcer aetiology.
Boxer 1969	Healing data not reported.
Casoni 2001	Not enough information given to determine ulcer aetiology; excluded severe peripheral atherosclerotic disease.
Castell 2016	Outcome data not presented by ulcer aetiology.
Chaloner 1992	Not enough information given to determine ulcer aetiology; subjective outcome measures not within scope of review.
Da Costa 1997	Healing data not reported.
Daltrey 1981	Outcome data not presented by ulcer aetiology.
Falabella 1998	Not enough information given to determine ulcer aetiology.
Fumal 2002	Arterial ulcers were included (along with neurological disorder-related, diabetes-related and drug intake-related) but outcomes were not given by ulcer aetiology.
Gago Fornells 2002	Not enough information given to determine ulcer aetiology; outcome of maceration reduction not within scope of review.
Gamborg Nielson 1989	Two groups had identical treatments.
Gibson 1986	No data on healing presented.
Gibson 1995	This study was previously awaiting classification, but we have been unable to obtain a full-text copy.
Hanumanthappa 2012	Not enough information given to determine ulcer aetiology.
Harding 2001	Although 8% of the participants had arterial ulcers, the outcome data were not presented by ulcer aetiology.
Hartman 2002	This study was included in the previous version of the review, but upon further investigation the study does not fit either an RCT or CCT study design, as the control group is not adequate.
Holm 1990	No data on healing presented.

Study	Reason for exclusion
Holst 1998	No data on healing presented.
Huber 1991	Only one person with an arterial ulcer; no comparator.
Ishibashi 1990	Not enough information given to determine ulcer aetiology, only described as 'leg ulcer'.
Jansen 2009	Outcome of wound pain not within scope of review.
Janssen 1989	Outcome data not presented by ulcer aetiology.
Johnson 1992	Outcome of wound pain not within scope of review.
Jorgensen 2003	Not enough information given to determine ulcer aetiology.
JPRN-UMIN000033048	Outcome of bacterial load is not within the scope of this review.
Jørgensen 2009	Outcome of wound pain and intervention comparison with local best practice not within the scope of the review.
Kalis 1993	Includes ulcers of mixed aetiology and does not give outcome data by aetiology.
Knighton 1988	No data on healing presented.
Knighton 1991	No data on healing presented.
Kordestani 2008	Not enough information given to determine ulcer aetiology, only described as 'leg ulcer'.
Krupski 1991	Outcome data not presented by ulcer aetiology.
Larsen 1997	Not enough information given to determine ulcer aetiology, and subjective performance outcomes not within scope of review.
Leaper 1986	Described as ulcers of 'mixed aetiology' with not enough information given to determine specific aetiology.
Leaper 1991	The treatment Sherisorb is no longer available.
Luongo 2003	Not enough information given to determine ulcer aetiology.
Meaume 2014	Outcome data not presented by ulcer aetiology.
Meaume 2017	Outcome data not presented by ulcer aetiology.
Mian 1991	Outcome data not presented by ulcer aetiology.
Milward 1991	Outcome data not presented by ulcer aetiology.
Mo 2015	Outcome data not presented by ulcer aetiology.
Moffatt 2014	Not enough information given to determine ulcer aetiology, but compression used so most likely venous.
Morely de Benzaquen 1990	This study was previously awaiting classification, but we have been unable to obtain a full text copy.

Study	Reason for exclusion
Morimoto 2013	Outcome data not presented by ulcer aetiology.
Moss 1984	Not enough information given to determine ulcer aetiology; "Forty-two outpatients with chronic leg ulcers, mostly presumed to be venous...".
Motta 2004	Outcomes not given by aetiology; unclear if arterial ulcers were included; outcomes of bacterial load not within scope of our review.
Munter 2006	Not enough information to determine if arterial only leg ulcers were included; dressing compared with local best practice not within scope of review.
NCT01036438	Not enough information given to determine ulcer aetiology, but compression used so most likely venous.
NCT01449422	Not enough information given to determine ulcer aetiology, but compression used so most likely venous.
NCT02046226	Meets inclusion criteria, but terminated due to lack of recruitment (seven recruited participants did not complete study).
Neander 2004	Intervention was applied to skin around ulcer, not ulcer.
Nyfors 1982	Not enough information given to determine ulcer aetiology; excluded severe peripheral atherosclerotic disease.
Pendse 1993	Not enough information given to determine ulcer aetiology.
Polignano 2001	Not enough information given to determine ulcer aetiology; used compression bandages; outcomes of angiogenesis not within scope of review.
Purcell 2017	Outcome data not presented by ulcer aetiology.
Quatresooz 2006	Not enough information given to determine ulcer aetiology.
Raposio 2015	Outcome data not presented by ulcer aetiology.
Romanelli 2016	Outcome data not presented by ulcer aetiology.
Schmutz 1997	Unable to obtain study paper. Excluded from Cochrane review: Dressing for healing venous leg ulcers, "Report of design of trial no results given. Author contacted but no reply" (Palfreyman 2006).
Senet 2011	Excluded participants with "deep arterial disease".
Serra 2005	Not enough information given to determine ulcer aetiology, only described as 'vascular ulcers'.
Sibbald 2011	Outcome data not presented by ulcer aetiology.
Steed 1991	Outcome data not presented by ulcer aetiology.
Stromberg 1984	Outcomes not within scope of review; data presented on 'successes' which included 'appearance of granulation tissue' or 'reduction in area'.
Svedman 1983	Although arterial ulcers were included, outcome data not presented by ulcer aetiology.
Tarvainen 1988	Outcome data not presented by ulcer aetiology; included compression bandages.

Study	Reason for exclusion
Thomas 1989	Outcome data not presented by ulcer aetiology, also it is unclear if participants with arterial disease did not have mixed venous/arterial disease.
Varelias 2006	Outcomes not within scope of review: immunohistochemical analysis for matrix metalloproteinase-2, -9 and tissue inhibitor of matrix metalloproteinase-2 expression.
Vin 1997	Outcome data not presented by ulcer aetiology.
Vuerstaek 2006	Outcome data not presented by ulcer aetiology.
Wagner 1990	Outcome data not presented by ulcer aetiology; outcomes not within scope of review.
Weed 2004	Outcome data not presented by ulcer aetiology.
Wollina 1997	Not enough information given to determine ulcer aetiology.
Woo 2012	Outcome data not presented by ulcer aetiology.
Wu 1996	No data on healing
Zykova 2014	Outcome data not presented by ulcer aetiology.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Capoano 2017

Methods	Trial design: unclear Setting: Italy Primary or secondary care: secondary Funding source: not mentioned
Participants	People (n = 100) with ulcers of the legs
Interventions	1) 50 participants treated with conventional therapies; 2) 50 participants treated with autologous leuco-platelet concentrate (LPC) and Hyalofill-F, a partial benzyl ester derivative of hyaluronan, as a scaffold
Outcomes	Area of lesion Limb salvage Neovascularisation
Notes	Unclear if study was randomised or if all participants had arterial ulcers Additional information requested from contact author 23 May 2019

NCT00658983

Methods	Trial design: RCT

NCT00658983 *(Continued)*	
	Setting: unclear Primary or secondary care: unclear Funding source: Medtronic, Johnson & Johnson
Participants	Chronic lower leg ulcer
Interventions	Autologous platelet enriched gel Metalloproteinase inhibitor
Outcomes	Wound healing
Notes	Unclear if participants include arterial ulcers Additional information requested from contact investigator 30 May 2019

LPC: leuco-platelet concentrate
RCT: randomised controlled trial

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

NCT02583958	
Trial name or title	Assessment of efficacy and safety for a new wound dressing URGO 310 3166 in the local treatment of venous or mixed leg ulcers: a European RCT
Methods	Trial design: RCT Setting: France Primary or secondary care: unclear Funding source: Laboratoires URGO
Participants	People with venous or mixed leg ulcers
Interventions	Intervention: URGO 310 3166 dressing Comparison: Aquacel Extra hydrofibre dressing
Outcomes	Relative regression of wound surface area Percentage of debrided wounds Adverse events QoL
Starting date	October 2014
Contact information	Principal investigator: Sylvie Meaume, MD; Hospital Rothschild, Paris, France
Notes	Status: recruiting; estimated completion date June 2017

NCT02839226

Trial name or title	Safety and efficacy of topical AR/101 compared with placebo, in accelerating granulation tissue formation of hard-to-heal wounds
Methods	Trial design: RCT Setting: Israel Primary or secondary care: unclear Funding source: Arava Bio Tech Ltd.
Participants	People with hard-to-heal wound(s) of different etiologies including arterial ulcers, diabetic ulcers and venous ulcers, of at least 3 months duration
Interventions	People with wounds of ≥ 5 cm^2 and ≤ 100 cm^2 of at least 3 months duration that fail to respond to treatment with SoC during the screening run-in phase will be enrolled into the study. Eligible participants with wounds will be randomised and treated topically with AR/101+ SoC or placebo + SoC once daily for up to 14 days.
Outcomes	Comparison of the formation of new granulation tissue, according to a Granulation Score Percentage of participants ready for skin grafting or healing by secondary intention Per cent of participant responders of ≥ 75% granulation tissue during two weeks of treatment Mean time to response (≥ 75% of granulation tissue) during treatment
Starting date	August 2016
Contact information	Sourasky Medical Center, Tel Aviv, Israel, 96105 Contact: Eyal Gur, MD; Tamar Tennenbaum, MD
Notes	Status: unknown (recruitment not yet started)

NCT03275831

Trial name or title	A pilot study to investigate the efficacy of PluroGel in healing venous and mixed aetiology leg ulcers
Methods	Trial design: RCT Setting: UK Primary or secondary care: unclear Funding source: Medline Industries
Participants	People with venous and mixed aetiology leg ulcers
Interventions	Participants will be randomised at week 2 to receive either topical PluroGel or Intrasite gel (an alternative topical hydrogel product)
Outcomes	Change in wound size Change in average per cent reduction of slough in wound bed over 4 week treatment Participant evaluation Staff evaluation

NCT03275831 *(Continued)*

Starting date	8 January 2018
Contact information	Aneurin Bevan University Health Board, Newport, South Wales, United Kingdom, NP20 4SZ Cardiff & Vale University Health Board, Cardiff, Wales, United Kingdom, CF14 4XN Contact: Keith G Harding Contact: Nicola Ivins
Notes	Status: recruiting

NCT03468816

Trial name or title	Wound dressing with moisture sensor
Methods	Trial design: RCT Setting: Sweden Primary or secondary care: unclear Funding source: Vårdcentralen Åby
Participants	People with leg ulcers
Interventions	Six participants will be recruited in the study and two different sensors will be compared in a cross-over design. After inclusion the leg ulcer will be dressed with a sensor of type A or type B
Outcomes	Sensor activation Complications Level of usability
Starting date	1 April 2018
Contact information	Contact: MD Berglind Hudkliniken Recruiting Linköping, Region Östergötland, Sweden
Notes	Status: recruiting

QoL: quality of life
RCT: randomised controlled trial
SoC: standard of care

APPENDICES

Appendix 1. Database search strategies

Source	Search strategy	Hits retrieved
CENTRAL via CRSO	#1 MESH DESCRIPTOR Leg Ulcer EXPLODE TREES 1 1658	1557

(Continued)

#2 MESH DESCRIPTOR Skin Ulcer EXPLODE ALL TREES 2405

#3 ((arter* or foot or leg or lower or mixed) adj3 ulcer*):TI,AB,KY 2677

#4 #1 OR #2 OR #3 3756

#5 MESH DESCRIPTOR Biological Dressings EXPLODE ALL TREES 82

#6 MESH DESCRIPTOR Occlusive Dressings EXPLODE ALL TREES 449

#7 MESH DESCRIPTOR HYDROGELS EXPLODE ALL TREES 305

#8 MESH DESCRIPTOR ALGINATES EXPLODE ALL TREES 232

#9 dressing*:TI,AB,KY 4199

#10 (ActivHeal or Allevyn or Avazorb or Biatain or Copa or LyoFoam or PermaFoam or PolyMem or Suprasorb or Tegaderm or Tielle or Transobent or Trufoam or Urgo-Cell):TI,AB,KY 244

#11 (hydrocolloid* or alginate* or hydrogel*):TI,AB,KY 2114

#12 (foam or bead or film*):TI,AB,KY 5673

#13 (tulle or gauze):TI,AB,KY 825

#14 (non adj2 adher*):TI,AB,KY 909

#15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 14998

#16 MESH DESCRIPTOR Administration, Topical EXPLODE ALL TREES 14404

#17 MESH DESCRIPTOR Anti-Infective Agents, Local EXPLODE ALL TREES 8227

#18 MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES 27517

#19 MESH DESCRIPTOR Anti-Inflammatory Agents EXPLODE ALL TREES 41974

#20 MESH DESCRIPTOR GLUCOCORTICOIDS EXPLODE ALL TREES 16978

#21 MESH DESCRIPTOR ESTROGENS EXPLODE ALL TREES 7217

#22 MESH DESCRIPTOR ENZYMES EXPLODE ALL TREES 28651

#23 MESH DESCRIPTOR Growth Substances EXPLODE ALL TREES 25458

#24 MESH DESCRIPTOR COLLAGEN EXPLODE ALL TREES 2294

#25 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 129058

#26 #16 AND #25 5837

#27 (topical adj2 (steroid* or corticosteroid* or glucocorticoid*)):TI,AB,KY 1909

#28 (topical adj2 (oestrogen or estrogen)):TI,AB,KY 42

#29 (topical adj2 enzym*):TI,AB,KY 11

#30 (topical adj2 growth factor*):TI,AB,KY 31

#31 (topical adj2 collagen):TI,AB,KY 39

#32 (topical adj2 silver):TI,AB,KY 47

#33 (topical adj3 (agent* or preparation* or therap* or treatment*)):TI,AB,KY 7477

#34 MESH DESCRIPTOR OINTMENTS EXPLODE ALL TREES 1788

(Continued)

	#35 MESH DESCRIPTOR HONEY EXPLODE ALL TREES 136 #36 honey:TI,AB,KY 486 #37 (ointment* or lotion* or cream*):TI,AB,KY 10198 #38 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 17152 #39 #15 OR #26 OR #38 33816 #40 #4 AND #39 3756 #41 01/01/2014 TO 28/01/2019:CD 579835 #42 #40 AND #41 1557	
Clinicaltrials.gov	Leg Ulcer OR Skin Ulcer OR arterial leg ulcers OR foot ulcer OR mixed ulcer | dressing OR dressings OR hydrogel OR alginates OR Anti-Infective Agents OR Anti-Bacterial Agents OR Anti-Inflammatory Agents OR GLUCOCORTICOIDS OR ESTROGENS OR ENZYMES OR Growth Substances OR COLLAGEN	157
ICTRP Search Portal	Leg Ulcer OR Skin Ulcer OR arterial leg ulcers OR foot ulcer OR mixed ulcer | dressing OR dressings OR hydrogel OR alginates OR Anti-Infective Agents OR Anti-Bacterial Agents OR Anti-Inflammatory Agents OR GLUCOCORTICOIDS OR ESTROGENS OR ENZYMES OR Growth Substances OR COLLAGEN	86
Medline (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) 1946 to present 2017, 2018 and 2019 only	1 exp Leg Ulcer/ 2 exp Skin Ulcer/ 3 ((arter* or foot or leg or lower or mixed) adj3 ulcer*).ti,ab. 4 or/1-3 5 exp Biological Dressings/ 6 exp Occlusive Dressings/ 7 exp HYDROGELS/ 8 exp ALGINATES/ 9 dressing*.ti,ab. 10 (ActivHeal or Allevyn or Avazorb or Biatain or Copa or LyoFoam or PermaFoam or PolyMem or Suprasorb or Tegaderm or Tielle or Transobent or Trufoam or UrgoCell).ti,ab. 11 (hydrocolloid* or alginate* or hydrogel*).ti,ab. 12 (foam or bead or film*).ti,ab. 13 (tulle or gauze).ti,ab. 14 (non adj2 adher*).ti,ab. 15 or/1-14 16 exp Administration, Topical/ 17 exp Anti-Infective Agents, Local/ 18 exp Anti-Bacterial Agents/ 19 exp Anti-Inflammatory Agents/	1160

(Continued)

20 exp GLUCOCORTICOIDS/

21 exp ESTROGENS/

22 exp ENZYMES/

23 exp Growth Substances/

24 exp COLLAGEN/

25 or/17-24

26 16 and 25

27 (topical adj2 (steroid* or corticosteroid* or glucocorticoid*)).ti,ab.

28 (topical adj2 (oestrogen or estrogen)).ti,ab.

29 (topical adj2 enzym*).ti,ab.

30 (topical adj2 growth factor*).ti,ab.

31 (topical adj2 collagen).ti,ab.

32 (topical adj2 silver).ti,ab.

33 (topical adj3 (agent* or preparation* or therap* or treatment*)).ti,ab.

34 exp OINTMENTS/

35 exp HONEY/

36 honey.ti,ab.

37 (ointment* or lotion* or cream*).ti,ab.

38 or/27-37

39 15 or 26 or 38

40 4 and 39

41 randomized controlled trial.pt.

42 controlled clinical trial.pt.

43 randomized.ab.

44 placebo.ab.

45 drug therapy.fs.

46 randomly.ab.

47 trial.ab.

48 groups.ab.

49 or/41-48

50 exp animals/ not humans.sh.

51 49 not 50

52 40 and 51

53 (2014* or 2015* or 2016* or 2017* or 2018* or 2019*).ed.

(Continued)

	54 52 and 53	
EMBASE 2017, 2018 and 2019 only	1 exp leg ulcer/ 2 exp skin ulcer/ 3 ((arter* or foot or leg or lower or mixed) adj3 ulcer*).ti,ab. 4 or/1-3 5 exp biological dressing/ 6 exp occlusive dressing/ 7 exp hydrogel/ 8 exp alginic acid/ 9 dressing*.ti,ab. 10 (ActivHeal or Allevyn or Avazorb or Biatain or Copa or LyoFoam or PermaFoam or PolyMem or Suprasorb or Tegaderm or Tielle or Transobent or Trufoam or UrgoCell).ti,ab. 11 (hydrocolloid* or alginate* or hydrogel*).ti,ab. 12 (foam or bead or film*).ti,ab. 13 (tulle or gauze).ti,ab. 14 (non adj2 adher*).ti,ab. 15 or/1-14 16 exp topical drug administration/ 17 exp topical antiinfective agent/ 18 exp antiinfective agent/ 19 exp antiinflammatory agent/ 20 exp glucocorticoid/ 21 exp estrogen/ 22 exp enzyme/ 23 exp growth promotor/ 24 exp collagen/ 25 or/17-24 26 16 and 25 27 (topical adj2 (steroid* or corticosteroid* or glucocorticoid*)).ti,ab. 28 (topical adj2 (oestrogen or estrogen)).ti,ab. 29 (topical adj2 enzym*).ti,ab. 30 (topical adj2 growth factor*).ti,ab. 31 (topical adj2 collagen).ti,ab. 32 (topical adj2 silver).ti,ab.	2433

(Continued)

	33 (topical adj3 (agent* or preparation* or therap* or treatment*)).ti,ab. 34 exp ointment/ 35 exp honey/ 36 honey.ti,ab. 37 (ointment* or lotion* or cream*).ti,ab. 38 or/27-37 39 15 or 26 or 38 40 4 and 39 41 randomized controlled trial/ 42 controlled clinical trial/ 43 random$.ti,ab. 44 randomization/ 45 intermethod comparison/ 46 placebo.ti,ab. 47 (compare or compared or comparison).ti. 48 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 49 (open adj label).ti,ab. 50 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 51 double blind procedure/ 52 parallel group$1.ti,ab. 53 (crossover or cross over).ti,ab. 54 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 55 (assigned or allocated).ti,ab. 56 (controlled adj7 (study or design or trial)).ti,ab. 57 (volunteer or volunteers).ti,ab. 58 trial.ti. 59 or/41-58 60 40 and 59 61 (2017* or 2018* or 2019*).em. 62 60 and 61 63 from 62 keep 2001-2433	
CINAHL 2017, 2018 and 2019 only	S55 S53 AND S54 S54 EM 2017 OR EM 2018 OR 2019 EM	501

(Continued)

S53 S39 AND S52

S52 S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51

S51 MH "Random Assignment"

S50 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies"

S49 MH "Crossover Design"

S48 MH "Factorial Design"

S47 MH "Placebos"

S46 MH "Clinical Trials"

S45 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study"

S44 TX crossover OR "cross-over"

S43 AB placebo*

S42 TX random*

S41 TX trial*

S40 TX "latin square"

S39 S4 AND S38

S38 S15 OR S25 OR S37

S37 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36

S36 TX ointment* or lotion* or cream*

S35 TX honey

S34 (MH "Honey")

S33 (MH "Ointments")

S32 topical N3 (agent* or preparation* or therap* or treatment*)

S31 topical N2 silver

S30 topical N2 collagen

S29 topical N2 growth factor*

S28 topical N2 enzym*

S27 topical N2 (oestrogen or estrogen)

S26 topical N2 (steroid* or corticosteroid* or glucocorticoid*)

S25 S16 AND S24

S24 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23

S23 (MH "Collagen")

S22 (MH "Growth Substances+")

S21 (MH "Enzymes+")

(Continued)

	S20 (MH "Estrogens+") S19 (MH "Glucocorticoids+") S18 (MH "Antiinflammatory Agents+") S17 (MH "Antiinfective Agents, Local+") S16 (MH "Administration, Topical+") S15 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 S14 TX non N2 adher* S13 TX tulle or gauze S12 TX foam or bead or film* S11 TX hydrocolloid* or alginate* or hydrogel* S10 TX ActivHeal or Allevyn or Avazorb or Biatain or Copa or LyoFoam or PermaFoam or PolyMem or Suprasorb or Tegaderm or Tielle or Transobent or Trufoam or UrgoCell S9 TX dressing* S8 (MH "Alginates") S7 (MH "Hydrogel Dressings") S6 (MH "Occlusive Dressings") S5 (MH "Biological Dressings") S4 S1 OR S2 OR S3 S3 TX (arter* or foot or leg or lower or mixed) N3 ulcer* S2 (MH "Skin Ulcer+") S1 (MH "Leg Ulcer+")	
AMED 2017, 2018 and 2019 only	1 exp Skin Ulcer/ 2 ((arter* or foot or leg or lower or mixed) adj3 ulcer*).ti,ab. 3 or/1-2 4 dressing*.ti,ab. 5 (ActivHeal or Allevyn or Avazorb or Biatain or Copa or LyoFoam or PermaFoam or PolyMem or Suprasorb or Tegaderm or Tielle or Transobent or Trufoam or UrgoCell).ti,ab. 6 (hydrocolloid* or alginate* or hydrogel*).ti,ab. 7 (foam or bead or film*).ti,ab. 8 (tulle or gauze).ti,ab. 9 (non adj2 adher*).ti,ab. 10 or/1-9 11 exp Antiinflammatory agents/	7

(Continued)

12 exp Estrogens/

13 exp Enzymes/

14 exp Growth substances/

15 exp Collagen/

16 or/11-15

17 10 and 16

18 (topical adj2 (steroid* or corticosteroid* or glucocorticoid*)).ti,ab.

19 (topical adj2 (oestrogen or estrogen)).ti,ab.

20 (topical adj2 enzym*).ti,ab.

21 (topical adj2 growth factor*).ti,ab.

22 (topical adj2 collagen).ti,ab.

23 (topical adj2 silver).ti,ab.

24 (topical adj3 (agent* or preparation* or therap* or treatment*)).ti,ab.

25 exp Honey/

26 honey.ti,ab.

27 (ointment* or lotion* or cream*).ti,ab.

28 or/18-27

29 10 or 17 or 28

30 3 and 29

31 exp CLINICAL TRIALS/

32 RANDOM ALLOCATION/

33 DOUBLE BLIND METHOD/

34 Clinical trial.pt.

35 (clinic* adj trial*).tw.

36 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw.

37 PLACEBOS/

38 placebo*.tw.

39 random*.tw.

40 PROSPECTIVE STUDIES/

41 or/31-40

42 30 and 41

43 ("2017" or "2018" or "2019").yr.

44 42 and 43

45 from 44 keep 1-7

WHAT'S NEW

Date	Event	Description
31 May 2019	New search has been performed	New search run. One new study included, 19 studies excluded, two new studies assessed as 'awaiting classification' and four new ongoing studies identified.
31 May 2019	New citation required but conclusions have not changed	New search run. One new study included, 19 studies excluded, two new studies assessed as 'awaiting classification' and four new ongoing studies identified. New author joined review team. Text updated to reflect current Cochrane standards. 'Summary of findings' table added. No change to conclusions.

HISTORY

Protocol first published: Issue 4, 1999
Review first published: Issue 1, 2003

Date	Event	Description
16 March 2015	New citation required but conclusions have not changed	New authors have taken over this review. Searches rerun; no new studies included, 42 new studies excluded, one previously included study now considered excluded. Review updated using current Cochrane reporting standards including risk of bias. No change to conclusions
16 March 2015	New search has been performed	Searches rerun; no new studies included, 42 new studies excluded, one previously included study now considered excluded
12 August 2008	Amended	Converted to new review format.
10 November 2006	New citation required but conclusions have not changed	Re-ran searches. New trial added to included studies and new trials added to excluded studies.

CONTRIBUTIONS OF AUTHORS

CB: evaluated studies for inclusion and exclusion, performed risk of bias, and managed the updating of the review text.
FP: performed risk of bias, and assisted in the updating of the review text, with expert input for the background and discussion of the topic.
RF: managed the updating of the review text.

DECLARATIONS OF INTEREST

CB: none known. CB is employed as Assistant Managing Editor for Cochrane Vascular. Editorial tasks were carried out by other members of the Cochrane Vascular editorial base
FP: has declared that she received payment for consultancy at the Molnycke Healthcare Key Opinion Leaders Group. This is a wound care company that supplies dressings, that are used in arterial leg ulcers. She received travel expenses and her institution received payment for speaking at NHI pressure ulcer session
RF: none known

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- No sources of support supplied

External sources

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  The Cochrane Vascular editorial base is supported by the Chief Scientist Office

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2019 update

The original protocol and previous versions of this review planned to report 'economic analysis'. This has now been removed as an outcome as the team and Cochrane Vascular editorial base do not have the required expertise to present a full economic analysis of interventions. Any information provided on cost in future updates will be reported in the discussion if appropriate.

2015 update

In the Nelson 2007 version of the review, the authors classified Hartman 2002 as an included study. However, on further investigation into the trial design, we decided that the control group was not adequate to describe this as an RCT or CCT. We therefore reclassified Hartman 2002 as an excluded study.

In the Types of interventions section, we have added 'compression' interventions as exclusionary criteria as we felt it was an important distinction to make. Making this alteration did not effect the inclusion or exclusion of any previously considered studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Wound Healing; Administration, Topical; Arteries; Bandages, Hydrocolloid; Leg Ulcer [*therapy]; Occlusive Dressings; Ointments [*therapeutic use]; Randomized Controlled Trials as Topic; Varicose Ulcer [therapy]

MeSH check words

Humans