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Debridement for venous leg ulcers (Review)

Gethin G, Cowman S, Kolbach DN

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Debridement for venous leg ulcers.
Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD008599.
DOI: 10.1002/14651858.CD008599.pub2.

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[Intervention Review]

Debridement for venous leg ulcers

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Editorial group: Cochrane Wounds Group.
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2015.

Citation: Gethin G, Cowman S, Kolbach DN. Debridement for venous leg ulcers. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD008599. DOI: 10.1002/14651858.CD008599.pub2.

ABSTRACT

Background

Venous ulcers (also known as varicose or venous stasis ulcers) are a chronic, recurring and debilitating condition that affects up to 1% of the population. Best practice documents and expert opinion suggests that the removal of devitalised tissue from venous ulcers (debridement) by any one of six methods helps to promote healing. However, to date there has been no review of the evidence from randomised controlled trials (RCTs) to support this.

Objectives

To determine the effects of different debriding methods or debridement versus no debridement, on the rate of debridement and wound healing in venous leg ulcers.

Search methods

In February 2015 we searched: The Cochrane Wounds Group Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE and EBSCO CINAHL. There were no restrictions with respect to language, date of publication or study setting. In addition we handsearched conference proceedings, journals not cited in MEDLINE, and the bibliographies of all retrieved publications to identify potential studies. We made contact with the pharmaceutical industry to enquire about any completed studies.

Selection criteria

We included RCTs, either published or unpublished, which compared two methods of debridement or compared debridement with no debridement. We presented study results in a narrative form, as meta-analysis was not possible.

Data collection and analysis

Independently, two review authors completed all study selection, data extraction and assessment of trial quality; resolution of disagreements was completed by a third review author.

Main results

We identified 10 RCTs involving 715 participants. Eight RCTs evaluated autolytic debridement and included the following agents or dressings: biocellulose wound dressing (BWD), non-adherent dressing, honey gel, hydrogel (gel formula), hydrofibre dressing, hydrocolloid dressings, dextranomer beads, Edinburgh University Solution of Lime (EUSOL) and paraffin gauze. Two RCTs evaluated

enzymatic preparations and one evaluated biosurgical debridement. No RCTs evaluated surgical, sharp or mechanical methods of debridement, or debridement versus no debridement. Most trials were at a high risk of bias.

Three RCTs assessed the number of wounds completely debrided. All three of these trials compared two different methods of autolytic debridement (234 participants), with two studies reporting statistically significant results: one study (100 participants) reported that 40/50 (80%) ulcers treated with dextranomer beads and 7/50 (14%) treated with EUSOL achieved complete debridement (RR 5.71, 95% CI 2.84 to 11.52); while the other trial (86 participants) reported the number of ulcers completely debrided as 31/46 (76%) for hydrogel versus 18/40 (45%) for paraffin gauze (RR 0.67, 95% CI 0.45 to 0.99). One study (48 participants) reported that by 12 weeks, 15/18 (84%) ulcers treated with BWD had achieved a 75% to 100% clean, granulating wound bed versus 4/15 (26%) treated with non-adherent petrolatum emulsion-impregnated gauze.

Four trials assessed the mean time to achieve debridement: one (86 participants) compared two autolytic debridement methods, two compared autolytic methods with enzymatic debridement (71 participants), and the last (12 participants) compared autolytic with biosurgical debridement; none of the results achieved statistical significance.

Two trials that assessed autolytic debridement methods reported the number of wounds healed at 12 weeks. One trial (108 participants) reported that 24/54 (44%) ulcers treated with honey healed versus 18/54 (33%) treated with hydrogel (RR (adjusted for baseline wound diameter) 1.38, 95% CI 1.02 to 1.88; P value 0.037). The second trial (48 participants) reported that 7/25 (28%) ulcers treated with BWD healed versus 7/23 (30%) treated with non-adherent dressing.

Reduction in wound size was assessed in five trials (444 participants) in which two autolytic methods were compared. Results were statistically significant in one three-armed trial (153 participants) when cadexomer iodine was compared to paraffin gauze (mean difference 24.9 cm^2, 95% CI 7.27 to 42.53, P value 0.006) and hydrocolloid compared to paraffin gauze (mean difference 23.8 cm^2, 95% CI 5.48 to 42.12, P value 0.01). A second trial that assessed reduction in wound size based its results on median differences and, at four weeks, produced a statistically significantly result that favoured honey over hydrogel (P value < 0.001). The other three trials reported no statistically significant results for reduction in wound size, although one trial reported that the mean percentage reduction in wound area was greater at six and 12 weeks for BWD versus a non-adherent dressing (44% versus 24% week 6; 74% versus 54% week 12).

Pain was assessed in six trials (544 participants) that compared two autolytic debridement methods, but the results were not statistically significant. No serious adverse events were reported in any trial.

Authors' conclusions

There is limited evidence to suggest that actively debriding a venous leg ulcer has a clinically significant impact on healing. The overall small number of participants, low number of studies and lack of meta-analysis in this review precludes any strong conclusions of benefit. Comparisons of different autolytic agents (hydrogel versus paraffin gauze; Dextranomer beads versus EUSOL and BWD versus non-adherent dressings) and Larvae versus hydrogel all showed statistically significant results for numbers of wounds debrided. Larger trials with follow up to healing are required.

PLAIN LANGUAGE SUMMARY

Debridement for venous leg ulcers

Background

Venous leg ulcers are a common type of leg wound. They can cause pain, stress, social isolation and depression. These ulcers take approximately 12 weeks to heal and the best and first treatment to try is compression bandages. In an attempt to improve the healing process it is thought that removing dead or dying tissue (debridement) from the surface of the wound can speed up healing. Six different methods can be used to achieve debridement: use of an instrument such as a scalpel (with or without anaesthesia - surgical debridement and sharp debridement, respectively); washing solutions and dressings (mechanical debridement); enzymes that break down the affected tissue (enzymatic debridement); moist dressings or natural agents, or both, to promote the wound's own healing processes (autolytic debridement); or maggots (biosurgical debridement).

Objectives

We assessed evidence from medical research to try to determine how effective these different methods of debridement are in debriding wounds. We also wanted to understand what effect, if any, debridement has on the healing of venous ulcers, and whether any method of debridement is better than no debridement when it comes to wound healing.

Search methods

We searched a wide range of electronic databases and also reports from conferences up to 10 February 2015. We included studies written in any language that included men and women of any age, cared for in any setting, from any country, and we did not set a limit on the years in which studies were published. We were only interested in robust research, and so restricted our search to randomised controlled trials (in which people are randomly allocated to the methods being tested). All trial participants were required to have a venous ulcer with dead tissue (slough) present in the wound.

Results

We found ten studies that included a total of 715 participants. These were conducted in a range of countries and care settings. Participants had an average age of 68 years, and there were more women than men. Most of the studies were small, with half of them having fewer than 67 participants. The trials tested a range of debridement methods including: autolytic methods such as non-adherent dressings; very small beads; biocellulose dressings; honey; gels; gauze and methods using enzymes. Autolytic methods of debridement, were the most frequently tested. We identified no studies that tested surgical, sharp or mechanical methods of debridement and no studies that tested debridement against no debridement.

It was not possible to say whether any of the methods evaluated performed better than the rest. There was some evidence to suggest that sloughy ulcers that had more than 50% of slough removed after four weeks were more likely to heal by 12 weeks; and some evidence to suggest that ulcers debrided using honey were more likely to heal by 12 weeks than ulcers debrided with hydrogel. What remains uncertain at this time is whether debridement itself, or any particular form of debridement is beneficial in the treatment of venous ulcers.

The overall quality of the evidence we identified was low, as studies were small in size, and most were of short duration. There were differences between them in terms of the amount of slough in the wound bed of the ulcers at the start of the trial, in treatment regimes, the duration of treatments, and the methods used to assess how well the debridement treatments had worked. In six trials, the people assessing the wounds were aware of the type of treatment each patient was receiving, which may have affected the impartiality of their evaluations. Five studies did not provide information on all the results (outcomes) in their trials, and this missing information on important benefits or harms of the debridement method being evaluated meant that those trials were at a high risk of bias and of producing unreliable results. Only two studies reported side effects due to the treatment; these included maceration (or wetness) of the skin around the ulcers, infection and skin inflammation.

BACKGROUND

Description of the condition

Venous leg ulcers (also known as varicose or stasis ulcers) are caused by chronic venous disease (Margolis 2000). While the exact physiological process that leads to the development of a venous ulcer is not yet fully understood, it is known that the underlying venous reflux and high venous pressures are significant contributory factors (Hahn 1999; O'Brien 2000). Venous ulcers affect approximately 0.2% of the population at any point in time (Nelzen 1996; O'Brien 2000; Moffatt 2004), and cause pain, anxiety, social isolation and depression (Callam 1988; Rich 2003). While prevalence increases with age to approximately 1.3% in those over 70 years, it is important to note that almost 50% of ulcers occur before the age of 65 years (O'Brien 2000; Moffatt 2004). Compression therapy in the form of bandages or stockings is regarded as the first line of treatment in uncomplicated venous ulcers (O'Meara 2012). However, healing outcomes remain poor, as on average only 50% will heal after 26 weeks of compression therapy, increasing to 87% at 52 weeks (Milic 2009). In addition, venous ulcers are associated with high recurrence rates of 50% within three months of healing (Callam 1987; Thomson 1996), 16% at 12 months (Clarke-Moloney 2014), and 36% by five years (Nelson 2006). A venous ulcer with an area less than 5 cm^2 and a duration of less than six months at baseline (at start of treatment) are two positive

predictors of healing at 24 weeks (Margolis 2000). Beyond this, little is known about healing outcomes based on the condition of the wound bed at the start of treatment, although ulcers with more than 50% of their surface covered with fibrin reportedly take longer to heal than those without (Milic 2009).

The underlying pathogenic abnormalities of chronic wounds such as venous ulcers cause a continual build-up of devitalised (hypoxic) and necrotic (dead) tissue, and expert opinion proposes that regular debridement is necessary to reduce the necrotic burden and to achieve healthy granulation tissue (Schultz 2003; Wolcott 2012; Strohal 2013). Emerging research suggests that serial sharp debridement may improve healing outcomes through removal of microbial biofilm, and the potential for a time-dependent window of opportunity in which antimicrobial therapy may be of benefit has been shown in one study (Wolcott 2012). Debridement is the removal of devitalised, necrotic or infected tissue, or fibrin or foreign material from a wound, such as a venous leg ulcer (NICE 2001). The process of debridement includes any method that removes cell debris, dead fibrinous material, metabolic waste, exudate and infected or contaminated material (NICE 2001; Ayello 2004a). These methods include surgical, sharp, enzymatic, mechanical, autolytic, chemical and biosurgical (larvae/maggots) techniques. It is important that the choice of both debriding method and debriding agent is based on best scientific evidence, taking into account both cost and effectiveness data (Lewis 2001); the decision maker must also consider the skill and resources of the clinician and patient goals.

Description of the intervention

Surgical debridement

Surgical debridement is performed in the operating theatre and is undertaken when there is extensive devitalised or necrotic tissue, or advancing cellulitis (infection of lower layers of skin), infected bone or sepsis (Baharestani 1999). This method is rapid, but can be painful and has associated risks of bleeding, transient bacteraemia (bacteria in the blood), damage to vital structures including tendon sheaths and nerves, and potential risk from anaesthesia (Baharestani 1999). The number of personnel and degree of expertise required to perform surgical debridement increases the cost, and limits the availability, of the procedure (Eloy 1999). It is, however, a rapid method of debridement and is highly selective to underlying tissue (Himel 1995; Ayello 2004a). It must be used with caution in patients with clotting disorders or on anticoagulant therapy (Baharestani 1999; Ayello 2004a), and also patients with diabetes or peripheral vascular disease, or both (Leaper 2002).

Sharp debridement

This is the removal of devitalised or necrotic tissue or foreign material from within and around the wound to expose healthy tissue using a sterile scalpel, scissors, or both (Sieggreen 1997; Leaper 2002). It is often performed at the bedside or in a procedure room (Leaper 2002). It has been termed the 'gold standard' of wound debridement (Leaper 2002), but Sieggreen 1997 proposes that it carries the greatest risk of tissue damage of any of the debridement methods. It is imprecise, but the main benefit is the rapidity with which dead tissue can be removed, which is useful when there is advancing necrosis or sepsis (Sieggreen 1997). Practitioners using this method need training, and competency must be demonstrated, including an understanding of the underlying anatomical structures and how to carry out the procedure safely (Leaper 2002; Davies 2004). This method is less aggressive than surgical debridement, but the associated risks are the same (except for anaesthesia), and pain management is important (Baharestani 1999). A recent systematic review of topical agents or dressings for pain in venous leg ulcers identified six trials that showed Eutectic Mixture of Local Anaesthetics 5% (EMLA) cream to be statistically significantly superior to placebo cream or 'no anaesthetic' for the treatment of pain caused by leg ulcer debridement when measured on a 100 mm scale (mean difference -20.65 mm, 95% CI -12.19 to -29.11; Briggs 2012).

Mechanical debridement

Mechanical debridement involves using an active physical process to remove debris from the wound bed (Davies 2004). This form of debridement is non-selective, slow, and often painful (Ayello 2004b; Davies 2004). Irrigation with saline (at a pressure of between 4 lb/inch^2 to 15 lb/inch^2), saline aerosol sprays or syringe using a 30 ml 18 to 19 gauge needle can achieve the high pressures required (Ayello 2004b; Davies 2004). Two of the best known methods of mechanical debridement are wet-to-dry saline dressings and whirlpool therapy.

Wet-to-dry dressings are non-selective, slow, and contribute to establishing an environment with increased potential for infection in large wounds with extensive necrosis (Baharestani 1999). In this technique wet gauze is applied to a wound and allowed to dry out. Once dried it is removed from the wound bed and takes with it viable and non-viable tissue that has adhered to the gauze.

Whirlpool therapy is used to loosen and wash away surface debris, surface bacteria, necrotic tissue, dressing residue and wound exudate (Baharestani 1999). Caution must be exercised in the type of whirlpool selected, and also with regard to the wound pathogenesis (cause), vascularity, coagulopathies (clotting disorders), neuropathies (damage or disease of nerves), mental status, general physical status, and mobility status of the patient (Baharestani 1999).

Autolytic debridement

Autolytic debridement occurs to some extent in all wounds; it is a highly selective process in which the patient's macrophage cells destroy bacteria by means of endogenous proteolytic enzymes such as collagenase, elastase and myeloperoxidase that liquefy and separate necrotic tissue and pseudoeschar spontaneously from healthy tissue (Baharestani 1999). Wound fluid contains macrophages and neutrophils that digest and dissolve necrotic tissue (Sieggreen 1997; Ayello 2004a). Autolytic debridement uses the body's endogenous (self-produced) enzymes to rid a wound slowly of necrotic tissue. In a moist wound, phagocytic cells and proteolytic enzymes can soften and liquefy the necrotic tissue, which is then digested by macrophages (Ayello 2004a). White blood cells, antibodies, lytic enzymes and growth factors concentrate in the wound fluid (Sieggreen 1997). Moist dressings allow endogenous enzymes in the wound fluid to liquefy necrotic tissue selectively (Sieggreen 1997). One of the potential problems is the risk of maceration (damage due to wetness) to surrounding skin as moisture levels are particularly high underneath the retentive dressing (Davies 2004).

Autolytic debridement is a highly selective form of debridement that requires minimal clinical training, is painless, and, although slow, leaves a clearly demarcated line between living and dead tissue (Sieggreen 1997; Ayello 2004a). It requires at least some level of wound exudate in order to be effective (Ayello 2004b). Older populations have been observed to produce decreased amounts of endogenous proteases (enzymes that break down protein), such as collagenase in their wound fluid (Himel 1995). Baharestani 1999 argues that this decreased production and activity of endogenous collagenase may lead to insufficient debridement of necrotic tissue, decreased deposition of granulation tissue and matrix remodeling in the wound, as well as to decreased proliferation and migration of keratinocytes, all of which are required for effective healing.

Autolytic debridement relies upon the activity of leukocytes (white blood cells) and the presence of endogenous proteolytic enzymes within wound fluid, and thus is dependent on the local wound environment, in particular the state of wound hydration, but also the wound temperature, pH and availability of enzymatic co-factors (Sieggreen 1997; Baharestani 1999).The use of autolytic debridement is not recommended for clinically infected wounds, those with a high potential for anaerobic (oxygen free) infection, or when there is ischaemia (impeded blood flow) of the limb or digits, as it may potentially lead to more serious infection (Baharestani 1999; Ayello 2004b; Davies 2004).

Enzymatic debridement

Enzymatic debridement is accomplished by the topical (surface) application of an exogenous (not self-produced) enzyme that works with endogenous enzymes to digest necrotic tissue discriminantly (Baharestani 1999). The concept of using proteolytic enzymes to digest dead tissue in dirty, infected wounds is an old one that may stem from the observations of natives of tropical countries where the pap-rich latex from the skin of the green fruit of the papaw tree (*Carica papaya*) has long been used for treating eczema, warts, ulcers and other sores (Brett 2003). Various types of enzymes target specific necrotic tissue such as protein, fibrin and collagen (Sieggreen 1997). Topical enzymatic preparations are derived from microbes, animals or plants (Brett 2003). These enzymatic agents are applied only to necrotic areas as they can irritate normal tissues and cause transient erythema (redness) in the peri-wound tissue (Sieggreen 1997). Enzymes can be inactivated with topical anti-infective agents containing heavy metals or acidic solutions that alter the pH (Sieggreen 1997; Ayello 2004a). It is proposed that caution should be exercised in the use of enzymatic agents by practitioners in patients that are debilitated or at a high risk of infection, and that prophylactic antibiotics should be administered to prevent bacteria from entering the bloodstream when the necrotic tissue separates from the live tissue (Sieggreen 1997).

Biosurgical debridement

Biosurgical debridement involves the use of sterile maggots (green bottle fly larvae: *Lucilia sericata*). The exact mechanism that lead these maggots to act as debriding agents are not entirely understood, but the form of debridement produced may be considered as being either mechanical or biochemical. Mechanical debridement is achieved through two processes: the 'mouth hooks' of the maggots; and their rough bodies that scratch the necrotic tissue (Gottrup 2011). They may also secrete a mixture of proteolytic (protein dissolving) enzymes, including trypsin and chymotrypsin-like collagenases, that transform nonviable tissue into a liquid substance that is easier for the maggots to digest (Blake 2007). However, the enzymes that maggots produce have the potential to damage keratinised epidermis (outer layer of skin) if applied in excess, or left in place for too long after debridement has been completed (Thomas 1999).

How the intervention might work

The underlying pathogenic abnormalities of chronic wounds such as venous ulcers cause a continual build-up of devitalised and necrotic tissue, and it is widely believed that regular debridement is necessary to reduce the necrotic burden and achieve healthy granulation tissue (Schultz 2003). Debridement is considered by some to be the single most important factor in the management of contaminated wounds and it has been argued that wound healing is impaired until it has been done (Gottrup 2011; Wolcott 2012; Strohal 2013). The potential consequences of failing to remove devitalised or necrotic tissue include a slower healing process, protein loss, risk of osteomyelitis (infection of bone), generalised infection and sepsis (Sieggreen 1997, Wolcott 2009). Additionally, the presence of necrotic tissue limits the ability to visualise the base of the wound and thus actual wound depth cannot be ascertained.

However, it is unclear whether actual debridement promotes faster healing, or whether wounds that are healing debride themselves.

Why it is important to do this review

While expert opinion suggests that healing is impaired in the presence of devitalised or necrotic tissue, or both, there is a need to evaluate the evidence from studies that set out to evaluate different methods of debridement, or of debridement versus no debridement, in a systematic review. Other Cochrane Reviews have considered the evidence for debriding foot ulcers in people with diabetes and surgical wounds (Dryburgh 2008; Edwards 2010). The systematic review of debridement for surgical wounds identified five relevant RCTs and concluded that currently there is no evidence to support any particular method of debridement or debriding agent for surgical wounds (Dryburgh 2008). The systematic review of debridement in diabetic foot ulcers identified five relevant studies and concluded that there is evidence (from three studies) that hydrogels compared to good wound care or moist saline gauze are significantly more effective in healing diabetic foot ulcers (risk ratio (RR) 1.84; (95% confidence interval (CI) 1.3 to 2.61). However, the evidence for debridement in venous leg ulcers has not yet been summarised.

As some methods of debridement are associated with pain (Bowers 2009; Ferreira-Valente 2011; Strohal 2013), it is important to understand the levels of pain associated with the interventions used to achieve debridement, and to document this in the review.

OBJECTIVES

To determine the effects of different debriding methods or debridement versus no debridement, on the rate of debridement and wound healing in venous leg ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), either published or unpublished, which compared:

- debridement with no debridement;
- different methods of debridement.

Studies using quasi-randomisation (e.g. alternation or odd/even case numbers) were not eligible and were excluded. There was no restriction on date of publication, language or publication status.

Types of participants

People of any age in any care setting, with a venous leg ulcer (also described as venous stasis or varicose ulcer) that contained devitalised or necrotic tissue, or both, were eligible for inclusion. We did not restrict eligibility based on the way in which venous ulcers were diagnosed, but studies must have referred to participants as having a venous ulcer.

Types of interventions

All methods of debridement (i.e. the removal of devitalised or necrotic tissue, or both, from the wound) compared with no debridement or any other method of debridement in people with venous ulcers.

Types of outcome measures

Primary outcomes

- The percentage (or number) of wounds completely debrided during the trial period.
- Time to complete debridement.
- Wound healing as measured by the time to complete healing or the number of wounds completely healed during the trial period.

Secondary outcomes

- The rate of reduction in wound size expressed in either absolute or relative terms.
- Pain measured on a validated scale
- Number of complications or adverse events reported.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify reports of relevant randomised clinical trials:

- Cochrane Wounds Group Specialized Register (Searched 10/02/15)
- The Cochrane Central Register of Controlled Trials (CENTRAL) - *The Cochrane Library*, (Issue 1, 2015)
- Ovid MEDLINE & Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (1946 to February 10 2015)
- Ovid EMBASE (1974 to February 9 2015)
- EBSCO CINAHL (1982 to February 9 2015)

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

#1 MeSH descriptor Debridement explode all trees
#2 (debrid* or slough* or deslough*):ti,ab,kw
#3 MeSH descriptor Larva explode all trees
#4 (larva* or maggot* or biosurgery or bio-surgery):ti,ab,kw
#5 (wound* NEXT (irrigat* or cleanse*)):ti,ab,kw
#6 whirlpool:ti,ab,kw
#7 (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase):ti,ab,kw
#8 MeSH descriptor Papain explode all trees
#9 papain:ti,ab,kw
#10 (hypochlorite or hydrogen peroxide):ti,ab,kw
#11 (malic acid or benzoid acid or salicylic acid or propylene glycol):ti,ab,kw
#12 "dakin solution":ti,ab,kw
#13 (dextranomer* or cadexomer or xerogel or eusol or debrisan):ti,ab,kw
#14 (polysaccharide NEXT (bead* or paste*)):ti,ab,kw
#15 (iodoflex or iodosorb):ti,ab,kw
#16 (((gauze or adherent or absorbent or tulle or polysaccaride or alginate or foam or hydrofibre or hydrofiber) NEXT dressing*) or saline gauze or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm):ti,ab,kw
#17 "wet-to-dry dressings":ti,ab,kw
#18 MeSH descriptor Honey explode all trees
#19 honey:ti,ab,kw
#20 MeSH descriptor Hydrogel explode all trees
#21 (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon):ti,ab,kw
#22 MeSH descriptor Zinc Oxide explode all trees
#23 "zinc oxide":ti,ab,kw
#24 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
#25 MeSH descriptor Leg Ulcer explode all trees
#26 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower NEXT extremit*) NEAR/2 ulcer*):ti,ab,kw
#27 (#25 OR #26)
#28 (#24 AND #27)

This strategy was adapted to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL (Appendix 1; Appendix 2; Appendix 3). The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) (Lefebvre 2011). The Ovid EMBASE search was combined with the trial filter developed by the UK Cochrane Centre (Lefebvre 2011). The CINAHL search was combined with the trial filter developed by the Scottish Intercollegiate Guidelines Network (SIGN 2009). There were no restrictions with respect to language, date of publication or study setting.

Searching other resources

We searched the bibliographies of all relevant publications identified by these strategies for further studies. In addition, we contacted members of the industry (Smith & Nephew and Convatec) to determine whether they had conducted any additional studies that we had not identified.

Data collection and analysis

Selection of studies

Two authors (GG, SC) independently assessed the titles and abstracts of all studies identified by the search and obtained full text copies of all relevant and potentially relevant trials. Two review authors (GG, SC) independently selected the trials using the inclusion criteria. A third review author (DH) independently cross-checked the final list of studies to ensure they met the inclusion and exclusion criteria. Disagreements were resolved by discussion.

Data extraction and management

One review author (GG) extracted data from included trials and recorded them on a standardised form. A second author (SC) checked the extracted data and reviewed them for accuracy; any disagreements were resolved by discussion with a third author (DK). Data from the trial by Gethin 2007 was extracted by SC and checked by DK. If the data from the trial report were inadequate, we sought additional information from the trial authors. We collected data on the topics listed below.

- Author, title, source of reference.
- Description of trial design.
- Care setting.
- Sample size calculation.
- Inclusion/exclusion criteria.
- Description of trial participants.
- Interventions in all groups.
- Outcomes.
- Adequacy of reporting of withdrawals.

One review author (GG) checked the data and entered them into RevMan 5.2 (RevMan 2012); another review author (SC) independently verified the input. We calculated treatment effects using RevMan 5.2.

Assessment of risk of bias in included studies

Each eligible study was critically appraised using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline

imbalance) (see Appendix 4 for details of criteria on which the judgements were based). We assessed blinding and completeness of outcome data for each outcome separately.

A narrative discussion of the risk of bias is presented, in addition to a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation according to study. This display of internal validity indicates the weight the reader may give to the results of each study.

Measures of treatment effect

The results for binary outcomes (e.g. number of wounds completely debrided, number of wounds healed) are presented as risk ratios (RR) with corresponding 95% confidence intervals (CI). The RR shows how many more or less times the outcome of interest (debridement or healing) occurs in the treatment group versus the control group. Continuous data (e.g. reduction in wound area) are presented as means and medians with corresponding 95% CI where available. Time to complete wound healing and time to debridement are time-to-event data and the most appropriate way of summarising this type of data is to use methods of survival analysis and express the intervention effect as a hazard ratio. It is not appropriate to analyse time-to-event data using methods for continuous outcomes (e.g. using mean times-to-event) as the relevant times are only known for the subset of participants who have had the event. Time to event data incorrectly presented as continuous data are presented in a narrative format.

Assessment of heterogeneity

We assessed the presence of clinical heterogeneity by comparing the trials in terms of study location and setting, characteristics of participants, co-morbidities and treatments participants may have been receiving on trial entry, definition of outcomes and main outcomes. For methodological diversity we made an assessment of the randomisation process, risk of bias and analytical method (intention-to-treat versus treated). We explored statistical diversity initially by looking at the estimates of treatment effect of included studies and considering whether we were confident that a combined estimate would give a meaningful description; we then considered whether study population (age and baseline characteristics) and the interventions were sufficiently similar. We assessed statistical heterogeneity either by using a forest plot to assess whether confidence intervals (CIs) from individual study estimates overlapped, or by using the I^2 statistic that examines the percentage of total variation across studies due to heterogeneity rather than to chance (Higgins 2011). Values of I^2 under 25% indicate a low level of heterogeneity and justify the use of a fixed-effect model for meta-analysis. Values of I^2 between 25% and 75% are considered moderate and a random-effects model should be used if pooling is otherwise appropriate. Values of I^2 over 75% indicate high levels of heterogeneity, and that meta-analysis is highly likely to be inappropriate.

Data synthesis

As set out in the protocol, we planned to group trials according to the method of debridement they employed. We intended to examine the effectiveness of debridement on the whole, and the contribution of individual components of debridement. We have presented a narrative summary of those trials that were sufficiently similar in terms of methods of debridement. Where moderate statistical heterogeneity was present, we have used a random-effects model for meta-analysis.

RESULTS

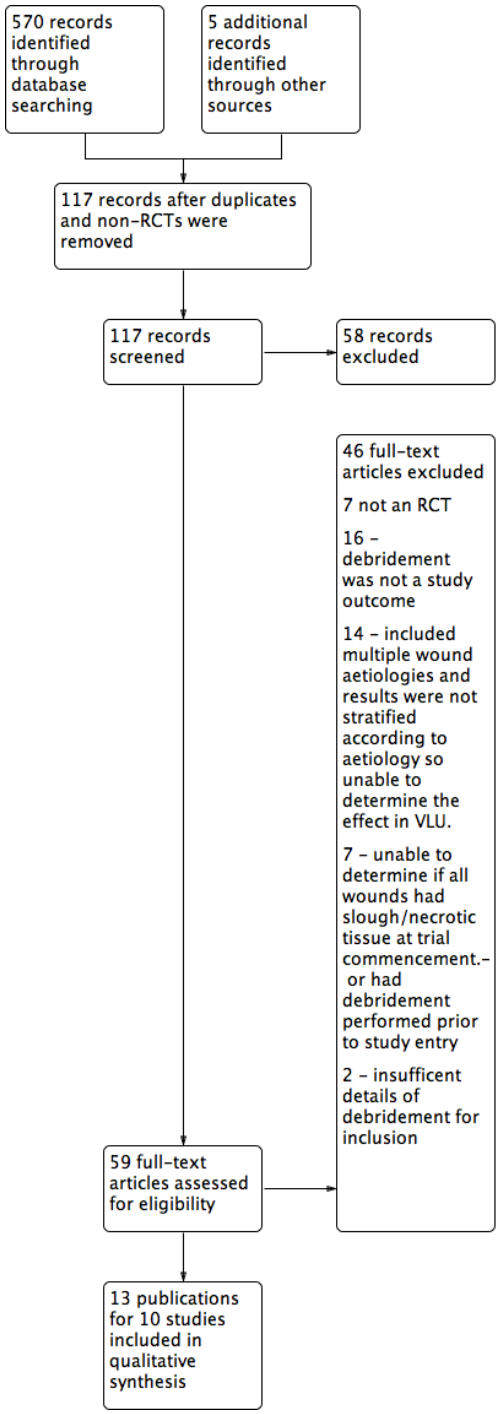
Description of studies

See:Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified a total of 575 citations. Our Initial review of citations eliminated duplicates and those studies that were not RCTs or that did not include venous ulcers with devitalised or necrotic tissue. A total of 117 remained, for which we obtained abstracts. We reviewed these to determine if they met the inclusion criteria for the review, and excluded a further 58. We retrieved full text papers of the remaining 59, and included ten studies (13 publications) in the review. A summary of the search results is presented in the PRISMA study flow diagram Figure 1. See also Characteristics of included studies and Characteristics of excluded studies. We contacted the authors of three trials for further details (Caputo 2008; Dumville 2009; Alvarez 2012), and we wish to thank authors Alvarez 2012 and Dumville 2009 for their response. We did not consider it feasible to contact the authors of some of the older trials (published before 1990), due to the length of time since the trials had been carried out. Replies from industry (Smith & Nephew, and Convatec) did not yield any additional studies.

Figure 1. Study flow diagram



Included studies

We included 13 publications of 10 RCTs that reported 12 comparisons in a total of 715 people in this review. The dates of publication of trial results ranged from 1980 to 2012. The number of participants in the included trials ranged from 12 to 153. The median sample size was 67, with three studies having more than 100 participants and 50% having fewer than 50. Three trials reported an a priori sample size estimation, but each study failed to recruit the actual numbers required (Konig 2005; Gethin 2007; Alvarez 2012). The remaining trials did not report any information about sample size estimation. The mean age of participants across all studies was 68.5 years. Women predominated in a 2: 1 ratio. Only one study reported baseline patient co-morbidities (Gethin 2007); the prevalence of these were: hypertension 30.5% (n = 33); current smoker 16.6% (n = 18); history of deep vein thrombosis (DVT) 8.3% (n = 9), and recurrent ulceration 53.7% (n = 58).

Across the studies there was variability in care setting and the country in which the study was conducted. Eight studies were conducted in Europe, one in South Africa (Groenewald 1980), and one in the USA (Alvarez 2012). The Hansson 1998 trial was multinational and conducted across four European countries. It is notable that the majority of studies were conducted across multiple clinical sites within the host country. Participants were treated in their own homes, community clinics, specialist vascular and dermatology clinics, and wound healing units.

All participants included in the trials in this review were deemed to have venous ulcers.The diagnosis of venous ulceration varied among trials with five stating that an ankle brachial pressure index (ABPI) was performed; the purpose of which is to rule out significant arterial disease (Jasiel 1996; Hansson 1998; Gethin 2007; Wild 2010; Alvarez 2012). The ABPI reading for inclusion was a minimum of 0.8 in four studies, with one using a minimum cut off point of 0.75 (Alvarez 2012). The remaining five studies stated that participants had venous disease or proven venous disease but the method of determination of this diagnosis was not stated.

Seven of the ten RCTs evaluated different autolytic debridement methods (Groenewald 1980; Skog 1983; Jasiel 1996; Hansson 1998; Gethin 2007; Wild 2010; Alvarez 2012). The autolytic agents used in these trials included biocellulose wound dressing (BWD), non-adherent dressing, honey, hydrogel, hydrofibre, hydrocolloids, dextranomer beads, Edinburgh University Solution of Lime (EUSOL), and paraffin gauze. Two trials compared autolytic debridement with enzymatic debridement (Westerhof 1990; Konig 2005). One trial compared biosurgical (larvae) with autolytic debridement (Wayman 2000). No RCTs of debridement in venous ulcers evaluated surgical, sharp or mechanical methods.

Two studies specifically stated the minimum amount of slough required in the wound bed for inclusion, which was set at 50% (Gethin 2007; Alvarez 2012). Other studies indicated that people with necrotic or sloughy venous ulcers were included, but did not state the percentage of slough at the start.

The methods used to assess debridement varied amongst the included studies, with the most frequent method being a percentage calculation of the amount of slough/necrotic tissue in the wound bed (Westerhof 1990; Jasiel 1996; Wayman 2000; Konig 2005; Gethin 2007; Alvarez 2012). Wild 2010 used a wound assessment tool that incorporated percentage of slough. One study used an analogue scale (Skog 1983), with a graded scale being used by a second (Hansson 1998). Eight studies also used photographs as a means of assessment (Groenewald 1980; Skog 1983; Jasiel 1996; Hansson 1998; Westerhof 1990; Konig 2005; Wild 2010; Alvarez 2012).

All studies measured wound size using tracings made on transparent film or with digital planimetry. One study defined healing as a wound that had fully epithelized, with the absence of drainage and without the need for a dressing (Alvarez 2012), healing was not an outcome in seven of the 10 studies (Skog 1983; Westerhof 1990; Jasiel 1996; Hansson 1998; Wayman 2000; Konig 2005; Wild 2010) and the remainder did not provide a definition.

Pain was not reported as an outcome in three RCTs (Jasiel 1996; Wayman 2000; Konig 2005). The most frequently cited method used to assess pain was a visual analogue scale (VAS), with a 4-point scale (Westerhof 1990), 5-point scale (Groenewald 1980; Gethin 2007), or 10-point scale (Wild 2010; Alvarez 2012). None of the scales used are currently validated specifically for use in individuals with venous ulceration.

Duration of studies varied, with the shortest study period being one week (Westerhof 1990). Three studies measured outcomes at 21 days (Groenewald 1980; Jasiel 1996; Konig 2005), while five evaluated outcomes at four weeks (Skog 1983; Hansson 1998; Wayman 2000; Gethin 2007; Wild 2010). Three studies had multiple assessment points (Skog 1983; Hansson 1998; Alvarez 2012). Two studies followed up participants for healing outcomes at 12 weeks (Gethin 2007; Alvarez 2012).

The frequency of dressing changes, when reported, varied across studies: from twice daily (Westerhof 1990), to daily (Jasiel 1996; Konig 2005), every third day (Wayman 2000), or weekly (Gethin 2007; Alvarez 2012). The rest of the trials did not specify the frequency of change.

The use of compression therapy was relatively consistent throughout, with eight of the 10 studies using compression during the treatment period. There was considerable variation in the application of compression, not only in the type of compression, but also in the frequency of application and the person who applied the compression. In one study participants applied their own short-stretch compression (Konig 2005), while in the other studies par-

ticipants attended clinics or were treated by a visiting nurse. Short-stretch bandaging was used in Hansson 1998, Konig 2005 and Wild 2010, and four-layer bandaging in the study by Gethin 2007. Unna boot was used in Groenewald 1980, and long stretch bandages in Jasiel 1996. One trial used multiple types of compression across clinical sites (Alvarez 2012). One trial simply stated 'compression bandage' (Skog 1983). The Wayman 2000 and Westerhof 1990 trials did not report using compression therapy.

Four studies did not report wound duration at baseline (Groenewald 1980; Hansson 1998; Konig 2005; Wild 2010). In the remainder, wound duration ranged from a minimum of two months (Westerhof 1990; Wayman 2000; Alvarez 2012), to a report of 20 years (Jasiel 1996). The majority of participants across all studies had wounds with durations of more than six months. Wound size ranged from 0.84 cm ² to 375 cm² (Jasiel 1996); two studies did not report wound size at baseline (Westerhof 1990; Konig 2005). Five studies reported the mean rather than the median (Groenewald 1980; Skog 1983; Jasiel 1996; Hansson 1998; Wild 2010). Means and medians can be very different from each other if the data are skewed; medians are often reported when data are skewed as they are not influenced by extreme values in the way that means are (Higgins 2011).

As the focus of this review was the efficacy of debridement, we examined all studies for inclusion criteria specific to the presence of slough or necrotic tissue on study entry. Two studies specified the amount of slough that should be present in the wound bed for inclusion (Gethin 2007; Alvarez 2012). One study stated that wounds that were deemed to require debridement were included (Wayman 2000). The remaining studies, while aiming to evaluate the efficacy of the intervention versus control in wound debridement and while requiring wounds to have slough, did not state the minimum or maximum amount of slough that should be present. Review of trials showed variability in the percentage of slough at baseline, this ranged from 33% (Skog 1983), to 40% to 50% (Konig 2005), to more than 75% (Hansson 1998; Westerhof 1990; Wild 2010).

Excluded studies

After reviewing the papers, we excluded 46 studies as they did not meet the inclusion criteria. These are summarised in the Characteristics of excluded studies table. Seven trials were not RCTs (Groenewald 1981; Mekkes 1992; Williams 2005; Marazzi 2006; Gray 2008; Cardinal 2009; Romanelli 2009).

The primary focus of this review was to determine the efficacy of any method of debridement in achieving debridement in venous leg ulcers. In addition, we aimed to determine what effect - if any - this method of debridement had on healing outcomes. Therefore, we limited the trials included in this review to those that had debridement as one of the aims of their study. We excluded 16 trials that did not have efficacy of debridement as a study outcome (Floden 1978; Eriksson 1984; Fischer 1984; Harcup 1986; Lindsay 1986; Burgess 1993; Grotewohl 1994; Nelson 1995; Armstrong 1996; Lok 1999; Contretas-Ruiz 2004; Jorgensen 2005; Munter 2006; Leach 2006; Bressieux 2007; Olyaie 2013).

Fourteen trials included participants with ulcers of various aetiologies and did not stratify results, so conclusions about efficacy specifically for venous ulcers could not be determined (Boxer 1969; Sawyer 1979; Hellgren 1983; Stromberg 1984; Stewart 1987; Forsling 1988; Hillstrom 1988; Robinson 1995; Falabella 1998; Caputo 2008; Dumville 2009; Roldan 2010; Dereure 2012; Mudge 2014).

According to results and baseline characteristics of seven trials, not all of the wounds had slough at the start of the study, and results were not stratified, so conclusions about efficacy could not be determined (Gordon 1975; Hulkko 1981; Laudanska 1988; Holloway 1989; Gamborg 1990; Bowszyc 1994; Andersen 2002).

Two studies did not report sufficient detail about the intervention in order to determine the method of debridement used (Westerhof 1987; Tarvainen 1988).

Risk of bias in included studies

Overall we judged that the trials were at high risk of bias (Figure 2; Figure 3). Baseline comparability of treatment groups was achieved for age, wound size and duration in half of the studies. Seven trials did not use blinded outcome assessment, but made attempts to minimise the impact of this detection bias through the use of digital imagery, photographs and wound tracings. An overall summary of the risk of bias can be found in Figure 2 and a graphical breakdown per trial is shown in Figure 3. Two of the review authors (GG and SC) had a study included in this review (Gethin 2007). In order to guard against bias, the third review author (DK) cross-checked all extracted data and the 'Risk of bias' summary for this trial.

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

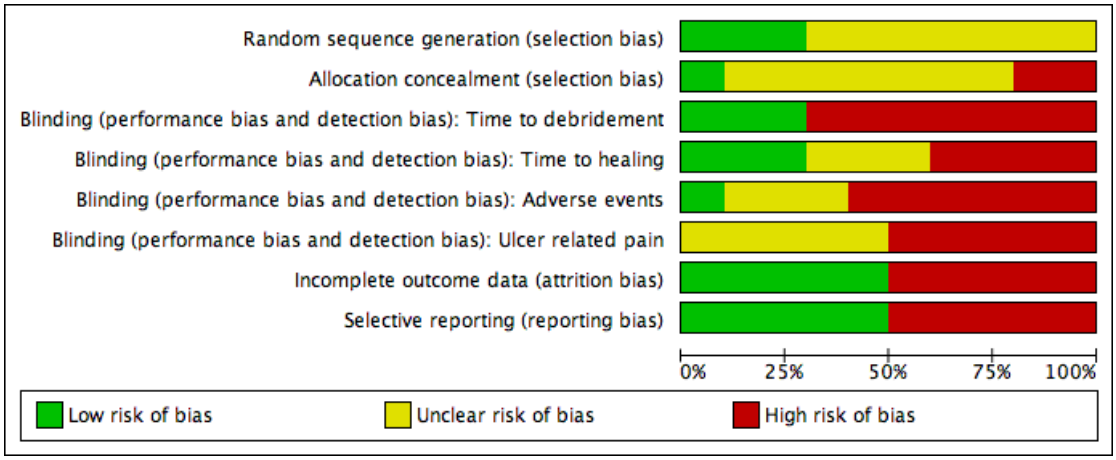
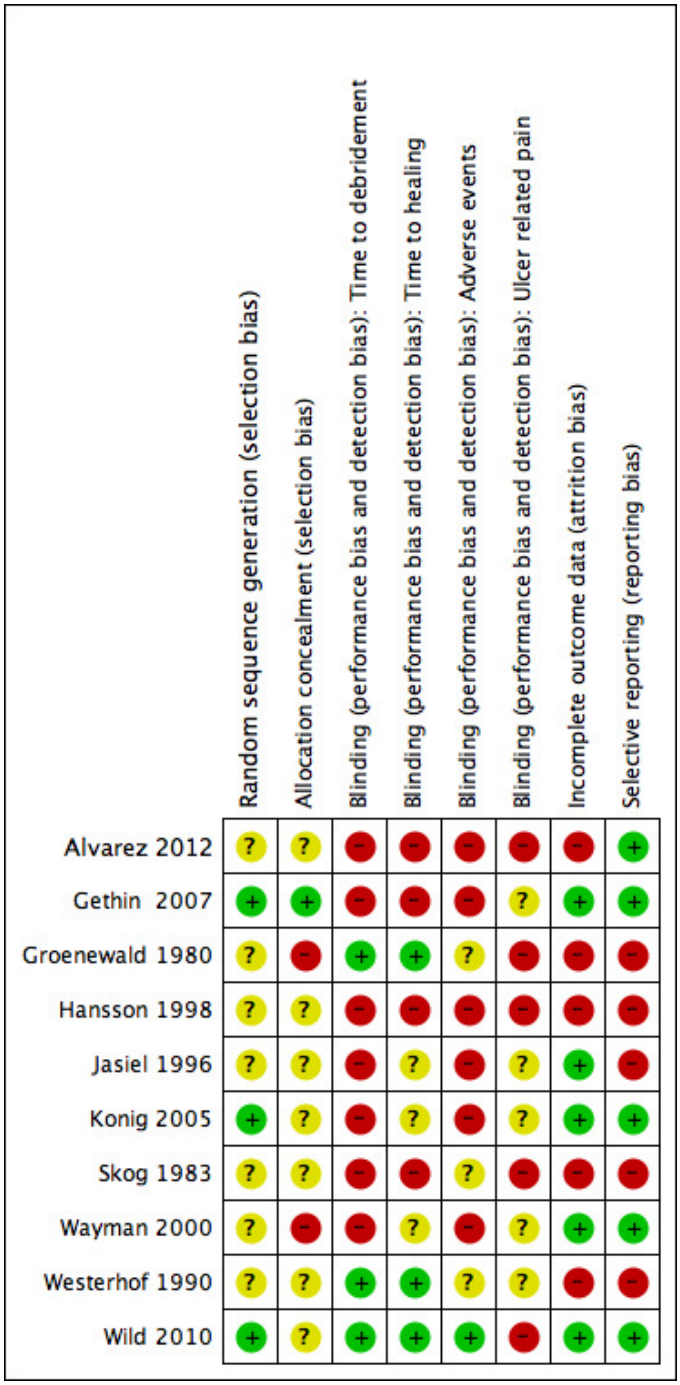


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Generation of the randomisation sequence

Three studies had a low risk of bias for generation of the randomisation sequence. Although the other seven studies stated they were randomised, there were insufficient details provided about the method used to generate the sequence to enable us to make a judgement of risk of bias. Nonetheless, baseline comparability between groups was established for the variables of age, wound size and wound duration in five studies (Skog 1983; Jasiel 1996; Wayman 2000; Gethin 2007; Alvarez 2012). Two studies reported baseline comparability for age and wound size only (Hansson 1998; Wild 2010), and one study reported baseline comparability for wound duration and age (Westerhof 1990), with the Konig 2005 study reporting baseline data for age only. The percentage of slough in the wound bed at baseline was reported in only four studies and this was balanced across treatment groups (Westerhof 1990; Konig 2005; Gethin 2007; Wild 2010). Thus, for generation of the randomisation sequence we have determined that three of the 10 studies had a low risk of bias (Konig 2005; Gethin 2007; Wild 2010), with the remainder having an unclear risk.

Allocation concealment

Only one study was at low risk of bias for this domain (Gethin 2007), as it adequately described the method of allocation concealment. Groenewald 1980 reported dividing participants into two groups and Wayman 2000 reported using sealed envelopes, but it was possible that those responsible for allocating could foresee the next assignment and, therefore, both were deemed to be at a high risk of bias. The risk of selection bias in the remaining seven studies was unclear due to lack of information in the published reports. One study in this review had a low risk of bias for allocation concealment, two had a high risk and the remainder had an unclear risk.

Blinding

Performance bias refers to any systematic differences between groups in the care that is provided, or in exposure to factors other than the intervention of interest (Higgins 2011). Detection bias refers to systematic differences between groups in how outcomes are determined (Higgins 2011). Blinding of participants and personnel minimises performance bias, and blinding of outcome assessors minimises the potential for detection bias. None of the studies included in this review indicated any form of performance bias in that groups received similar care (except for the intervention) and no additional benefits were bestowed upon either the experimental or the control groups. Blinded outcome assessment is often a challenge in trials of wound care, as in some cases the treatment is apparent, for example the use of larvae or iodine-containing products. However, blinding of assessors was achieved in three studies (Groenewald 1980; Westerhof 1990; Wild 2010). Details of the methods used to achieve blinding of assessors varied and included: 'the clinical observer did not know which treatment was used. The computer image analysis was performed blinded', in Westerhof 1990 and Groenewald 1980 reported that two independent investigator evaluated the ulcers, while Wild 2010 used photographs analysed by trained clinicians using a digital tool that assessed size and the wound bed - these assessors were blinded to treatment allocation. Outcome evaluations were supported through the use of photographs in seven studies (Groenewald 1980; Skog 1983; Westerhof 1990; Jasiel 1996; Hansson 1998; Wild 2010; Alvarez 2012), and wounds were traced and size recorded using grids or planimetry in two studies (Gethin 2007; Alvarez 2012).

Seven trials were deemed to have a high risk of bias for the how debridement was determined (Skog 1983; Jasiel 1996; Hansson 1998; Konig 2005; Wayman 2000; Gethin 2007; Alvarez 2012), with three having a low risk of bias (Groenewald 1980; Westerhof 1990; Wild 2010). The exact method used to evaluate debridement varied and was open to an element of subjective opinion, for example percentages of necrotic tissue determined through visual inspection. The incorporation of visual inspection together with a review of photographs helped minimise this bias, but the lack of blinding cannot be ignored.

We judged three studies to be at high risk of bias for how healing was determined, (Skog 1983; Hansson 1998; Gethin 2007), three at low risk (Groenewald 1980; Westerhof 1990; Wild 2010), and the remaining studies to be at unclear risk. However, it should be noted that healing was not an outcome in three studies (Jasiel 1996; Wayman 2000; Konig 2005).

We concluded that for the determination of debridement, the risk of bias was low in three trials and for the determination of healing it was low in three trials.

Incomplete outcome data

Eight studies In this review recorded adverse events and attrition rates. Three studies specifically stated that analysis was on an intention-to-treat (ITT) basis (Gethin 2007; Wild 2010; Alvarez 2012), in addition, two other studies that had no withdrawals also used an ITT analysis, as they analysed all participants (Westerhof 1990; Wayman 2000). Five studies reported on attrition rates and were deemed to have low risk of bias (Jasiel 1996; Wayman 2000; Konig 2005; Gethin 2007; Wild 2010). Five trials were deemed to be at a high risk of bias (Groenewald 1980; Skog 1983; Westerhof 1990;

Hansson 1998; Alvarez 2012): Groenewald 1980 did not account for all participants at the end of the trial period; Hansson 1998 reported that participants left the study at various time points; Skog 1983 excluded 21 sets of data from the final analysis; and Westerhof 1990 did not provide information on withdrawals to would have allowed us to make a definitive judgement of the risk of bias. Given the above, we have concluded that five trials were at high risk of attrition bias and the remainder at low risk.

Selective reporting

Incomplete outcome data and the lack of information on all expected outcomes means that we rated five studies as having a high risk of reporting bias (Groenewald 1980; Skog 1983; Westerhof 1990; Jasiel 1996; Hansson 1998). These included lack of detail on adverse events (Groenewald 1980); a high number of data sets excluded from final analysis (Skog 1983); pain, oedema and erythema assessed within the trial, but not reported (Westerhof 1990); lack of specific detail on outcomes (Jasiel 1996); and reporting of the percentage of patients with slough rather than the percentage of wounds with slough or the percentage of the wound bed covered in slough (Hansson 1998). The remaining five studies reported all planned outcomes and thus were deemed to be at a low risk of bias (Wayman 2000; Konig 2005; Gethin 2007; Wild 2010; Alvarez 2012).

Effects of interventions

Debridement with no debridement

No trials compared debridement with no debridement.

Different methods of debridement

Heterogeneity in study design methodologies, study duration and debriding agents precluded quantitative meta-analysis, so a narrative review is provided.

Two autolytic debridement methods

Seven studies, with a total of 630 participants, compared different forms of autolytic debridement (Groenewald 1980; Skog 1983; Jasiel 1996; Hansson 1998; Gethin 2007; Wild 2010; Alvarez 2012). We have presented the results according to the primary and secondary outcomes of this review.

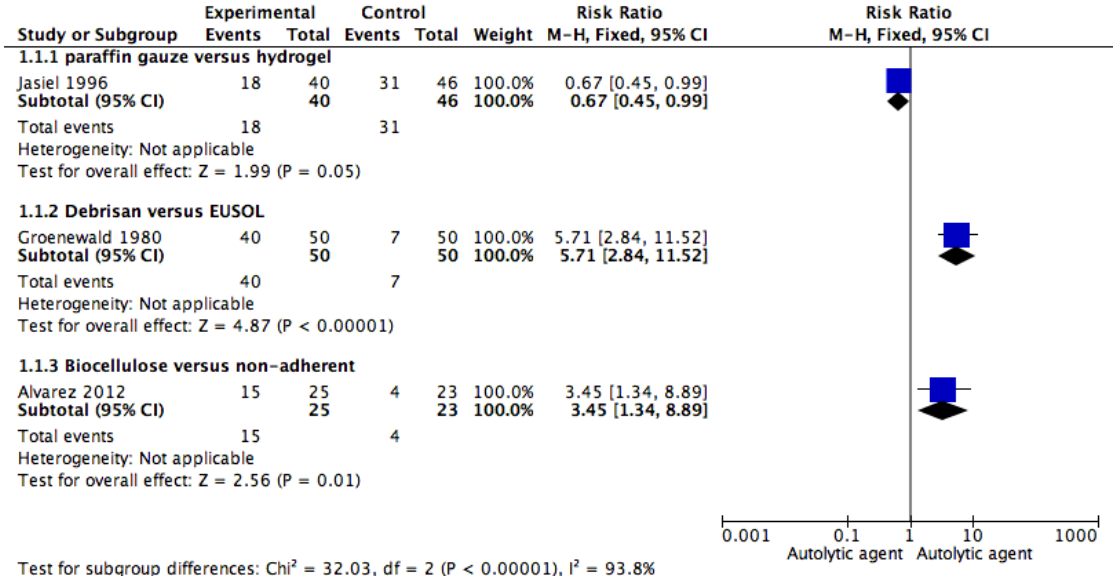
Primary outcomes

1.1.0 Number of wounds completely debrided

Three studies (234 participants) included the number of wounds completely debrided as a study outcome (Groenewald 1980; Jasiel 1996; Alvarez 2012). Comparators included; hydrogel, dextranomer beads, EUSOL, BWD, non-adherent dressing and paraffin gauze.

The Groenewald 1980 study reported that 40/50 (80%) treated with dextranomer beads and 7/50 (14%) treated with EUSOL achieved complete debridement after one week of treatment (RR 5.71, 95% CI 2.84 to 11.52; P value < 0.0001; Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Autolytic versus autolytic, outcome: 1.1 Wounds completely debrided



The Jasiel 1996 study reported the numbers of completely debrided ulcers after three weeks of treatment as 31/46 (76%) for hydrogel versus 18/40 (45%) for paraffin gauze (RR 0.67, 95% CI 0.45 to 0.99; P value 0.05; Analysis 1.1).

In the Alvarez 2012 study participants were treated for 12 weeks, after which time it was reported on a per protocol basis that 15/18 (84%) in the BWD group and 4/15 (26%) in the nonadherent dressing-treated group achieved a 75% to 100% clean, granulating wound bed, and it was further reported that using Fisher's exact test, using nominal type 1 error rate of 0.05, showed the better 'starter function' of BWD to be statistically significant (RR 3.45, 95% CI 1.34 to 8.89; P value < 0.0001; Analysis 1.1).

1.2.0 Time to achieve debridement

The Jasiel 1996 study compared hydrogel with paraffin gauze and reported no statistical differences in the number of days until debridement for each group, but precise figures were not reported. Groenewald 1980 reported the mean time to achieve a clean wound bed as 5.9 days in the dextranomer beads-treated group versus 15.4 days in the EUSOL-treated group, and reported this difference as being statistically significant P value < 0.001.

1.3.0 Number of wounds healed

Two studies (156 participants) reported on the number of wounds healed (Gethin 2007; Alvarez 2012). Gethin 2007 reported healing at 12 weeks in 24/54 (44%) of those treated for four weeks with honey versus 18/54 (33%) of those treated for four weeks with hydrogel. Analysis of the results with binomial regression to adjust for initial wound diameter provided a RR of 1.38 (95% CI 1.02 to 1.88; P value 0.037). Analysis of numbers healed as a dichotomous outcome gave a RR of 1.33 (95% CI, 0.82 to 2.16). This study also reported that wounds achieving a reduction of 50% or more slough at four weeks, regardless of treatment group, had a higher probability of healing at 12 weeks, and this was statistically significant (P value 0.029).

The Alvarez 2012 trial reported the numbers healed at 12 weeks on a per protocol basis as 7/18 for the BWD group versus 7/15 for the non-adherent dressing group. However, as 13 participants withdrew (seven BWD versus eight non-adherent dressing) during the course of the 12-week trial, it is not known if any of them had healed at 12 weeks. We re analysed using RevMan 5.2 (Analysis 1.2), and can show that based on reported numbers healed and by including all participants randomised into the study the difference is not statistically significant, RR 0.92 (95% CI, 0.38 to 2.22).

Secondary outcomes

1.4.0 Reduction in wound size

Reduction in wound size was the most frequently reported outcome, which was reported in five studies with 444 participants (Skog 1983; Hansson 1998; Gethin 2007; Wild 2010; Alvarez 2012). The variety of agents used to achieve debridement, together

with differences in reporting time and reporting methods (mean values versus median, and total reduction versus percentage reduction), precluded any pooled analysis.

Three studies reported reduction in wound size after four weeks of treatment (Hansson 1998; Gethin 2007; Wild 2010). In the Hansson 1998 three-armed study that involved 153 participants and used autolytic debridement, mean reductions in wound size of 35.5% (SD 40.0), 34.4% (SD 47.7) and 10.6% (SD 80.4) were reported for cadexomer iodine, hydrocolloid and paraffin gauze, respectively Analysis 1.3. For cadexomer iodine versus hydrocolloid the difference was not statistically significant (mean difference 1.10, 95% CI -11.14 to 13.34); when cadexomer iodine was compared with paraffin gauze the difference was statistically significant (mean difference 24.90%, 95% CI 7.27 to 42.53; P value 0.006); and when hydrocolloid was compared with paraffin gauze the difference was also statistically significant (mean difference 23.80%, 95% CI 5.48 to 42.12; P value 0.01; Analysis 1.3). The Wild 2010 trial also recorded mean values that showed a total mean reduction in ulcer size of 43.5% (t = 0.082) when treated with biocellulose dressing versus a 17.9% reduction (t = 0.008) when treated with hydrofibre dressing. This trial reported that the between-group difference was not statistically significant.

Gethin 2007 recorded median values for 108 participants and, after four weeks, showed a median percentage reduction in ulcer size of 34% in the group treated with honey versus 13% in those treated with hydrogel, and this was statistically significant (P value < 0.001).

After six weeks Skog 1983 reported on 74 participants treated with cadexomer iodine versus standard care and showed a 34% versus 5% mean reduction in wound size (P value < 0.02). In this report standard care included cleansing the wound with dilute hydrogen peroxide or potassium permanganate followed by the application of a non-adherent dressing. Also after six weeks Alvarez 2012 reported a mean percentage reduction in wound area of 44% versus 24% in wounds treated by BWD versus non--adherent dressing.

At 12 weeks Hansson 1998 reported a mean reduction in wound size of 66.1% (SD 25.4) with cadexomer iodine, 17.9% (SD 51.6) with hydrocolloid, and 50.9% (SD 53.2) with paraffin gauze; the differences between the cadexomer iodine and hydrocolloid were statistically significant (MD not reported; P value 0.0127). At 12 weeks Alvarez 2012 reported a mean percentage reduction in wound area of 74% in the BWD group versus 54% in the non-adherent dressing group.

Overall, autolytic debridement was reported as achieving a mean reduction in wound size ranging from 3% at one week, to 43% after four weeks, 34% after six weeks and 74% after 12 weeks. As the numbers in any one treatment arm did not exceed 56, and there was no meta-analysis, we could not draw strong conclusions. However, the study by Gethin 2007 showed that overall, those participants who had a greater reduction in wound slough after four weeks (combined groups) also had higher rates of healing at 12 weeks.

1.5.0 Pain

No study reported the use of a pain scale validated for use in venous leg ulcers. No study reported on measures to assess validity of pain scales for use in participants with venous ulceration. As pain is something to be considered when choosing a debriding method we have provided a narrative summary of results here. However, the methods of assessing pain, reporting times and reporting methods precluded any pooled analysis (Analysis 1.4).

Six studies with 544 participants reported pain as an outcome (Groenewald 1980; Skog 1983; Hansson 1998; Gethin 2007; Wild 2010; Alvarez 2012), but only three of the studies made reference to the type of scale used to assess pain and provided details and a supporting reference for the source of the scale (Gethin 2007; Wild 2010; Alvarez 2012), however, they did not specify whether the scale was validated.

In the Groenewald 1980 study, 65% (n = 65) of participants had pain at the start of the treatment period; after 24 hours pain had reduced in 66%. Results were presented at six time points with eight of the 30 participants in the dextranomer beads group experiencing pain, and 13 of those treated with EUSOL having an initial increase in pain. All participants treated with dextranomer beads had a subsequent reduction in pain within the next 24 hours; no participant reported pain after 10 days. Alternatively, four of those treated with EUSOL had an increase in pain that did not improve later, and at 21 days two participants continued to have pain.

Skog 1983 reported changes in the mean pain score using a VAS (size of scale was not reported), before treatment, after one week and at six weeks in 74 participants treated with cadexomer iodine versus standard care. For those treated with cadexomer iodine the scores were: 32 before treatment, 27 at week 1, and 10 at week 6; for those receiving standard care the scores were 33 before treatment, 29 at week 1, and 23 at week 6; the differences between groups were statistically significant (P value < 0.05).

The Gethin 2007 trial with 108 participants reported that in 39% (n = 7) of the 18 cases of infection, pain increased during the treatment period. This trial used a five-point VAS.

The Wild 2010 study, with 40 participants, used a 10-point VAS and reported pain at dressing changes on days seven, 14 and 28. Results showed that the BWD-treated group had pain scores of 2.25 (SD 1.06) at seven days, 2.70 (SD 0.86) at 14 days, and 1.30 (SD 0.47) at 28 days. In comparison,the hydrofibre-treated group had scores of 3.73 (SD 1.26) at day seven, 5.25 (SD 1.37) at day 14, and 3.20 (SD 1.20) at day 28, however no baseline scores were provided to allow for meaningful comparisons.

The three-armed Hansson 1998 study (153 participants) reported the percentage of participants who had pain at baseline, week four, week eight and week 12. At all time points the percentage of participants reporting pain reduced, with an overall reduction of

66% to 29% by week 12 in those treated with cadexomer-iodine, 73% to 57% in the hydrocolloid group, and 57% to 15% in the paraffin group.

Finally, the Alvarez 2012 study reported that over the 12-week period, a larger proportion of participants treated with BWD had no pain or mild pain compared with the control group, and that at week seven there was a statistically significantly difference (P value < 0.05). No pain scores were provided at any time point.

In summary, pain was reported in six studies, and while the use of a VAS was the most common method, there was inconsistency between studies with regard to the size and type of scale used. There was no reference to validation of these scales for use in pain assessment in venous ulceration, but there was an overall reduction in pain when wounds were debrided.

1.6.0 Adverse events

None of the studies provided a definition of an adverse event and no serious adverse events were recorded. A summary of findings is presented in Analysis 3.1. Four studies either did not report adverse events or stated that none had occurred due to the study treatment. The Jasiel 1996 trial reported one adverse event in the paraffin gauze group that involved maceration and infection, and two in the hydrogel group - one 'possibly' due to treatment involving erysipelas (skin rash) and one oedematis (fluid retention) reaction. The trialists also reported that one participant was withdrawn from the paraffin gauze group due to thrombophlebitis (a blood clot in a vein) and one from the hydrogel group due to infection that was not attributed to the study treatments. The Hansson 1998 study reported that 12 participants in the iodine group, seven in the hydrocolloid group and nine in the paraffin gauze group were withdrawn due to allergic reactions, dermatitis, pain or poor compliance, but stated these were not due to the study treatments. The Alvarez 2012 study reported 14 adverse events that were attributed to the study treatment; these included a clinically infected ulcer (n = 8), cellulitis (n = 3) and dermatitis (n = 3), however, these participants continued with the study.

Enzymatic debridement compared with autolytic debridement

Two studies (71 participants) compared enzymatic debridement with autolytic debridement (Westerhof 1990; Konig 2005).

Primary outcome

2.1.0 Number of wounds completely debrided

Neither study reported on the number of wounds that were completely debrided.

2.2.0 Time to achieve debridement

The Westerhof 1990 trial randomised 29 participants with 31 wounds to treatment with either enzymatic debridement (using krill enzymes) or to autolytic debridement using a standard protocol of 2% acetic acid for two days, followed by 10% povidone iodine for two days, followed by saline dressings for three days. The treatment period was seven days. Results showed that the mean time to achieve debridement was seven days for the enzymatic regime versus 10 days for the standard protocol (although the treatment period was seven days). Interestingly, both groups in this study had twice daily application of wound treatments, which was much more frequent than in the other debridement studies.

Konig 2005 randomised 42 participants to either enzymatic debridement or autolytic debridement. Participants in both groups applied their dressings daily, but evaluations were completed by clinicians. After 14 days of treatment, the enzyme-treated group had a slough reduction of 8.5% versus a reduction of 18.7% in the autolytic debridement group. After a further seven days (total 21 days) those treated with the enzymatic agent had an increase in slough of 9.1% compared to a further reduction of 10.9% in the autolytic group. At the end of 21 days, 18 of those treated with the enzymatic agent and six treated with the autolytic agent crossed over to the alternative therapy. Outcomes from this crossover period are not reported here.

2.3.0 Number of wounds healed

Neither study reported on the number of wounds healed.

Secondary outcomes

2.4.0 Reduction in wound size

After one week, Westerhof 1990 recorded a mean reduction in wound size of 13% (SD 35) in the enzyme-treated group versus 3% (SD 33) in the autolytic group. The mean difference was 10.00% (95% CI 0.57 to 19.43; Analysis 2.1), however, 12 participants were excluded from this final analysis.

2.5.0 Pain

The Westerhof 1990 trial did not refer to a validated pain assessment scale, but reported that "both treatments caused a similar reduction in pain". Pain was not one of the study outcomes in Konig 2005.

2.6.0 Adverse events

Westerhof 1990 reported that "there were no signs of side effects" in either group. The Konig 2005 study did not report on adverse events.

Biosurgical debridement compared with autolytic debridement

One trial of 12 participants compared biosurgical (larvae) with an autolytic agent (hydrogel) over a one-month period (Wayman 2000).

Primary outcomes

3.1.0 Number of wounds completely debrided

All six participants (100%) treated with biosurgical debridement versus two (33%) of the participants treated with autolytic debridement had wounds desloughed in one month (RR 2.6, 95% CI 0.94 to 7.17; P value 0.065; Analysis 3.1).

3.2.0 Time to achieve debridement

Results for this outcome were presented as the number of nursing visits to achieve debridement, with visits occurring every three days. This was reported as being statistically significant (P value 0.003).The authors stated that "debridement occurred more rapidly in the larvae treated group where participants only required one application of larvae. In the hydrogel group only two participants were de-sloughed within the month". The trial report was not explicit about the mean time required to achieve debridement, but on the basis of the number of visits it can be deduced that the mean number of days to complete debridement was three versus 22.

3.3.0 Number of wounds healed

Wayman 2000 did not report on the number of wounds healed.

Secondary outcomes

3.4.0 Reduction in wound size

Wayman 2000 did not report on reduction in wound size.

3.5.0 Pain

Wayman 2000 did not report on pain.

3.6.0 Adverse events

Wayman 2000 did not report any adverse effects.

DISCUSSION

While the rationale for using debridement to remove devitalised or necrotic tissue and expose a healthier wound bed seems logical, strong evidence of its role in enhancing healing of venous ulcers is deficient. It is notable therefore that debridement, which is purported to play a significant role in enhancing wound healing and is supported by many position statements and documents, is as yet so poorly researched. While ten studies have met the inclusion criteria for this review, they only represent a total of 715 participants, with one study having evaluated debrisan (dextranomer beads), which are no longer manufactured (Groenewald 1980). This is a small number of participants when one considers that venous ulcers affect up to 1% of the population, affecting approximately 600,000 people annually in the USA alone, cost approximately USD 9600 each to treat, and that the period over which debridement has been investigated spans 34 years (O'Brien 2000; Sen 2009). Studies varied in their aims and objectives; some evaluated the time required to achieve complete debridement, while others evaluated the efficacy of an agent at a specific time point.

Debridement

The mechanism through which debridement works is not completely understood, but may be due in part to any of, or a combination of, the following: removal of old (senescent) dead or dying cells, reduction in the bacterial burden of the wound, and improvement of the microcirculation and removal of biofilm (Baharestani 1999; Davies 2004; Gottrup 2011). Factors that influence the choice of method to achieve debridement are based on the aetiology of the wound, treatment goals, patient goals, skills and resources of the clinician, and costs. This review has failed to identify an optimal debridement method or duration of treatment.

The largest study (n = 267) of biosurgical debridement versus autolytic debridement was excluded from this review as 32 participants with non-venous ulcers were included, and results were not stratified according to wound aetiology (Dumville 2009). However, this paper does provide some important insights on the use of larvae as a debriding agent in lower limb ulceration and some comments are warranted here. The study randomised 267 participants to three treatment arms: loose larvae; bagged larvae; or hydrogel. Time to complete healing was the primary outcome, and importantly all ulcers required more than 25% of the surface area to be covered with slough in order to be included. Time to healing did not differ between groups (P value < 0.62). Median time to healing for all larvae-treated participants was 236 days versus 245 for the hydrogel group. The hazard ratio for larvae versus hydrogel of 1.13 (95% CI 0.76 to 1.68; P value 0.54) indicated a slightly increased likelihood of healing in the larvae group, but this difference was not clinically or statistically significant. Time to debridement in this study showed a median time of 14 days for the loose larvae group (95% CI 10 to 17); 28 days for bagged larvae (CI 95% 13 to 15); and 72 days for hydrogel (95% CI 56

to 131).

In the Dumville 2009 study, the rate of debridement using larvae - at any time in either group - was twice that of hydrogel: the hazard ratio for combined larvae versus hydrogel was 2.31 (95% CI 1.65 to 3.24; P value < 0.001). However, significantly more pain was experienced by participants in both larvae groups (P value < 0.001) compared to the hydrogel group; furthermore, larvae were more expensive. Mean ulcer-related pain scores were higher in either larvae group compared with hydrogel (mean difference in pain score: loose larvae versus hydrogel 46.74 (95% CI 32.44 to 61.04; P value < 0.001); bagged larvae versus hydrogel 38.58 (95% CI 23.46 to 53.70; P value < 0.001; Dumville 2009).

Debridement and wound healing

Healing rates of venous ulcers seem to have plateaued in recent years, with trials reporting healing rates of more than 50% to 60% at 12 weeks being very infrequent. Additionally, venous ulcers are further challenged by their recurrent nature with 50% recurring within three months of healing. There is an urgent need for early intervention in venous ulcer management in order to treat patients at the lowest level of complexity and to improve these outcomes, as studies have shown that only 13% of ulcers that exceed 5 cm^2, with duration of more than six months, are expected to heal after 26 weeks (Margolis 2000). This is in contrast to those ulcers under 5 cm^2 with duration less than six months, in which 95% are expected to heal in the same time (Margolis 2000). This is also supported by a recent Cochrane Review of compression in venous ulcers, in which a longer time to healing was predicted for larger ulcers and ulcers of longer duration independently of one another, and of treatment (O'Meara 2012). We examined all included studies with reference to balance of these variables across treatment groups. Baseline comparability of studies included in our review demonstrated wound chronicity with 96% of ulcers being more than six months duration and all studies having wounds larger than 5 cm^2. Therefore, it is possible that the healing trajectories of those patients with sloughy venous ulcers many not be similar to those without slough, and this should be investigated further in future trials.

The impact of debridement on healing outcomes was established in two studies with follow-up periods of 12 weeks and 12 months (Hansson 1998; Gethin 2007). However, the Hansson 1998 study reported on a per protocol basis, so healing outcomes for all participants is not known. Follow up for periods of 12 weeks and longer are important, as it permits the benefits - or otherwise - of such interventions in achieving the ultimate aim of healing in venous ulcers to be quantified. Although these findings come from the two largest studies in this review, the results should be treated with caution as they may not be generalisable to all patients with venous ulcers or to all patients with sloughy venous ulcers, as no single treatment arm exceeded 56 participants and a total of five different agents were represented.

Pain

The validity of pain assessment tools is well established in a range of areas of research with visual analogue scales (VAS), numeric rating scales (NRS), verbal rating scales (VRS), and faces scales being the most frequently cited (Bowers 2009). A comparative study to assess validity of these scales provided strong support for validity (Ferreira-Valente 2011), however the participants were healthy volunteers rather than people with chronic wounds. Notwithstanding this limitation, a recent Cochrane Review of topical agents for pain in venous leg ulcers (Briggs 2012), which included data from six RCTs and a total of 343 participants, identified seven different methods used to assess pain, the most frequently used one being the VAS (n = 4). Other methods used included physician-rated pain, 4-point, 5-point and 100-point numeric scales. There is a lack of consensus on which scale is best suited to venous leg ulcers, and a recommendation that a choice of scale is best made in accordance with patient preference (Bowers 2009). Very little research has been done on the validity of pain assessment scales specific to venous ulcers. Outcomes of studies in this review have shown that pain is a feature of necrotic venous ulcers, and, while studies reported improvements in pain scores, the lack of any standardised method to evaluate pain, limited the ability to synthesise the findings. Pain assessment is an integral part of holistic wound assessment and should form part of evaluations of interventions such as debridement. It is important that wound symptoms such as pain are evaluated in an objective manner in studies of debridement as some methods of debridement are more painful than others, in particular mechanical, surgical, sharp and biosurgical debridement methods (Dumville 2009; Strohal 2013).

Adverse events

Overall, the reporting of adverse events was poor. As none of the studies provided the definition of an adverse event that guided their study, we cannot be sure whether the lack of reporting was due to individual study interpretation of what constituted an adverse event or, alternatively, that no adverse events occurred. One study reported adverse events that were possibly due to the treatment (Jasiel 1996): one adverse event in the paraffin gauze group involved maceration and infection, while in the hydrogel group another involved erysipelas (infection with rash), and one participant had an oedematis reaction. Another study recorded 14 adverse events possibly due to the interventions (Alvarez 2012). Of these, eight ulcers became clinically infected, three developed cellulitis and three developed dermatitis. No serious adverse events were reported in any study. In comparison, the Dumville 2009 study (which was excluded from this review due to the mixed aetiology of the wounds) reported 340 adverse events in 131 participants: 13.8% of these were classed as serious. This may raise the possibility of under-reporting of adverse events in the studies in our review, but does cast some light on the rates of adverse events

in RCTs of people with venous leg ulcers.

Limitations

This review is subject to a number of limitations. Firstly, It was not possible to evaluate the overall possibility of publication bias, as not all trials reported the same outcomes and the trials were too heterogenous to combine. Although the search strategy was comprehensive, in addition to handsearching the reference lists of included trials and other sources, we did not find any trials that compared debridement with no debridement, or that used surgical, sharp or mechanical debridement techniques. Empirical evidence has shown that up to 64% of trials are either never begun, not completed, or remain unpublished (Chan 2004), and it is possible that this is true for studies of debridement. The lack of prospective registration of trials in this area means we do not know the extent of failure to complete or report.

A second limitation relates to sample size. In this review, the largest treatment arm in any of the included studies had 56 participants (Hansson 1998). This is a small number upon which to base treatment effect estimates; it is recognised that treatment effect estimates are significantly larger in smaller trials (Dechartres 2013), and that statistically significant outcomes have more than twice the chance of being reported fully compared with non significant results (Chan 2004).

Thirdly, not all wounds had the same starting point in relation to the amount of slough within the wound bed. While baseline comparability was established within trials, it cannot be established between trials. This lack of comparability limits our ability to quantify the impact of different methods of debridement.

Fourthly, methods to evaluate pain were inconsistent across trials. We have been unable to identify any validated venous ulcer-specific pain assessment scale, and so pain assessment in this cohort relies on pain scales from other areas of clinical practice and research.

Fifthly, an important consideration in evaluating the results of this review is the exclusion of studies for which debridement was not the primary or secondary outcome or for which the presence of slough was not an inclusion criteria. It was important that studies in this review all evaluated the effects of their debridement method or compared debridement versus no debridement. From a clinical perspective, unless there is slough in the wound bed, debridement is not indicated. Therefore, the ulcer bed had to have slough and have this reported or, if wounds with and without slough were included, results should have been stratified accordingly.

AUTHORS' CONCLUSIONS

Implications for practice

There is consensus in the wound care literature that debridement is necessary to promote wound healing (NICE 2001; Schultz 2003; Strohal 2013). While this would seem to be a logical step in the wound bed preparation process, our review has found that the evidence base to support this is very limited. One study did suggest that debridement may improve healing (Gethin 2007), but the smallness of the evidence base means that one cannot conclude with confidence that debridement improves healing, or which method of debridement, or duration of debridement confers most benefit in the healing of venous ulcers. This is important as the number of products being developed to promote debridement is increasing and practitioners need to question the evidence base that supports these products.

Implications for research

Given the current prevalence of venous ulcers and the projected increase in prevalence due to many factors, including increase in chronic illness, increase in risk factors for chronic illness, and increased life expectancy (Sen 2009), the issue of debridement needs to be addressed through robust research in order to guide the clinician in management options. Efforts should be made for collaborative studies to provide empirical evidence on the role of debridement in enhancing healing of venous ulcers.

The research base for the benefits of debridement on healing outcomes in venous ulcers is small. While the methodological quality in terms of randomisation and allocation concealment has improved over time, sample size remains a problem. The following are recommended for future research in this area.

- Presentation of findings using the CONSORT statement (Schulz 2010). This aims to improve the reporting of randomised controlled trials.
- Adequate generation of randomisation sequence with sample size based on an a priori calculation.
- Single-centre studies may be challenged to recruit enough participants for studies researching such specific areas such as debridement of venous ulcers and, therefore, we would recommend more collaboration across sites and that multicenter studies are conducted.
- Allocation to treatment should be concealed; this may be achieved through a remote telephone randomisation service. This service should be easily achievable and may be supported through links with clinical research units or trials units, or both.
- Assessment of outcomes should be undertaken by assessors blinded to treatment allocation, or through independent evaluation of photographs.
- The endpoint of debridement trials should be the efficacy of the debridement method and the benefits of this on healing outcomes.
- Recommendations from the Food and Drug Adminsitration (USA) and Centre for Medical Technology

Policy recommend trial duration in studies of venous ulcers should be 20 weeks (FDA 2006; Sonnad 2012), which would allow comparisons to be made across trials, and provide a more robust evaluation of the benefits and harms of interventions.

- This review has found little evidence to show whether debridement benefits healing. In addition, there is a lack of consensus regarding the point at which one should consider debridement. Should it be, for example, when wounds have more than 25% of the area covered in slough, or more, or less? It is challenging to know when an agent has been effective and to compare this across trials. We would recommend that studies evaluating the efficacy of a debriding agent should have at least 25% necrotic or sloughy tissue in the wound bed, with follow-up to determine the impact on healing outcomes.

- Studies of debridement should include baseline characteristics of wound size and wound duration, as these are prognostic indicators of healing outcomes in venous ulcers. This would facilitate greater potential for comparison with other studies.

- Analysis should be on an intention-to-treat basis.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of:

- the peer referees: Andrea Nelson, Anne-Marie Bagnall, Nicky Cullum, Andrew Jull, Caroline Main, Gill Worthy, Una Adderley, Trudie Young, and Suzanne Cunliffe;

- Ruth Foxlee and Amanda Briant, Trials Search Co-ordinators of the Wounds Group for their assistance in developing the search strategy;

- Sally Bell-Syer, to whom we are indebted for her editorial comments, invaluable support and advice in the completion of this review;

- Dirk Ubbink for assistance with translation of papers

- Declan Devane for assistance with data analysis.

- Elizabeth Royle for copy-editing the final review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alvarez 2012

Methods	RCT Setting: 4 clinical centres in New England, USA
Participants	n = 50 eligible; 48 randomised: Group A: n = 25; Group B: n = 23 Mean age: Group A: 69 years; Group B: 63 years Mean ulcer size: Group A: 743.9 mm^2; Group B: 629 mm^2 Mean ulcer duration: Group A: 10.9 months; Group B: 8.9 months Inclusion criteria • Confirmed non-healing venous ulcers • ABPI > 0.75 • Minimum ulcer duration 2 months • > 50% of wound bed covered in slough Exclusion criteria • Clinical signs of infection • Cellulitis • Osteomyelitis • Inadequate nutrition • Uncontrolled diabetes • Any other clinically-significant conditions that would impair wound healing, including renal, hepatic, haematologic, neurologic, or immunological disease • Those receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy within 1 month prior to study entry
Interventions	Group A: BWD Suprosorb X Group B: Adaptic (non-adherent petrolatum emulsion-impregnated cellulose acetate gauze) All wounds were cleansed with normal saline, without use of forceful irrigation All participants received compression therapy in the form of Unna Boot or 4-layer bandage system Dressing changes were performed weekly Study duration: 12 weeks, or until healing
Outcomes	• Efficacy of the dressings to achieve autolytic debridement over 12-week period • Time to 75%-100% granulation tissue • Time to > 50% epithelization • Ulcer area reduction over 12 weeks • Patient-reported ulcer pain
Notes	Classed as autolytic versus autolytic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomisation schedule (in permutated blocks of 100 so that n = 25 were assigned to each group). Randomisation was done using sealed envelopes which were opened after pre-test measurements were taken" Comment: insufficient information on how this was generated to make a determination of risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was done using sealed envelopes which were opened after pre-test measurements were taken" Comment: although the term 'randomisation' was used, this would seem to refer to allocation concealment. As the envelopes were not sequentially numbered or described as opaque, this introduces a potential risk of bias, therefore a precise determination of the risk of bias cannot be made
Blinding (performance bias and detection bias) Time to debridement	High risk	Quote: "evaluations were done by the centre's investigator or study coordinator. Digital photographs were assessed by a clinician who was blinded as to the treatment allocation" Comment: participants were not blinded to treatment allocation; evaluations were unblinded, which introduces a high risk of bias. It is unclear whether those assessing photographs determined the outcomes, and thus the risk of bias remains high
Blinding (performance bias and detection bias) Time to healing	High risk	Quote: "evaluations were done by the centre's investigator or study coordinator. Digital photographs were assessed by a clinician who was blinded as to the treatment allocation" Comment: participants were not blinded to treatment allocation; evaluations were unblinded, which introduces a high risk of bias. It is unclear whether those assessing photographs determined the outcomes, and thus the risk of bias remains high
Blinding (performance bias and detection bias) Adverse events	High risk	Quote: "evaluations were done by the centre's investigator or study coordinator. Digital photographs were assessed by a clinician who was blinded as to the treatment

Alvarez 2012 (*Continued*)

		allocation" Comment: participants were not blinded to treatment allocation; evaluations were unblinded, which introduces a high risk of bias. It is unclear whether those assessing photographs determined the outcomes, and thus the risk of bias remains high
Blinding (performance bias and detection bias) Ulcer related pain	High risk	Quote: "patient-reported ulcer pain was assessed before dressing removal for each dressing change during the 12-week treatment period, using either a validated visual analogue scale (VAS) or a verbal rating scale (VRS)" Comment: participants were not blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	All participants were accounted for at the end of the study period, but of the 50 originally enrolled, 48 were randomised and only 33 were included in the final analysis
Selective reporting (reporting bias)	Low risk	All outcomes were reported on

Gethin 2007

Methods	RCT Setting: variety of clinics including leg ulcer clinics, vascular clinics, also community nursing units in Ireland
Participants	n = 108: Group A: n = 54; Group B: n = 54 Mean age: Group A: 68.5 years; Group B: 68.3 years Mean ulcer size: Group A: 10.52 cm^2 Group B: 9.87 cm^2 Mean ulcer duration: Group A: 39.46 weeks; Group B: 29.93 weeks Baseline comparability established between groups Inclusion criteria • Venous ulceration • > 50% of wound area covered in slough at baseline • Ulcer size < 100cm^2 Exclusion criteria • Malignant ulcer or cavity wounds • Clinical diagnosis of wound infection • Currently taking antibiotics for any reason • Immunosuppression therapy • Poorly controlled diabetes • Pregnant or lactating women • Previous enrolment in the study

Gethin 2007 (*Continued*)

Interventions	Group A: topical Manuka honey (n = 54) direct to wound bed (Wound care 18+, Comvita, New Zealand) weekly for 4 weeks. Dosage: 5 g/20 cm² Group B: hydrogel (n = 54; IntraSite gel, Smith & Nephew) weekly for 4 weeks. Dosage: 3 g/20 cm² All wounds were cleansed with tap water prior to dressing change Treatment period was 4 weeks, after which dressing choice was based on the clinical judgement of the attending clinician. Participant were followed up at 12 weeks to determine healing outcomes All participants had compression therapy, the most common being 4-layer compression Participants were withdrawn if they commenced on antibiotic therapy for any reason during the 4-week treatment period
Outcomes	• Mean percentage reduction in slough after 4 weeks • Percentage of wounds healed at 12 weeks • Reduction in wound size • Adverse events
Notes	Funding: Health Research Board of Ireland Classed as autolytic versus autolytic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised via remote phone allocation to either treatment group". "The allocation sequence was generated using serially numbered, sealed, opaque envelopes, prior to the study by two persons independent of the study". "The sequence was generated in two stages each of which was independent of the researcher. A number of coloured cards either treatment or controls were prepared for the total number of participants required for recruitment. These were then shuffled and placed in sealed envelopes.The sealed envelopes were then shuffled again and were sequentially numbered.This process was completed by two people who were not involved in the study." Comment: judged as being at low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: remote phone allocation
Blinding (performance bias and detection bias) Time to debridement	High risk	Comment: assessors were not blinded. Multiple assessors across 10 sites were involved, thus reducing the potential for sys-

Gethin 2007 (*Continued*)

		tematic performance or detection bias, but the lack of blinding means we have deemed this to be at a high risk of bias
Blinding (performance bias and detection bias) Time to healing	High risk	Comment: definition of healing was not provided, but wound size was measured objectively using digital planimetry, however, assessors were not blinded
Blinding (performance bias and detection bias) Adverse events	High risk	Comment: all adverse events were reported; assessors were not blinded
Blinding (performance bias and detection bias) Ulcer related pain	Unclear risk	Comment: this was not reported as a study outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all withdrawals were accounted for and reasons for withdrawals were recorded
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported in full

Groenewald 1980

Methods	RCT Setting: foot and leg clinic in South Africa
Participants	n = 100: Group A: 50 (11 male; 39 female); Group B: 50 (9 male; 41 female) Note 5 participants withdrew and were replaced by 5 more Mean age: not reported Mean ulcer size: reported as small, medium, large and shallow or deep Percentage of wounds covered in debris (slough) at start: Group A: 84%; Group B: 80% Inclusion criteria: not specified, but reported that patients with lower leg ulceration due to venous hypertension were seen in this clinic Exclusion criteria: not reported
Interventions	Group A: dextranomer beads (Debrisan beads) to a depth of 2 mm-3 mm, covered by perforated plastic foil covered multi-layer gauze bandage kept in place by a standard gauze bandage Group B: gauze swabs soaked in EUSOL solution. In those with *Pseudomonas* infection 0.35% acetic acid solution was used instead. Surrounding skin painted with tincture of merthiolate. Antifungal agents used as indicated for surrounding skin. Povidine iodine ointment was swabbed onto the ulcer and a pressure bandage applied Both groups has similar cleansing procedures Frequency of dressing change not reported

Groenewald 1980 (*Continued*)

Outcomes	• Percentage or number of wounds completely debrided. • Time to complete debridement • Ulcer healing • Pain: not assessed using a validated pain assessment tool
Notes	Per protocol analysis Autolytic versus autolytic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the method of sequence generation was not reported, therefore a judgement of risk of bias could not be made
Allocation concealment (selection bias)	High risk	Quote; "one hundred patients were divided into two randomised equal groups" Comment: participants or investigators enrolling participants could possibly forsee assignments and thus introduce selection bias 5 participants withdrew and were replaced by 5 more
Blinding (performance bias and detection bias) Time to debridement	Low risk	Quote: "single-blind". This is stated in the abstract Comment: stated that two "independent investigators" performed such evaluations. While photographs were used for healing, they were not used for assessment of debridement. A 5-point scale was used to evaluate outcomes with 1 representing absence or lowest possible level and 5 the most active or severe level
Blinding (performance bias and detection bias) Time to healing	Low risk	Comment: healing was not defined, but the use of photographs and tracings would reduce the possibility of bias. As above, the study states "single-blind", thus reducing the risk of bias
Blinding (performance bias and detection bias) Adverse events	Unclear risk	Comment: none reported, yet not all participants completed the study; 5 were withdrawn, but the timing of withdrawal, or reasons for withdrawal were not stated, and thus a judgement of risk of bias could not be made

Groenewald 1980 (*Continued*)

Blinding (performance bias and detection bias) Ulcer related pain	High risk	Comment: method of pain evaluation was not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 5 "dropped out" during the study but reasons for drop out were not provided and not all participants were accounted for at the end of the study
Selective reporting (reporting bias)	High risk	Comment: not all outcomes, adverse events or attrition were reported

Hansson 1998

Methods	RCT Setting: multi-national including Sweden, Denmark, Netherlands, United Kingdom
Participants	n = 153: Group A: n = 56; Group B: n = 48: Group C: n = 49 Mean age: Group A: 74 years; Group B: 74 years; Group C: 72 years Mean ulcer area: Group A: 8.8 cm^2; Group B: 10.7 cm^2; Group C: 7.1 cm^2 Inclusion criteria • Exuding or sloughy venous ulcers • Wound size 1 cm^2-100 cm^2 Exclusion criteria • Systolic ankle pressure < 80 mmHg • ABPI < 0.8 • Clinical infection • Diabetes • Known sensitivity to any of the products • Systemic antibiotics in last week before the study • Systemic corticosteroids or cytostatic drugs during last 4 weeks • Diseases that could effect ulcer healing including vasculitis, sclerosis, lupus erythematous, rheumatoid arthritis or patients undergoing investigations of the thyroid
Interventions	Group A: cadexomer iodine paste. Changed when indicated by colour change from brown to yellow-grey Group B: Duoderm hydrocolloid. Changed when leaking or saturated with fluid Group C: Jelonet. Changed when leaking or saturated with fluid All participants had short-stretch compression bandaging
Outcomes	Results were presented at 3 time points: 4, 8 and 12 weeks • Percentage of ulcers with slough • Percentage reduction in wound size. • Ulcer area reduction as percentage of baseline • Percentage of ulcers with pain

Hansson 1998 (*Continued*)

Notes	Comment: high number of adverse events and study withdrawals 12, 7, and 9 participants withdrawn from Groups A, B and C, respectively, for reasons unrelated to efficacy and excluded from the final analysis 12, 5, and 8 participants withdrawn from Groups A, B and C, respectively, for reasons of efficacy but were included in the final analysis on an ITT basis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a randomised, open, controlled, multicenter trial with a parallel group design". "Patients were randomised to receive one of three treatments" Comment: insufficient information about the sequence generation process to permit judgement on risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: the method of concealment was not sufficiently described to allow a definitive judgement of the level of risk
Blinding (performance bias and detection bias) Time to debridement	High risk	Comment: all wounds were traced using transparent film and felt tip pen in addition to being photographed, however, details of the assessor were not provided nor information about whether this assessment was blinded. Levels of slough were assessed as being 'none', 'mild', 'moderate' and 'extensive', which is a very subjective means of assessment, and open to variation among assessors
Blinding (performance bias and detection bias) Time to healing	High risk	Comment: all wounds were traced using transparent film and felt tip pen in addition to being photographed, however, details of the assessor were not provided nor information about whether this assessment was blinded, but since this was a multi-centre trial conducted across 4 countries, the potential for detection bias would have been reduced. No definition of healing was provided
Blinding (performance bias and detection bias) Adverse events	High risk	Comment: all adverse events were reported, but assessors were not blinded

Hansson 1998 (*Continued*)

Blinding (performance bias and detection bias) Ulcer related pain	High risk	Comment: pain assessed as 'none', 'mild', 'moderate' and 'extensive'. A pain scale was not used, and no attempt at addressing the validity of this method of assessment was made
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: all withdrawals were accounted for, but the high number of withdrawals increases the risk of bias
Selective reporting (reporting bias)	High risk	Comment: all outcomes were reported, but the method of reporting lacked detail, for example, slough levels were reported as a percentage of the patient's whose ulcers were covered with slough, but not as a percentage of the actual wound area

Jasiel 1996

Methods	RCT Setting: 6 hospitals across Poland
Participants	n = 86: Group A: n = 46 (30 female; 16 male); Group B: n = 40 (24 female; 16 male) Mean age: Group A: 66.2 years; Group B: 64.1 years Mean wound duration: Group A: 15 months (variance 2 weeks-60 months); Group B: 20.1 months (variance 3 weeks-20 years) Mean ulcer size: Group A: 47.5 cm^2 (variance 0.84 cm^2-360 cm^2) Group B: 33.0 cm^2 (variance 1 cm^2-375 cm^2) Inclusion criteria • Male or female over 18 years able to give written informed consent • Necrotic venous ulcers with low to medium exudate • ABPI $\geq$ 0.8 Exclusion criteria • Pregnant or lactating women • Ankle circumference < 18 cm • Diabetes mellitus • Participant in another clinical trial during the previous 3 months, or already included in this clinical trial
Interventions	Group A: Sterigel (hydrogel) applied every 1-2 days. Cleansed with normal saline. Covered with melolin dressing; compression therapy applied Group B: paraffin gauze applied every 1-2 days. Regime similar to that for Group A All wounds photographed and traced at baseline Full evaluation of wound status made at each dressing change Tracings and photographs taken at every third visit Duration of treatment: 21days or until the wound had debrided, whichever was sooner

Outcomes	• Debridement (reported as number of ulcers debrided) • Time to debridement (days)
Notes	Per protocol analysis Autolytic versus autolytic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patient was randomised to receive either Sterigel or paraffin gauze using a code developed by the statistician" Comment: the lack of information about the method used to generate the code means we could not make a judgement of risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: no information was provided upon which a judgement of risk of bias could be made
Blinding (performance bias and detection bias) Time to debridement	High risk	Comment: all wounds were photographed and traced, readings were taken at multiple time points and necrotic tissue was recorded on a percentage scale. No information about whether assessors were blinded to treatment allocation
Blinding (performance bias and detection bias) Time to healing	Unclear risk	Comment: this was not a study outcome
Blinding (performance bias and detection bias) Adverse events	High risk	Comment: all adverse events were reported, but assessors were not blinded
Blinding (performance bias and detection bias) Ulcer related pain	Unclear risk	This was not a study outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for in the final analysis
Selective reporting (reporting bias)	High risk	Comment: lacked specifics and sufficient detail about the percentage of the wound bed covered in slough at the start of the study period, and at the time of completion of the study

Konig 2005

Methods	RCT Setting: outpatients attending a wound healing unit in Germany
Participants	n = 42 Mean age: 71.7 years for all participants (males: 72.4 years; females: 71.7 years) Inclusion criteria • Venous leg ulcers with chronic venous insufficiency • Ulcer duration > 6 weeks • Outpatients > 18 years • Able to perform self care of their wound and apply compression independently Exclusion criteria • Concomitanat disease suggesting impediments to healing • Disabling disease including malignant tumours, tuberculosis and HIV • Administration of steroids (> 8 mg prednisolone daily) • Peripheral arterial disease from Fontaine's stage 11a
Interventions	Group A: TenderWet 24, changed every 24 hours Group B: Iruxol N, changed every 24 hours All participants changed their own dressing and applied short-stretch compression bandages Subjective assessment of the wound bed conducted by two assessors at days 0, 7, 14, and 21
Outcomes	• Percentage reduction of slough (day 14) • Percentage reduction of slough (day 21)
Notes	All patients had a wash-out period of 7 days prior to commencement of study treatments Autolytic versus enzymatic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated list"
Allocation concealment (selection bias)	Unclear risk	Comment: there was no information about how allocation was achieved, and the lack of detail did not permit a precise judgement on risk of bias to be made
Blinding (performance bias and detection bias) Time to debridement	High risk	Quote: " A dermatologist and second assessor from the wound-healing unit undertook weekly assessments that included subjective description of the wound with respect to percentage reduction of slough/eschar" Comment: as participants were assessed weekly, yet dressing changes were com-

Konig 2005 (*Continued*)

		pleted daily, it is difficult to determine the time of debridement and thus the risk of bias must be considered to be high. In addition, the study was not stated as being blinded
Blinding (performance bias and detection bias) Time to healing	Unclear risk	Comment: not a study outcome
Blinding (performance bias and detection bias) Adverse events	High risk	Comment: no reports of adverse events. All participants completed the 14 day treatment period. Assessors were not blinded
Blinding (performance bias and detection bias) Ulcer related pain	Unclear risk	Comment: not assessed in this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for at the end of the trial period
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported

Skog 1983

Methods	RCT Setting: outpatients attending clinics across 10 sites in Sweden
Participants	n = 95 (21 excluded from results): Group A: n = 38 (10 male, 28 female); Group B: n = 36 (8 male, 28 female) Mean age: Group A: 68.1 years; Group B: 72.1 years Mean ulcer duration: Group A: 26.5 months; Group B: 22.2 months Mean ulcer size: Group A: 20.1 cm^2; Group B: 34 cm^2 Depth of ulcer: Group A: deep n = 11; superficial n = 26; very superficial n = 1 Group B: deep n = 12; superficial n = 23; very superficial n = 1 Inclusion criteria • Chronic infected venous ulcers that had failed to respond to previous treatments • Minimum diameter of 2 cm and minimum area of 3 cm^2 Exclusion criteria • Known sensitivity to iodine • Peripheral arterial disease Size, depth, photographs, bacteriological culture swab taken at baseline
Interventions	Group A: cadexomer iodine powder. Ulcers cleaned in running water and treatment applied to a depth of 3 mm and covered with dry dressing. Dressings changed daily, or, in extreme cases of high exudate, twice daily Group B: standard treatment. Cleansed with dilute hydrogen peroxide or dilute potas-

	sium permanganate and non-adherent dressing. Paraffin-impregnated dressings or saline dressings were the most commonly used Pain, pus and debris, exudate, granulation, erythema and oedema assessed using a VAS Duration of treatment was 6 weeks. All wounds assessed at 1 week
Outcomes	• Mean percentage reduction in pus and debris (1 week) • Mean percentage change in ulcer size (at 6 weeks) • Mean percentage reduction in pain scores (1 week). No comment on the use of a validated pain scale
Notes	21 participants excluded from final analysis - reasons for withdrawal reported Compression therapy used Results include 7 participants with ulcers of mixed aetiology. However,as compression was used throughout, all were considered as meeting the criteria for this review Autolytic versus autolytic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: there was no information provided on how the randomisation sequence was generated and therefore a judgement on risk of bias could not be made
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were allocated blindly and at random" Comment: the method of allocation was not stated and therefore a definitive judgement could not be made
Blinding (performance bias and detection bias) Time to debridement	High risk	Comment: the trial was not described as blind All assessments were conducted at 1, 2, 4, and 6 weeks by the same observer. Treatments were applied by a "visiting nurse". Ulcers were measured using planimetry and photographed, so attempts were made to provide objective evaluations of outcomes, but lack of blinding means that this domain is at high risk of bias
Blinding (performance bias and detection bias) Time to healing	High risk	Comment: changes in ulcer size were reported, but healing was not reported, yet this was a study outcome
Blinding (performance bias and detection bias) Adverse events	Unclear risk	Comment: adverse events were recorded and reportedly were not related to treatment products

Skog 1983 (*Continued*)

Blinding (performance bias and detection bias) Ulcer related pain	High risk	Comment: recordings were on a VAS, but there was no reference to validation of this scale and assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 21 sets of data were excluded from the final analysis
Selective reporting (reporting bias)	High risk	Comment: due to the high number of data sets excluded from the final analysis we have judged this as being at a high risk of bias. In addition, the healing outcome was not reported

Wayman 2000

Methods	RCT Setting: leg ulcer service in United Kingdom
Participants	n = 12: Group A: male:female ratio 2:4; Group B: male:female ratio 3:3 Mean age: Group A: 58 years (variance 48-72 years); Group B: 54 years (variance 40-75 years) Mean ulcer duration: Group A: 5 months (variance 2-8 months); Group B: 4 months (variance 2-6 months) Mean ulcer size: Group A: 18 cm^2 (13 cm^2-25 cm^2); Group B: 16 cm^2 (14 cm^2-22 cm^2) Inclusion criterion • Sloughy venous ulcer Exclusion criteria • Arterial insufficiency • Previous therapy failed
Interventions	Group A: larval therapy, sterile *Lucilia sericata* re-applied every 72 hours Group B: hydrogel therapy (Intrasite gel), applied as indicated by clinician and left in situ for maximum of 72 hours
Outcomes	• Time to debridement expressed as mean number of days to achieve debridement
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomised and entered into one of the two groups" Comment: insufficient information was provided to permit a judgement of risk of bias

Wayman 2000 (*Continued*)

Allocation concealment (selection bias)	High risk	Quote: "randomisation was by sealed envelope" Comment: participants or investigators enrolling participants could possibly foresee assignment and thus introduce selection bias; no statement that envelopes were opaque
Blinding (performance bias and detection bias) Time to debridement	High risk	Quote: "The nurse applying the dressings determined the success of debridement" Comment: the lack of blinding and of a second assessor or other method of objective outcome evaluation means that the risk of bias is high
Blinding (performance bias and detection bias) Time to healing	Unclear risk	Comment: not a study outcome
Blinding (performance bias and detection bias) Adverse events	High risk	Comment: none reported, but assessors were not blinded
Blinding (performance bias and detection bias) Ulcer related pain	Unclear risk	Comment: not assessed in this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for at the end of the trial
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported

Westerhof 1990

Methods	RCT Setting: dermatology department, the Netherlands
Participants	n = 29 participants with 31 wounds: Group A: 16 wounds; Group B: 15 wounds Median ulcer duration: Group A: 6 months; Group B: 4 months Mean wound area: Group A: 397 mm^2 (SD 277); Group B: 458 mm^2 (SD 185) Mean area covered in slough: Group A: 77%; Group B: 55% Inclusion criteria • Necrotic venous ulcers Exclusion criteria • Pregnancy • Arterial insufficiency • Vasculitis • Peripheral neuropathy

Westerhof 1990 (*Continued*)

	• Diabetes • Known allergies towards sea food protein
Interventions	Treatment period = 7 days Group A: freeze-dried, sterile, krill enzymes applied twice daily with saline gauze and occlusion Group B: standard 7-day protocol: 2% acetic acid for 2 days; 10% povidone iodine for 2 days; saline dressing for 3 days Participant and doctor evaluated wound outcomes using a scale Ulcer photographs were made daily using a fixed-focus Polaroid camera and analysed blindly The clinical observer did not know which treatment was being used
Outcomes	• Mean percentage reduction in slough • Median time to debridement (reported as time to achieve clean, granulating wound) • Reduction in wound size (reported as mean percentage after 7 days)
Notes	Aim of study was to cleanse ulcers prior to grafting Enzymatic versus autolytic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "trial was designed as randomised and observer blind ... patients were treated with either krill enzymes or the non-enzymatic treatment according to a randomisation list" Comment: the lack of information about the method used to generate the randomisation list meant we could not make a judgement on the risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: no data upon which to judge the risk of bias
Blinding (performance bias and detection bias) Time to debridement	Low risk	Quote: "the clinical observer did not know which treatment was used" Comment: 7-day treatment period allowed close observation. Ulcers were photographed, and the total wound area covered by necrosis was assessed by blinded computer image analysis
Blinding (performance bias and detection bias) Time to healing	Low risk	Quote: "the clinical observer did not know which treatment was used" Comment: 7-day treatment period al-

Westerhof 1990 (*Continued*)

		lowed close observation. Ulcers were photographed. Computer image analysis used. Reduction is size was assessed but not healing as a specific outcome
Blinding (performance bias and detection bias) Adverse events	Unclear risk	Comment: report states that in both groups maceration of peri wound area occurred, but was not reported as an adverse event and so we could not make a precise judgement about the risk of bias
Blinding (performance bias and detection bias) Ulcer related pain	Unclear risk	Comment: method of pain assessment was not stated, but was part of an overall global assessment of treatment effect, so we could not make an assessment of risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: reported overall results, but did not state baseline comparability and provided no indication of any withdrawals
Selective reporting (reporting bias)	High risk	Comment: specific data related to pain, oedema or erythema were not reported, but were assessed during the study period. Mean scores were provided but did not report the range, SD or CI

Wild 2010

Methods	RCT Setting: in-patients and out-patients. The country in which this trial was conducted was not stated explicitly, but the authors were from Austria/Germany and The Netherlands
Participants	n = 40: Group A: n = 20 (10 female versus 10 male); Group B: n = 20 (12 female versus 8 male) Mean age: Group A: 66.4 years (variance 51-79 years) Group B: 65.2 years (variance 42-76 years) Mean ulcer size: Group A: 548.58 mm² (variance 45.53 - 2744.16 mm²); Group B: 629.9 mm² (variance 43.05 -4254.03 mm²) Mean necrosis: Group A: 3.36% ± 12.61%; Group B: 4.2% ± 9.13% Mean yellow (slough): Group A: 75.2% ± 31.9%; Group B: 80.17% ± 13.8% Inclusion criteria • Target ulcer had to be secondary to chronic venous disease with the wound bed containing fibrin and/or slough Those with bilateral ulcers were randomised to one treatment only and the reference limb was taken as the one with the largest total area of ulceration
Interventions	Group A: Biocellulose dressing (Suprasorb X) Group B: Hydrofibre dressing (Aquacel) For both groups frequency of application was at clinician's discretion, but usually every

	2 days. Both groups received short-stretch compression therapy Duration of treatment was 4 weeks
Outcomes	• Percentage or number of wounds completely debrided reported as: mean percentage reduction in slough (yellow tissue) (day 14, 21 and 28) • Total mean percentage reduction in ulcer size • Pain, assessed as impact on pain during dressing change (no report of using a validated pain assessment tool)
Notes	Autolytic versus autolytic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: " A computer generated randomisation schedule"
Allocation concealment (selection bias)	Unclear risk	Comment: no information was provided about the method of allocation concealment, so we could not make a judgement of risk of bias
Blinding (performance bias and detection bias) Time to debridement	Low risk	Quote: "The assessor was blinded to the treatment given" Comment: digital images were used for analysis, thus reducing the potential for subjective assessment. A scoring matrix called 'WHAT' [wound healing analysing tool] was also used, so it can be considered that reasonable attempts were made for objective evaluations
Blinding (performance bias and detection bias) Time to healing	Low risk	Comment: wound area measurements were performed, although the exact method was not made clear. The assessor was blinded to treatment allocation
Blinding (performance bias and detection bias) Adverse events	Low risk	Comment: no adverse events were reported
Blinding (performance bias and detection bias) Ulcer related pain	High risk	Comment: 10-point visual analogue scale was used, but no reference was made to validity of this scale
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no withdrawals were reported

Wild 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported

Abbreviations
ABPI: ankle-brachial pressure index
BWD: biocellulose dressing
CI: confidence interval
EUSOL: Edinburgh University Solution of Lime
ITT: intention-to-treat (analysis)
RCT: randomised controlled trial
SD: standard deviation
VAS: visual analogue scale

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

Study	Reason for exclusion
Andersen 2002	RCT; wounds varied in terms of whether devitalised tissue was present or not, so not all wounds had slough or necrotic tissue upon study entry and there was no requirement for slough to be present
Armstrong 1996	Debridement was not an outcome
Bowszyc 1994	RCT; debridement was not a primary or secondary outcome. Patients excluded if necrotic tissue present
Boxer 1969	Study included 47 participants with venous, arterial and pressure ulcers. Participants randomised, but it was not stated how many from each aetiology were in each group. Results were presented as per ulcer, not per participant and were not stratified according to aetiology. This meant that the efficacy of the intervention or control in venous ulcers was not stated
Bressieux 2007	Debridement was not an outcome
Burgess 1993	Debridement was not an outcome
Caputo 2008	RCT; included diabetic foot ulcers, pressure ulcers and venous leg ulcers, however, the results were not presented according to aetiology
Cardinal 2009	Retrospective review and not an RCT
Contretas-Ruiz 2004	RCT; debridement was not an outcome, as bacterial quantity and quality were the outcome of interest
Dereure 2012	Presence of necrotic tissue was an exclusion criterion for study entry
Dumville 2009	RCT; participants with mixed aetiology ulcers were included, but the results were not stratified according to aetiology

(*Continued*)

Eriksson 1984	RCT; debridement was not an outcome
Falabella 1998	RCT; 4 treatment groups. Wounds "chronic ulcers of lower extremity". Did not provide aetiology of ulcers, so we could not conclude that all were venous in origin
Fischer 1984	RCT; general outcomes reported. Aimed to determine benefit of antibiotic in addition to enzymatic preparation on healing. No requirement for slough to be present at commencement of the study
Floden 1978	RCT. Lacked sufficient information on presence or absence of slough at baseline, so not clear whether all wounds had slough on study entry. In addition, outcomes assessed as 'improved' or 'not improved' so we were unable to determine whether debridement was achieved, or time to debridement
Forsling 1988	RCT; wounds "chronic leg ulcers or traumatic wound with oozing surfaces containing debris and pus". Aetiology of ulcers not provided, baseline characteristics and outcomes were not aetiology-specific
Gamborg 1990	RCT; all participants underwent surgical wound debridement prior to study commencement, and debridement was not part of the study protocol
Gordon 1975	RCT; some participants did not have slough at commencement of the study and the results were not stratified according to those with or without slough
Gray 2008	Not an RCT
Groenewald 1981	Not an RCT
Grotewohl 1994	RCT; debridement was not an outcome
Harcup 1986	RCT; although pus/debris was reported as an outcome, there was no requirement for all ulcers to have slough at the start of the study and no stratification of results according to the presence or absence of slough at the start
Hellgren 1983	Included ulcers of venous, arterial and arteriovenous origins. Did not present results according to ulcer type, therefore we could not determine the effect in venous ulcers
Hillstrom 1988	RCT; included participants with mixed aetiology and venous ulcers, and did not stratify the results according to aetiology
Holloway 1989	RCT; baseline information on slough not provided, so debridement effects could not be specifically determined. The presence of slough was not a study entry criterion
Hulkko 1981	RCT; report stated that "Before the start of topical therapy ... hard necrosis was excised from the wound", so debridement commenced prior to the study treatment period
Jorgensen 2005	Debridement was not an outcome
Laudanska 1988	RCT; baseline percentage of slough not known and presence of slough was not a study entry criterion
Leach 2006	Debridement was not an outcome

(*Continued*)

Lindsay 1986	Debridement was not an outcome
Lok 1999	RCT; evaluation of EMLA cream to facilitate the actual debridement. The method of debridement was not the primary objective
Marazzi 2006	Not an RCT
Mekkes 1992	Not an RCT
Mudge 2014	Included venous and mixed aetiology ulcers and did not stratify results according to aetiology, so we were unable to determine outcomes in venous ulcers
Munter 2006	RCT; debridement was not an outcome
Nelson 1995	RCT; debridement was not an outcome
Olyaie 2013	Debridement was not an outcome
Robinson 1995	RCT of leg ulcers, the aetiology was not specified, so we could not conclude they were venous in origin. Baseline data on participant or wound characteristics were not available
Roldan 2010	RCT; hard to heal wounds and not specifically venous leg ulcers. Results not specific to venous leg ulcers
Romanelli 2009	Pilot evaluation, not an RCT
Sawyer 1979	RCT; included wounds of varying aetiology and did not stratify results according to aetiology, so we were unable to determine effects in venous leg ulcers
Stewart 1987	RCT; included studies of various aetiologies but did not stratify results according to aetiology. Did not record baseline slough, make on-going formal assessment of slough, or report specific debridement outcome
Stromberg 1984	Included participants with wounds of various aetiologies. Did not stratify results according to aetiology and so we were unable to determine any effect in venous ulcers specifically
Tarvainen 1988	RCT; debridement effect not quantified
Westerhof 1987	RCT; there were no data on the 3 primary outcomes for this review. There was an overall 'global assessment' of the wound status using a grading scale, but no data on the number of wounds debrided or time to debridement
Williams 2005	Not an RCT

Abbreviations
EMLA: Eutectic Mixture of Local Anaesthetics
RCT: randomised controlled trial

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

Humbert 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	awaiting clarification from author

Meaume 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	awaiting clarification from author

DATA AND ANALYSES

Comparison 1. Autolytic versus autolytic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wounds completely debrided	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 paraffin gauze versus hydrogel	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 0.99]
1.2 Debrisan versus EUSOL	1	100	Risk Ratio (M-H, Fixed, 95% CI)	5.71 [2.84, 11.52]
1.3 Biocellulose versus non-adherent	1	48	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [1.34, 8.89]
2 Number of wounds healed	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Honey versus Hydrogel	1	108	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.82, 2.16]
2.2 Biocellulose versus non-adherent	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.38, 2.22]
3 Percentage reduction in wound size at 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Cadexomer iodine versus hydrocolloid	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Cadexomer iodine versus paraffin gauze	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Hydrocolloid versus paraffin gauze	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Changes in pain			Other data	No numeric data
5 Reported adverse events			Other data	No numeric data

Comparison 2. Enzymatic versus autolytic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Percentage reduction in wound size at 7 days	1	200	Mean Difference (IV, Fixed, 95% CI)	10.0 [0.57, 19.43]

Comparison 3. Biosurgical versus autolytic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wounds completely debrided:	1	12	Risk Ratio (IV, Fixed, 95% CI)	2.6 [0.94, 7.17]

Analysis 1.1. Comparison 1 Autolytic versus autolytic, Outcome 1 Wounds completely debrided.

Review: Debridement for venous leg ulcers

Comparison: 1 Autolytic versus autolytic

Outcome: 1 Wounds completely debrided

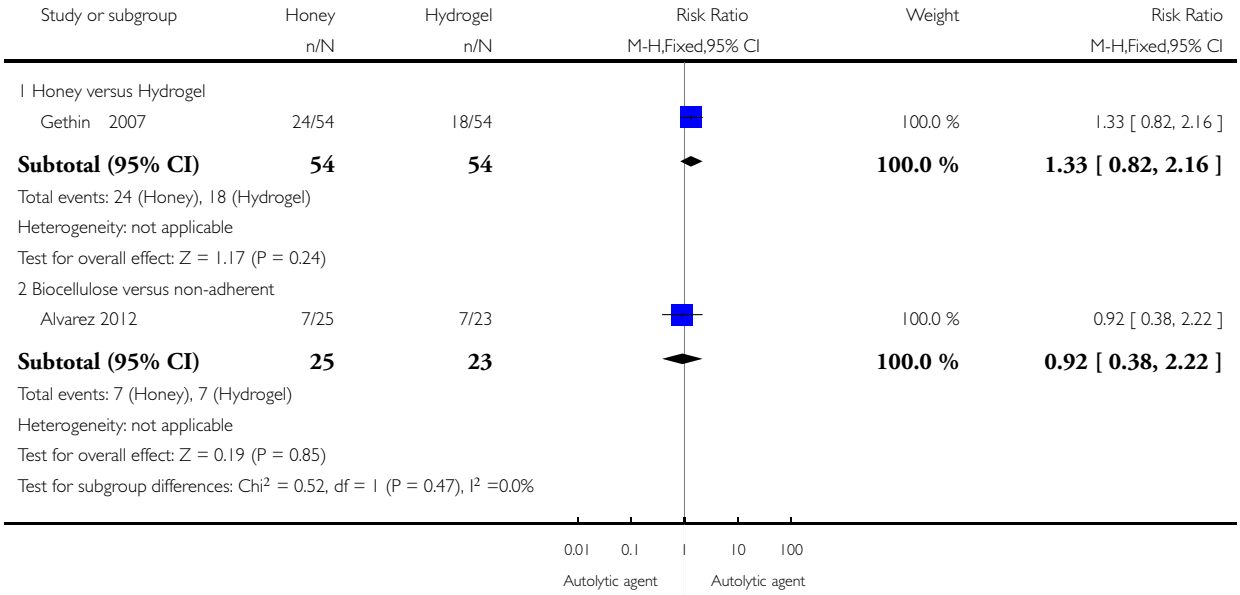
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 paraffin gauze versus hydrogel					
Jasiel 1996	18/40	31/46		100.0 %	0.67 [0.45, 0.99]
Subtotal (95% CI)	**40**	**46**		**100.0 %**	**0.67 [0.45, 0.99]**
Total events: 18 (Experimental), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.99 (P = 0.046)					
2 Debrisan versus EUSOL					
Groenewald 1980	40/50	7/50		100.0 %	5.71 [2.84, 11.52]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**5.71 [2.84, 11.52]**
Total events: 40 (Experimental), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.87 (P < 0.00001)					
3 Biocellulose versus non-adherent					
Alvarez 2012	15/25	4/23		100.0 %	3.45 [1.34, 8.89]
Subtotal (95% CI)	**25**	**23**		**100.0 %**	**3.45 [1.34, 8.89]**
Total events: 15 (Experimental), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					
Test for subgroup differences: Chi^2 = 32.03, df = 2 (P = 0.00), I^2 =94%					

Analysis 1.2. Comparison 1 Autolytic versus autolytic, Outcome 2 Number of wounds healed.

Review: Debridement for venous leg ulcers

Comparison: 1 Autolytic versus autolytic

Outcome: 2 Number of wounds healed

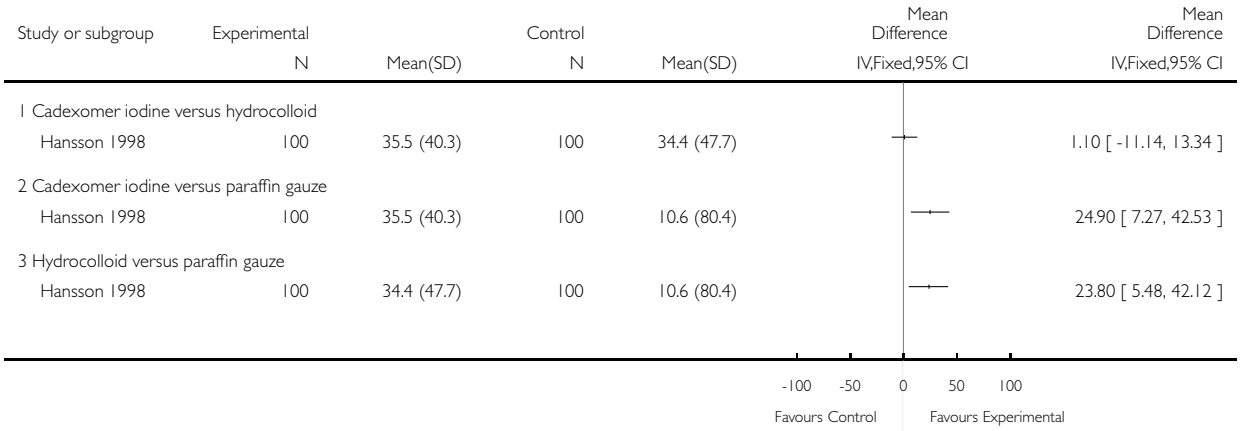


Analysis 1.3. Comparison 1 Autolytic versus autolytic, Outcome 3 Percentage reduction in wound size at 4 weeks.

Review: Debridement for venous leg ulcers

Comparison: 1 Autolytic versus autolytic

Outcome: 3 Percentage reduction in wound size at 4 weeks



Analysis 1.4. Comparison 1 Autolytic versus autolytic, Outcome 4 Changes in pain.

Changes in pain

Study	Intervention	Method to assess pain	Timing of pain results	Results	Comments
Alvarez 2012	Biocellulose dressing versus non-adherent dressing	Scale 1-10	Asssessed weekly for 12 weeks	'At each evaluation point, a larger proportion of patient streated with biocellulose dressing reported no pain or mild pain compared with control. No statistically significant differences reported	Although a scale was used, results according to the scale are not presented
Gethin 2007	Honey versus Hydrogel	Scale 1-5	Weekly	39% (n=7) of the cases of infection had an increase in pain during the treatment period	

Changes in pain (*Continued*)

Groenewald 1980	Debrisan versus EUSOL	Scale 1-5 with 5 representing the most severe level.	Assessed at baseline, days 3,7,10,14	30 patients in Debrisan and 35 in EUSOL group reported pain at baseline.Eight patients (30%) in Debrisan group, pain initially worsened and later improved. 13 (37%) in EUSOL group had initial deterioration in pain but did not improve in four of these	Results given at different time points on a per protocol basis. Although a scale was used, results according to the scale are not presented
Hansson 1998	Cadexomer iodine versus hydrocolloid versus paraffin gauze	Graded scale (not specified)	Baseline, 4,8,12 weeks	Reported the percentage of ulcers with pain in each group: baseline - 66,73,57; week 4 - 59, 50, 47; week 8 - 19, 48, 19; week 12 - 29, 57, 15	Results at each time point are for those remaining in the trial and not the number on entry to the trial
Skog 1983	Cadexomer iodine versus standard care	Analogue scale (no further details supplied)	1 week and 6 weeks	Mean percentage reduction at week 1 (Cadexomer iodine versus Standard care: 27% versus 29%; at week 6, 10% versus 23 %	
Wild 2010	Biocellulose dressing versus hydrofibre	10 point scale assessed during dressing changes	Day 7 and Day 28	At 28 days mean score 1.3 (SD+/- 0. 47) in Biocellulose group versus 3.20 (SD +/-1.20) in hydrofibre group	

Analysis 1.5. Comparison 1 Autolytic versus autolytic, Outcome 5 Reported adverse events.

Reported adverse events

Study	**Reports adverse events due to the study treatments**	**Reports adverse events not due to the study treatments**
Alvarez 2012	Clinically-infected ulcer n=8 (3 BWD group, 5 non-adherent group)	Nil

Reported adverse events (*Continued*)

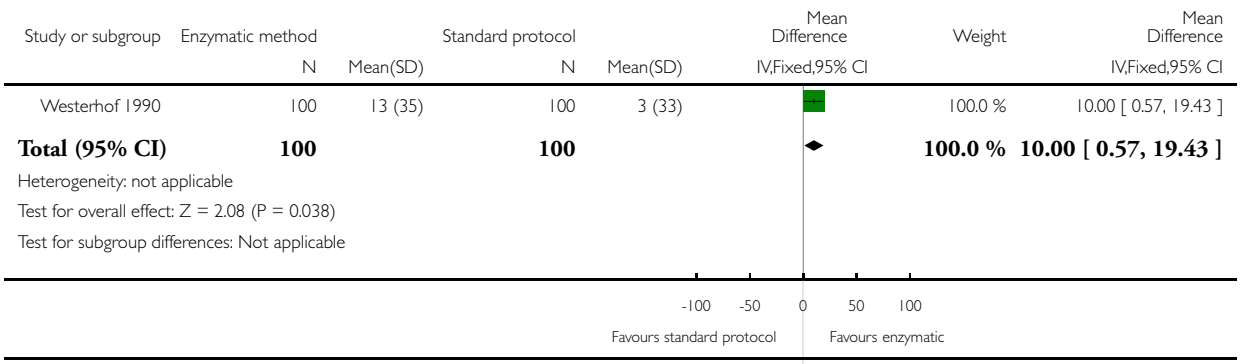
	Cellulitis n=3 (2 BWD group, 1 non-adherent group) Dermatitis n=3 (1 BWD group, 2 non-adherent group)	
Gethin 2007	States no adverse events	States no adverse events
Groenewald 1980	None reported	None reported
Hansson 1998	None reported	12 patients in cadexomer iodine, 7 in hydrocolloid group and 9 in paraffin gauze group were withdrawn due to: allergic reactions, dermatitis, pain and poor compliance - report stated this was not due to the study treatments
Jasiel 1996	One adverse event in paraffin gauze group which involved maceration and infection One adverse event in hydrogel group 'possibly' due to treatment involving erysipelas, one patient had oedematous reaction	One withdrawal in paraffin gauze group due to thrombophlebitis One patient in hydrogel group had infection.
Skog 1983	While withdrawals are noted, there are no adverse events reported	While withdrawals are noted, there are no adverse events reported
Wild 2010	None reported	None reported

Analysis 2.1. Comparison 2 Enzymatic versus autolytic, Outcome 1 Percentage reduction in wound size at 7 days.

Review: Debridement for venous leg ulcers

Comparison: 2 Enzymatic versus autolytic

Outcome: 1 Percentage reduction in wound size at 7 days



Analysis 3.1. Comparison 3 Biosurgical versus autolytic, Outcome 1 Wounds completely debrided:.

Review: Debridement for venous leg ulcers
Comparison: 3 Biosurgical versus autolytic
Outcome: 1 Wounds completely debrided:

Study or subgroup	Biosurgical n/N	Autolytic n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Wayman 2000	6/6	2/6		100.0 %	2.60 [0.94, 7.17]
Total (95% CI)	**6**	**6**		**100.0 %**	**2.60 [0.94, 7.17]**
Total events: 6 (Biosurgical), 2 (Autolytic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.065)					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Cinahl search strategy

S41 S28 AND S40
S40 S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39
S39 TX allocat* random*
S38 (MH "Quantitative Studies")
S37 (MH "Placebos")
S36 TX placebo*
S35 TX random* allocat*
S34 (MH "Random Assignment")
S33 TX randomi* control* trial*
S32 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S31 TX clinic* n1 trial*
S30 PT Clinical trial
S29 (MH "Clinical Trials+")
S28 S23 and S27
S27 S24 or S25 or S26

S26 TI lower extremit* N2 ulcer* or AB lower extremit* N2 ulcer*
S25 TI (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or stasis ulcer*) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or stasis ulcer*)
S24 (MH "Leg Ulcer+")
S23 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 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
S22 TI zinc oxide or AB zinc oxide
S21 (MH "Zinc Oxide")
S20 TI (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon) or AB (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon)
S19 (MH "Hydrogel Dressings")
S18 TI honey or AB honey
S17 (MH "Honey")
S16 TI wet-to-dry dressings or AB wet-to-dry dressings
S15 TI (dressing* or gauze or adherent or absorbent or tulle or polysaccaride or alginate or foam or hydrofibre or hydrofiber or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm) or AB (dressing* or gauze or adherent or absorbent or tulle or polysaccaride or alginate or foam or hydrofibre or hydrofiber or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm)
S14 TI (iodoflex or iodosorb) or AB (iodoflex or iodosorb)
S13 TI (polysaccharide bead* or polysaccharide paste) or AB (polysaccharide bead* or polysaccharide paste)
S12 TI (dextranomer* or cadexomer or xerogel or eusol or debrisan) or AB (dextranomer* or cadexomer or xerogel or eusol or debrisan)
S11 TI dakin solution or AB dakin solution
S10 TI (malic acid or benzoid acid or salicylic acid or propylene glycol) or AB (malic acid or benzoid acid or salicylic acid or propylene glycol)
S9 TI (hypochlorite or hydrogen peroxide) or AB (hypochlorite or hydrogen peroxide)
S8 TI whirlpool or AB whirlpool
S7 TI (wound irrigat* or wound cleans*) or AB (wound irrigat* or wound cleans*)
S6 TI papain or AB papain
S5 TI (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase) or AB (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase)
S4 TI (larva* or maggot* or biosurgery or bio-surgery) or AB (larva* or maggot* or biosurgery or bio-surgery)
S3 (MH "Larval Therapy")
S2 TI (debrid* or slough* or desloughs*) or AB (debrid* or slough* or desloughs*)
S1 (MH "Debridement")

Appendix 2. Embase search strategy

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1 exp Debridement/ (24174)
2 (debrid* or slough* or desloug*).ti,ab. (23612)
3 exp Maggot Therapy/ (253)
4 (larva* or maggot* or biosurgery or bio-surgery).ti,ab. (70949)
5 (wound* adj (irrigat* or cleanse*)).ti,ab. (338)
6 whirlpool.ti,ab. (431)
7 (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase).ti,ab. (149422)
8 exp Papain/ (6708)
9 papain.ti,ab. (7352)
10 (hypochlorite or hydrogen peroxide).ti,ab. (46733)
11 (malic acid or benzoid acid or salicylic acid or propylene glycol).ti,ab. (14854)
12 dakin solution.ti,ab. (6)
13 (dextranomer* or cadexomer or xerogel or eusol or debrisan).ti,ab. (1006)

14 (polysaccharide adj (bead* or paste*)).ti,ab. (12)
15 (iodoflex or iodosorb).ti,ab. (24)
16 (((gauze or adherent or absorbent or tulle or polysaccaride or alginate or foam or hydrofibre or hydrofiber) adj dressing*) or saline gauze or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll or combiderm or duoderm).ti,ab. (2618)
17 "wet-to-dry dressings".ti,ab. (33)
18 exp Honey/ (3867)
19 honey*.ti,ab. (14490)
20 exp Hydrogel Dressing/ (184)
21 (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon).ti,ab. (17464)
22 exp Zinc Oxide/ (6980)
23 zinc oxide.ti,ab. (3008)
24 or/1-23 (365554)
25 exp Leg Ulcer/ (11697)
26 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).ti,ab. (9398)
27 or/25-26 (14873)
28 24 and 27 (1568)
29 Randomized controlled trials/ (47601)
30 Single-Blind Method/ (17915)
31 Double-Blind Method/ (114385)
32 Crossover Procedure/ (38094)
33 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab. (1299427)
34 (doubl$ adj blind$).ti,ab. (143909)
35 (singl$ adj blind$).ti,ab. (14099)
36 or/29-35 (1364163)
37 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (19973255)
38 human/ or human cell/ (14512000)
39 and/37-38 (14465339)
40 37 not 39 (5507916)
41 36 not 40 (1176261)
42 28 and 41 (263)

Appendix 3. MEDLINE search strategy

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1 exp Debridement/ (11776)
2 (debrid* or slough* or desloug*).ti,ab. (18433)
3 exp Maggot Therapy/ (0)
4 (larva* or maggot* or biosurgery or bio-surgery).ti,ab. (62682)
5 (wound* adj (irrigat* or cleanse*)).ti,ab. (282)
6 whirlpool.ti,ab. (289)
7 (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase).ti,ab. (131101)
8 exp Papain/ (5663)
9 papain.ti,ab. (6611)
10 (hypochlorite or hydrogen peroxide).ti,ab. (36981)
11 (malic acid or benzoid acid or salicylic acid or propylene glycol).ti,ab. (11167)
12 dakin solution.ti,ab. (5)
13 (dextranomer* or cadexomer or xerogel or eusol or debrisan).ti,ab. (660)
14 (polysaccharide adj (bead* or paste*)).ti,ab. (8)
15 (iodoflex or iodosorb).ti,ab. (19)
16 (((gauze or adherent or absorbent or tulle or polysaccaride or alginate or foam or hydrofibre or hydrofiber) adj dressing*) or saline gauze or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll or combiderm or duoderm).ti,ab. (1968)

17 “wet-to-dry dressings”.ti,ab. (23)
18 exp Honey/ (2258)
19 honey*.ti,ab. (10557)
20 exp Hydrogel Dressing/ (0)
21 (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon).ti,ab. (12544)
22 exp Zinc Oxide/ (3473)
23 zinc oxide.ti,ab. (2213)
24 or/1-23 (300061)
25 exp Leg Ulcer/ (17022)
26 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).ti,ab. (6899)
27 or/25-26 (18347)
28 24 and 27 (1745)
29 randomized controlled trial.pt. (366322)
30 controlled clinical trial.pt. (87769)
31 randomi?ed.ab. (317972)
32 placebo.ab. (143634)
33 clinical trials as topic.sh. (168553)
34 randomly.ab. (189286)
35 trial.ti. (114571)
36 or/29-35 (859648)
37 exp animals/ not humans.sh. (3898895)
38 36 not 37 (790544)
39 28 and 38 (347)

Appendix 4. Criteria for a judgment of risk of bias

1. Was the allocation sequence randomly generated?

Low risk of bias

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

High risk of bias

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

Unclear

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

2. Was the treatment allocation adequately concealed?

Low risk of bias

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

High risk of bias

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

Unclear

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

3. Blinding was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

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

High risk of bias

Any one of the following.

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

Unclear

Either of the following.

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

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.

- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

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

Unclear

Either of the following

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

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

Low risk of bias

Either of the following.

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

High risk of bias

Any one of the following.

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

Unclear

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

6. Other sources of potential bias

Low risk of bias

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

High risk of bias

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

- had a potential source of bias related to the specific study design used; or
- stopped early due to some data-dependent process (including a formal-stopping rule); or
- had extreme baseline imbalance; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

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

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

WHAT'S NEW

Date	Event	Description
28 September 2015	Amended	Contact details updated and typo corrected

CONTRIBUTIONS OF AUTHORS

GG: Researched and developed the background information, contacted study authors and industry, developed the protocol, developed the review and co-ordinated the development of the review among the authors, undertook study selection, data extraction and quality assessment, interpretation of findings, development of discussion and liaison with the Cochrane Wounds Group.

SC: Contributed to review development and editing of the review, study selection, data extraction and quality assessment, discussion of findings.

DK: Contributed to commentary and review of the protocol, agreement and review of selected studies and data extraction, discussion of findings and final edit.

Contributions of editorial base :

Nicky Cullum: edited the protocol; advised on methodology, interpretation and protocol content. Approved the final review.
Julie Bruce, Editor, approved the final review.
Sally Bell-Syer: co-ordinated the editorial process, advised on methodology, interpretation and content, edited the review.
Ruth Foxlee and Amanda Briant: designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

The following authors (GG, SC) have completed a randomised controlled trial that was included in this review (Gethin G (2007) Manuka honey vs. hydrogel - a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. PhD Thesis). Data from this study was extracted by SC and verified by DK. GG entered data from all studies and this was checked by SC and DK.

GG has received honoraria for presenting at conferences on the topic of wound care.

SC: nothing to declare.

DK: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Library, Royal College of Surgeons in Ireland, Ireland.

Sourcing of references

External sources

- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Wounds. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no substantial differences between the protocol and the review.

NOTES

The following article from Journal of Clinical Nursing, 'Manuka honey vs. hydrogel - a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers' by Georgina Gethin and Seamus Cowman published online on 25 August 2008 in Wiley Online Library (wileyonlinelibrary.com) and in Volume 18, pp. 466-474, has been retracted by agreement between the journal Editor-in-Chief, the authors and John Wiley & Sons, Ltd. The retraction has been agreed due to errors in the data analysis which affect the article's findings. The review authors would like to confirm that the data in this review is taken from the source: Gethin G Manuka honey versus hydrogel - a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers - unpublished PhD thesis 2007.

INDEX TERMS

Medical Subject Headings (MeSH)

Bandages, Hydrocolloid; Borates [therapeutic use]; Debridement [*methods]; Hydrogel, Polyethylene Glycol Dimethacrylate [therapeutic use]; Randomized Controlled Trials as Topic; Sodium Hypochlorite [therapeutic use]; Varicose Ulcer [*therapy]; Wound Healing

MeSH check words

Humans