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Hydrogel dressings for healing diabetic foot ulcers (Review)

Dumville JC, O'Meara S, Deshpande S, Speak K

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[Intervention Review]

Hydrogel dressings for healing diabetic foot ulcers

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ABSTRACT

Background

Foot ulcers in people with diabetes are a prevalent and serious global health issue. Dressings form a key part of ulcer treatment, with clinicians and patients having many different types to choose from including hydrogel dressings. A clear and current overview of current evidence is required to facilitate decision-making regarding dressing use.

Objectives

To assess the effects of hydrogel wound dressings compared with alternative dressings or none on the healing of foot ulcers in people with diabetes.

Search methods

For this first update, in April 2013, we searched the following databases the Cochrane Wounds Group Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE; and EBSCO CINAHL. There were no restrictions based on language or date of publication.

Selection criteria

Published or unpublished randomised controlled trials (RCTs) that have compared the effects on ulcer healing of hydrogel with alternative wound dressings or no dressing in the treatment of foot ulcers in people with diabetes.

Data collection and analysis

Two review authors independently performed study selection, risk of bias assessment and data extraction.

Main results

We included five studies (446 participants) in this review. Meta analysis of three studies comparing hydrogel dressings with basic wound contract dressings found significantly greater healing with hydrogel: risk ratio (RR) 1.80, 95% confidence interval (CI) 1.27 to 2.56. The three pooled studies had different follow-up times (12 weeks, 16 weeks and 20 weeks) and also evaluated ulcers of different severities (grade 3 and 4; grade 2 and grade unspecified). One study compared a hydrogel dressing with larval therapy and found no statistically significant difference in the number of ulcers healed and another found no statistically significant difference in healing between hydrogel and platelet-derived growth factor. There was also no statistically significant difference in number of healed ulcers between two different brands of hydrogel dressing. All included studies were small and at unclear risk of bias and there was some clinical heterogeneity with studies including different ulcer grades. No included studies compared hydrogel with other advanced wound dressings.

Authors' conclusions

There is some evidence to suggest that hydrogel dressings are more effective in healing (lower grade) diabetic foot ulcers than basic wound contact dressings however this finding is uncertain due to risk of bias in the original studies. There is currently no research evidence to suggest that hydrogel is more effective than larval therapy or platelet-derived growth factors in healing diabetic foot ulcers, nor that one brand of hydrogel is more effective than another in ulcer healing. No RCTs comparing hydrogel dressings with other advanced dressing types were found.

PLAIN LANGUAGE SUMMARY

Hydrogel dressings to promote diabetic foot ulcer healing

Diabetes, a condition which leads to high blood glucose concentrations, is a common condition with around 2.8 million people affected in the UK (approximately 3% of the population). Dressings are a widely used treatment when caring for foot ulcers in people with diabetes. There are many types of dressings that can be used, which also vary considerably in cost. This review (five studies involving a total of 446 people) suggests that hydrogel dressings may be more effective than basic wound contact dressings in healing foot ulcers in people with diabetes although the original research may be biased. There is insufficient research comparing hydrogel with advanced dressing types to allow conclusions to be drawn regarding relative effectiveness in terms of ulcer healing.

Summary of findings for the main comparison. Hydrogel dressings compared to basic wound contact dressings for foot ulcers in people with diabetes

Hydrogel dressings compared to basic wound contact dressings for foot ulcers in people with diabetes

Patient or population: patients with foot ulcers in people with diabetes
Settings:
Intervention: Hydrogel dressings
Comparison: basic wound contact dressings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Basic wound contact dressings	Hydrogel dressings				
Number of ulcers healed Follow-up: mean 16 weeks	**Low risk of healing[1]**		**RR 1.80** (1.27 to 2.56)	198 (3 studies)	⊕⊕⊕⊖ **moderate** [2,3]	
	340 per 1000	**612 per 1000** (432 to 870)				
	Moderate risk of healing[1]					
	530 per 1000	**954 per 1000** (673 to 1000)				
	High risk of healing[1]					
	650 per 1000	**1000 per 1000** (825 to 1000)				
Adverse events Follow-up: mean 16 weeks	**Study population**		Not estimable	0 (3 studies)	See comment	Some adverse event data were reported, however, lack of methodological detail about reporting and type of data presented prevent further comment.
	See comment	See comment				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Baseline risk of healing obtained from external source in which data from 27,630 patients with a diabetic neuropathic foot ulcer was used to develop a simple prognostic model to predict likelihood of ulcer healing (Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med. 2003;115:627-31). It is important to note that given an outcome of ulcer healing, low risk refers to a low risk of healing and thus reflects the most severe patient populations. Conversely high risk refers to a high risk of healing.
[2] Many of the risk of bias domains were unclear limiting judgements that could be made.
[3] The confidence interval around the estimate of relative risk is consistent with a 27% relative increase in healing with hydrogel to a 256% relative increase in healing with hydrogel.

Summary of findings 2. Hydrogel dressings compared to Larval therapy for foot ulcers in people with diabetes

Hydrogel dressings compared to Larval therapy for foot ulcers in people with diabetes

Patient or population: patients with foot ulcers in people with diabetes
Settings:
Intervention: Hydrogel dressings
Comparison: Larval therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Larval therapy	Hydrogel dressings				
Number of ulcers healed Follow-up: 10 days	**Low risk of healing[1]**		**RR 0.40** (0.08 to 1.99)	140 (1 study)	⊕⊕⊝⊝ **low** [2,3]	
	340 per 1000	**136 per 1000** (27 to 677)				
	Moderate of healing[1]					
	530 per 1000	**212 per 1000** (42 to 1000)				

High risk of healing[1]		
650 per 1000	**260 per 1000** (52 to 1000)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Baseline risk of healing obtained from external source in which data from 27,630 patients with a diabetic neuropathic foot ulcer was used to develop a simple prognostic model to predict likelihood of ulcer healing (Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med. 2003;115:627-31). It is important to note that given an outcome of ulcer healing, low risk refers to a low risk of healing and thus reflects the most severe patient populations. Conversely high risk refers to a high risk of healing

[2] All domains classed at unclear risk of bias making judgement difficult.

[3] 7 participants achieved the endpoint of healing in the study, this is an underpowered comparison. The confidence interval around the estimate of relative risk is consistent with a 92% relative reduction in healing with hydrogel and a 199% relative increase in healing with hydrogel.

Summary of findings 3. Hydrogel dressing compared to platelet-derived growth factor for foot ulcers in people with diabetes

Hydrogel dressing compared to platelet-derived growth factor for Foot ulcers in people with diabetes

Patient or population: patients with Foot ulcers in people with diabetes
Settings:
Intervention: Hydrogel dressing
Comparison: platelet-derived growth factor

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Platelet-dervided growth factor	Hydrogel dressing				
Number of ulcers healed Follow-up: 20 weeks	**Low risk of healing[1]**		**RR 0.81** (0.5 to 1.32)	104 (1 study)	⊕⊕⊝⊝ **low** [2]	
	340 per 1000	**275 per 1000** (170 to 449)				

Moderate risk of healing[1]	
530 per 1000	**429 per 1000** (265 to 700)
High risk of healing[1]	
650 per 1000	**527 per 1000** (325 to 858)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Baseline risk of healing obtained from external source in which data from 27,630 patients with a diabetic neuropathic foot ulcer was used to develop a simple prognostic model to predict likelihood of ulcer healing (Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med. 2003;115:627-31). It is important to note that given an outcome of ulcer healing, low risk refers to a low risk of healing and thus reflects the most severe patient populations. Conversely high risk refers to a high risk of healing

[2] 40 participants achieved the endpoint of healing in the study, this is an underpowered comparison. The confidence interval around the estimate of relative risk is consistent with a 39% relative reduction in healing with hydrogel and a 26% relative increase in healing with hydrogel.

Summary of findings 4. Purilon hydrogel compared to Intrasite hydrogel for foot ulcers in people with diabetes

Purilon hydrogel compared to Intrasite hydrogel for foot ulcers in people with diabetes

Patient or population: patients with foot ulcers in people with diabetes
Settings:
Intervention: Purilon hydrogel
Comparison: Intrasite hydrogel

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intrasite hydrogel	Purilon hydrogel				

Number of ulcers healed Follow-up: 10 weeks	**Study population**		Not estimable	0 (1 study)	See comment	35% of ulcers healed in the Purilon group compared with 19% in the Intrasite group. The numbers used for these calculations are not presented. Limiting analyses
	See comment	See comment				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Diabetes, high glucose levels in the blood, is a common condition, with around 2.8 million people affected in the UK (approximately 4.3% of the population) (Diabetes UK). Global projections suggest that the worldwide prevalence of diabetes is expected to rise to 4.4% by 2030, meaning that approximately 366 million people will be affected (Wild 2004).

Success in treating diabetes has improved the life expectancy of patients. However, the increased prevalence of diabetes coupled with the extended time people live with the disease has led to a rise in the number of diabetes-related complications, such as neuropathy and peripheral arterial disease (PAD). It is estimated that lower extremity disease is twice as common in people with diabetes compared with people without (Gregg 2004). Both neuropathy and PAD are risk factors for diabetic foot ulceration (Pecoraro 1990; Reiber 1999), which is a problem reported to affect 15% or more of the diabetic population at some time in their lives. (Reiber 1996; Singh 2005). Around 1% to 4% of people with diabetes have foot ulcers at any given time (Abbott 2002; Kumar 1994). An ulcer forms as a result of damage to the epidermis and subsequent loss of underlying tissue. Specifically, the International Consensus on the Diabetic Foot defines a foot ulcer as a wound extending through the full thickness of the skin below the level of the ankle (Apelqvist 2000a). This is irrespective of duration and the ulcer can extend to muscle, tendon and bone. The Wagner wound classification system is well established and widely used for grading diabetic foot ulcers. The system assesses ulcer depth and the presence of osteomyelitis or gangrene in the following grades: grade 0 (pre- or post-ulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene) and grade 5 (whole foot gangrene) (Wagner 1981). However, newer grading systems, such as the PEDIS system (Schaper 2004) and the University of Texas Wound Classification System (Oyibo 2001) have been developed.

PAD and neuropathy can occur separately (ischaemic foot and neuropathic foot) or in combination (in the neuroischaemic foot). The over-arching term 'diabetic neuropathy' refers to a number of neuropathic syndromes. Chronic distal sensorimotor symmetrical neuropathy (abbreviated to distal symmetrical neuropathy) is the most common, affecting around 28% of people with diabetes. It can lead to ulceration through the following route(s) (Tesfaye 1996).

- Sympathetic autonomic neuropathy leads to decreased sweating causing anhidrotic (dry) skin, which is prone to cracks and fissures causing a break in the dermal barrier (Tesfaye 1996).
- Motor neuropathy causes wasting of the small, intrinsic muscles of the foot by de-enervation. As the muscles waste they cause retraction of the toes and lead to a subsequent deformity. The abnormal foot shape can promote ulcer development due to an increase in plantar pressures (Murray 1996).
- Sensory neuropathy results in impaired sensation, making the patient unaware of potentially dangerous foreign bodies and injuries.

People with diabetes-related foot ulceration are treated in a variety of settings, for example community clinics, surgeries and their own homes, by a variety of practitioners; this can make data collection challenging. A UK study estimated that 2% of community-based diabetic patients develop new foot ulcers each year (Abbott 2002). In terms of healing, a meta-analysis of trials in which people with neuropathic ulcers received good wound care reported that 24% of ulcers attained complete healing by 12 weeks and 31% by 20 weeks (Margolis 1999). However, the risk of ulcer recurrence post-healing is high. Pound 2005 reported that 62% of ulcer patients (n = 231) became ulcer-free at some stage over a 31-month observation period. However, of the ulcer-free group 40% went on to develop a new or recurrent ulcer after a median of 126 days. The ulcer recurrence rate over five years can be as high as 70% (Dorresteijn 2010; Van Gils 1999).

Diabetic foot ulcers can seriously impact on an individual's quality of life and as many as 85% of foot-related amputations are preceded by ulceration (Apelqvist 2000b; Pecoraro 1990). Patients with diabetes have a 10 to 20-fold higher risk of losing a lower limb or part of a lower limb due to non-traumatic amputation than those without diabetes (Morris 1998; Wrobel 2001).

Diabetic foot ulcers represent a major use of health resources, incurring costs not only for dressings applied, but also staff costs (for podiatry, nurses, doctors), tests and investigations, antibiotics and specialist footwear. Currie 1998 estimated the cost of healing a foot ulcer in a patient with diabetes at around GBP 1451. Hospital admissions add further to the costs. Ten years ago the cost of diabetic foot ulceration to the UK National Health Service was believed to be about GBP 12.9 million per year (Spencer 2000) and this figure is likely to have increased significantly. The economic impact is also high in terms of the personal costs to patients and carers, for example costs associated with lost work time and productivity while the patient is non-weight bearing or hospitalised.

Description of the intervention

Broadly, the treatment of diabetic foot ulcers includes pressure relief (or off-loading) by resting the foot or wearing special footwear or shoe inserts (or both); the removal of dead cellular material from the surface of the wound (debridement or desloughing); infection control; and the use of wound dressings. Other general strategies in the treatment of diabetic foot ulcers include: patient education; optimisation of blood glucose control; correction (where possible) of arterial insufficiency; and surgical interventions (debridement, drainage of pus, revascularisation, amputation).

Dressings are widely used in wound care, both to protect the wound and to promote healing. Classification of a dressing normally depends on the key material used. Several attributes of an ideal wound dressing have been described (BNF 2010), including:

- the ability of the dressing to absorb and contain exudate without leakage or strike-through;
- lack of particulate contaminants left in the wound by the dressing;
- thermal insulation;
- permeability to water and bacteria;
- avoidance of wound trauma on dressing removal;
- frequency with which the dressing needs to be changed;
- provision of pain relief; and
- comfort.

There is a vast choice of dressings available to treat chronic wounds such as diabetic foot ulcers. For ease of comparison this review has categorised dressings according to the British National Formulary 2010 (BNF 2010) which is freely available via the internet. We will use 'generic' names where possible, also providing UK trade names and manufacturers where these are available to allow cross-referencing with the BNF. However, it is important to note that the way dressings are categorised as well as dressing names, manufacturers and distributors of dressings vary from country to country, so these are provided as a guide only. Below is a description of all categories of dressings and includes the category of dressing (hydrogel) which is the focus of this review:

Basic wound contact dressings

Low-adherence dressings and wound contact materials: usually cotton pads which are placed directly in contact with the wound. They can be either non-medicated (e.g. paraffin gauze dressing) or medicated (e.g. containing povidone iodine or chlorhexidine). Examples are paraffin gauze dressing, BP 1993 and Xeroform (Covidien) dressing - a non-adherent petrolatum blend with 3% bismuth tribromophenate on fine mesh gauze.

Absorbent dressings: applied directly to the wound or used as secondary absorbent layers in the management of heavily exuding wounds. Examples include Primapore (Smith & Nephew), Mepore (Mölnlycke) and absorbent cotton gauze (BP 1988).

Advanced wound dressings

Hydrogel sheet and amorphous dressings: consist of a cross-linked insoluable polymers (i.e. starch or carboxymethylcellulose) and up to 96% water. These dressings are designed to absorb wound exudate or rehydrate a wound depending on the wound moisture levels. They are supplied in either flat sheets, an amorphous hydrogel or as beads. Examples are: ActiformCool (Activa) and Aquaflo (Covidien).

Films - permeable film and membrane dressings: permeable to water vapour and oxygen but not to water or microorganisms. Examples are Tegaderm (3M) and Opsite (Smith & Nephew).

Soft polymer dressings: dressings composed of a soft silicone polymer held in a non-adherent layer. They are moderately absorbent. Examples are: Mepitel (Mölnlycke) and Urgotul (Urgo).

Hydrocolloid dressings: are occlusive dressings usually composed of a hydrocolloid matrix bonded onto a vapour-permeable film or foam backing. When in contact with the wound surface this matrix forms a gel to provide a moist environment. Examples are: Granuflex (ConvaTec) and NU DERM (Systagenix). Fibrous alternatives have been developed which resemble alginates and are not occlusive but which are more absorbant than standard hydrocolloid dressings: Aquacel (ConvaTec).

Foam dressings: normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface. There are various versions and some foam dressings that include additional absorbent materials, such as viscose and acrylate fibres or particles of superabsorbent polyacrylate, or which are silicone-coated for non-traumatic removal. Examples are: Allevyn (Smith & Nephew), Biatain (Coloplast) and Tegaderm (3M).

Alginate dressings: highly absorbent and come in the form of calcium alginate or calcium sodium alginate and can be combined with collagen. The alginate forms a gel when in contact with the wound surface which can be lifted off with dressing removal or rinsed away with sterile saline. Bonding to a secondary viscose pad increases absorbency. Examples are: Curasorb (Covidien), SeaSorb (Coloplast) and Sorbsan (Unomedical).

Capillary-action dressings: consist of an absorbent core of hydrophilic fibres held between two low-adherent contact layers. Examples are: Advadraw (Advancis) and Vacutx (Protex).

Odour-absorbent dressings: dressings that contain charcoal and are used to absorb wound odour. Often these types of wound dressings are used in conjunction with a secondary dressing to improve absorbency. Example: CarboFLEX (ConvaTec).

Antimicrobial dressings

Honey-impregnated dressings: contain medical-grade honey which is proposed to have antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Examples are: Medihoney (Medihoney) and Activon Tulle (Advancis).

Iodine-impregnated dressings: release free iodine when exposed to wound exudate, which is thought to act as a wound antiseptic. An example is Iodozyme (Insense).

Silver-impregnated dressings: used to treat infected wounds as silver ions are thought to have antimicrobial properties. Silver versions of most dressing types are available (e.g. silver foam, silver hydrocolloid etc). Examples are: Acticoat (Smith & Nephew) and Urgosorb Silver (Urgo).

Other antimicrobial dressings: these dressings are composed of a gauze or low-adherent dressing impregnated with an ointment thought to have antimicrobial properties. Examples are: chlorhexidine gauze dressing (Smith & Nephew) and Cutimed Sorbact (BSN Medical).

Specialist dressings

Protease-modulating matrix dressings: alter the activity of proteolytic enzymes in chronic wounds. Examples are: Promogran (Systagenix) and Sorbion (H & R).

The diversity of dressings available to clinicians (including variation within each type listed above) makes evidence-based decision-making difficult when deciding the best treatment regimen for the patient. In a UK survey undertaken to determine treatments used for debriding diabetic foot ulcers, a diversity of treatments was reported (Smith 2003). It is possible that a similar scenario is true for dressing choice. A survey of Diabetes Specialist Nurses found that low/non-adherent dressings, hydrocolloids and alginate dressings were the most popular for all wound types, despite a paucity of evidence for either of these dressing types (Fiskin 1996). However, several new dressing types have been made available and heavily promoted in recent years. Some dressings now have an 'active' ingredient such as silver that are promoted as dressing treatment options to reduce infection and thus possibly also promote healing in this way. With increasingly sophisticated technology being applied to wound care, practitioners need to know how effective these often expensive dressings are compared with more traditional dressings.

How the intervention might work

Animal experiments conducted over 40 years ago suggest that acute wounds heal more quickly when their surface is kept moist, rather than left to dry and scab (Winter 1963). A moist environment is thought to provide optimal conditions for the cells involved in the healing process as well as allowing autolytic debridement, which is thought to be an important part of the healing pathway (Cardinal 2009). The desire to maintain a moist wound environment is a key driver for the use of wound dressings. Different wound dressings vary in their level of absorbency so that a very wet wound can be treated with an absorbent dressing (such as a foam dressing) to draw excess moisture away from the wound to avoid skin damage, whilst a drier wound can be treated with a more occlusive dressing to maintain a moist environment. Hydrogels are insoluble polymers that bind together a relatively large volume of water. This water can then be donated to wounds to maintain a moist environment. Additionally as the hydrogel polymer matrix is not fully hydrated, it can also absorb some wound exudate with the aim of optimising the moist level of the wound. When hydrogel material is formed into a fixed structure via cross-linking of the polymers it is considered a hydrogel sheet dressing.

Why it is important to do this review

Diabetic foot ulcers are a prevalent and serious global issue. Treatment with dressings forms a key part of the treatment pathway when caring for diabetic foot ulcers and there are many types of dressings that can be used, which also vary considerably in cost. Guidelines for the treatment of diabetic ulcer (e.g. Steed 2006) maintain that clinical judgement should be used to select a moist wound dressing.

However, previous reviews of the evidence for wound dressings as treatments for diabetic foot ulcers have not found evidence to support a specific dressing choice. Ten trials were eligible for inclusion in a UK Health Technology Assessment review of wound dressings published in 2000 (O'Meara 2000). The review included nine trials that investigated a dressing or topical treatment for healing diabetic foot ulcers. The review did not find any evidence to suggest that one dressing type was more or less effective in terms of treating diabetic foot ulcers. The methodological quality of trials was poor and all were small. Only one comparison was repeated in more than one trial. A further systematic review conducted some years ago reported similar findings (Mason 1999). A more recent systematic review on the effectiveness of interventions to enhance the healing of chronic ulcers of the foot (Hinchliffe 2008) (search date December 2006) included only eight trials (randomised and non-randomised) did not identify any evidence that one dressing type was superior to another in terms of promoting ulcer healing. A Cochrane Review of silver-based wound dressings and topical agents for treating diabetic foot ulcers (Bergin 2006; search date 2010) did not find any studies that met its inclusion criteria. Finally, a review of antimicrobial treatments for diabetic foot ulcers (Nelson 2006) included dressings and found that existing evidence was too weak to recommend any antimicrobial product.

This review is part of a suite of Cochrane Reviews investigating the use of dressings in the treatment of foot ulcers in people with diabetes. Each review will focus on a particular dressing type which in this review is the hydrogel dressing. These reviews will be summarised in an overview of reviews (Higgins 2009) which will draw together all existing Cochrane Review evidence regarding the use of dressings to treat foot ulcers in people with diabetes. Whilst other existing review evidence may also be included in this overview, following Cochrane guidance, this will only occur in the absence of a relevant Cochrane intervention review (Higgins 2009).

OBJECTIVES

To assess the effects of hydrogel wound dressings compared with alternative dressings or none on the healing of foot ulcers in people with diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

Published or unpublished randomised controlled trials (RCTs) that evaluated the effects of any type of hydrogel wound dressing in the treatment of diabetic foot ulcers, irrespective of publication status or language.

Types of participants

Trials recruiting people with type I or type II diabetes, with an open foot ulcer. Since study-specific classifications of ulcer diagnosis were likely to be too restrictive, we accepted study authors' definitions of what was classed a diabetic foot ulcer. There was no restriction in relation to the aetiology of the ulcer; trials recruiting people with ulcers of neuropathic, ischaemic or neuroischaemic causes were all eligible for inclusion.

We included participants of any age. We excluded trials which included patients with a number of different wound aetiologies in addition to diabetic foot ulcers (e.g. pressure ulcers, mixed arterial/venous arterial) unless the results for the subgroup of patients with a diabetic foot ulcer were reported separately or available from authors on contact.

Types of interventions

The primary intervention was the hydrogel wound dressing (BNF 2010). We included any RCT in which the presence or absence of a hydrogel dressing was the only systematic difference between treatment groups. We anticipated that likely comparisons would include hydrogel dressings compared with either a different hydrogel dressing or other dressing types and/or other interventions (which could be non-dressing treatments, i.e. topical applications).

Types of outcome measures

Primary outcomes

- Time to ulcer healing.
- Number of ulcers completely healed within a specific time period (we assumed that the period of time in which healing occurred was the duration of the trial unless otherwise stated).

Secondary outcomes

- Health-related quality of life (measured using a standardised generic questionnaire such as EQ-5D, SF-36, SF-12 or SF-6 or disease-specific questionnaire). We did not include ad-hoc measures of quality of life which are likely not to be validated and would not be common to multiple trials.

- Number and level of amputations.
- Adverse events, including pain (measured using survey/questionnaire/data capture process or visual analogue scale).
- Cost (including measurements of resource use such as number of dressing changes and nurse time).
- Ulcer recurrence.
- Change in ulcer area expressed as absolute changes (e.g. surface area changes in cm^2 since baseline) or relative changes (e.g. percentage change in area relative to baseline).

Search methods for identification of studies

For the search methods used in the original version of this review see Appendix 1

Electronic searches

For this first update we searched the following databases in April 2013:

- The Cochrane Wounds Group Specialised Register (searched 11 April 2013);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 3); Ovid MEDLINE (1950 to March Week 4 2013);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, April 10, 2013);
- Ovid EMBASE (1980 to 2011 April 05);
- EBSCO CINAHL (1982 to 4 April 2013).

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following exploded MeSH headings and keywords:

#1 MeSH descriptor Occlusive Dressings explode all trees
#2 MeSH descriptor Biological Dressings explode all trees
#3 MeSH descriptor Alginates explode all trees
#4 MeSH descriptor Hydrogels explode all trees
#5 MeSH descriptor Silver explode all trees
#6 MeSH descriptor Honey explode all trees
#7 (dressing* or alginate* or hydrogel* or "foam" or "bead" or "film" or "films" or tulle or gauze or non-adherent or "non adherent" or silver or honey or matrix):ti,ab,kw
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Foot Ulcer explode all trees
#10 MeSH descriptor Diabetic Foot explode all trees
#11 diabet* NEAR/3 ulcer*:ti,ab,kw
#12 diabet* NEAR/3 (foot or feet):ti,ab,kw
#13 diabet* NEAR/3 wound*:ti,ab,kw
#14 (#9 OR #10 OR #11 OR #12 OR #13)
#15 (#8 AND #14)

We adapted this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We combined the EMBASE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2009). There were no restrictions on the basis of date or language of publication.

Searching other resources

In the original version of this review we attempted to contact researchers to obtain any unpublished data when needed. We also searched the reference lists of the included studies and previous systematic reviews. We contacted appropriate manufacturers (Smith & Nephew, Convatec Ltd, Mölnlycke Health Care, 3M Healthcare, Coloplast Ltd) for details of any unpublished studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of retrieved studies for relevance. After this initial assessment, we obtained all studies felt to be potentially relevant in full. Two review authors then independently checked the full papers for eligibility, with disagreements resolved by discussion and, where required, the input of a third review author. We recorded all reasons for exclusion.

Data extraction and management

We extracted and summarised details of the eligible studies using a data extraction sheet. Two review authors extracted data independently and resolved disagreements by discussion. Where data were missing from reports we attempted to contact the study authors to obtain the missing information. We included studies published in duplicate once but maximally extracted data. We extracted the following data:

- country of origin;
- type of ulcer;
- unit of investigation (per patient) - single ulcer or foot or patient or multiple ulcers on the same patient;
- care setting;
- number of participants randomised to each trial arm;
- eligibility criteria and key baseline participant data;
- details of the dressing/treatment regimen received by each group;
- details of any co-interventions;
- primary and secondary outcome(s) (with definitions);
- outcome data for primary and secondary outcomes (by group);
- duration of follow up;
- number of withdrawals (by group);
- adverse events, including amputation; and
- source of funding.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2009). 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, issues with unit of investigation) (see Appendix 2 for details of the criteria on which the judgement was based). We assessed blinding and completeness of outcome data for each outcome separately. We completed a 'Risk of bias' table for each eligible study. We resolved disagreements about risk of bias assessment by discussion. Where a lack of reported

information resulted in an unclear decision, where possible we contacted authors for clarification.

We have presented our assessment of risk of bias findings using a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study. We also aimed to present this assessment in the narrative review.

We classified trials as being at high risk of bias if they are rated 'high' for any of three key criteria (randomisation sequence, allocation concealment and blinded outcome assessment).

Measures of treatment effect

Where possible, we present the outcome results for each trial with 95% confidence intervals (CI). We report estimates for dichotomous outcomes (e.g. ulcers healed during time period) as risk ratio (RR). We used the RR rather than odds ratio (OR), since ORs (when interpreted as RR) can give an inflated impression of the effect size when event rates are high, as is the case for many trials reporting healing of chronic wounds (Deeks 2002). We planned to reported outcomes relating to continuous data (e.g. percentage change in ulcer area) as mean difference (MD) and overall effect size (with 95% CI calculated). Where a study reported time to healing data (the probability of healing over a consecutive time period) we planned to report and plot these data (where possible) using hazard ratio estimates. If studies reporting time-to-event data (e.g. time to healing) did not report a hazard ratio or reported these data incorrectly as a continuous variable then, where feasible, we planned to estimate this using other reported outcomes such as the numbers of events through the application of available statistical methods (Tierney 2007).

Unit of analysis issues

We recorded whether trials measured outcomes in relation to an ulcer, a foot, a participant or whether multiple ulcers on the same participant are studied. We also recorded where multiple ulcers on a participant had been (incorrectly) treated as independent in a study, rather than within-patient analysis methods being applied. We have recorded this as part of the risk of bias assessment. Unless otherwise, where the number of wounds appeared to equal the number of participants we treated the ulcer as the unit of analysis in this review.

Dealing with missing data

Missing data are common in trial reports. Excluding participants post-randomisation from the analysis or ignoring those participants lost to follow up can, in effect, compromise the process of randomisation and thus potentially introduce bias into the trial. In individual studies, where "proportion of ulcers healed data" were presented, we assumed that where randomised participants were not included in an analysis, their wound did not heal (that is, they will be considered in the denominator but not the numerator). Where a trial did not specify participant group numbers prior to dropout, we planned to present only complete case data. We planned to present data for time to healing, area change and for all secondary outcomes as a complete case analysis.

Assessment of heterogeneity

We considered both clinical and statistical heterogeneity. Wherever appropriate, we pooled data using meta-analysis (conducted using RevMan 5.1 (RevMan 2011)), that is where studies appeared similar in terms of level of participants, intervention type and duration and outcome type. We assessed statistical heterogeneity using the Chi^2 test (a significance level of $P < 0.1$ was considered to indicate heterogeneity) and the I^2 statistic (Higgins 2003). The I^2 statistic examines the percentage of total variation across studies due to heterogeneity rather than to chance. Values of I^2 over 50% indicate a high level of heterogeneity. In the absence of clinical heterogeneity and in the presence of statistical heterogeneity (I^2 over 50%), we used a random-effects model. However, we did not pool studies where heterogeneity was very high (I^2 over 50%). Where there was no clinical or statistical heterogeneity we envisaged using a fixed-effect model.

Data synthesis

We combined studies using a narrative overview with meta-analyses of outcome data where appropriate (in RevMan 5.1). The decision to include studies in a meta-analysis depended on the availability of treatment effect data and assessment of heterogeneity. For time-to-event data, we planned to plot log rank observed minus expected events estimates using a fixed-effect model (a random-effects model is not available for this analysis in RevMan 5.1). Where relevant and possible we planned to conduct sensitivity analysis to investigate the potential impact of studies at high risk of bias on pooled results.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The systematic search yielded 346 abstracts which we screened for potential inclusion in the review. Of these, we obtained 103 reports in full (for 84 studies) for a more detailed assessment and five studies were eligible for inclusion in the review. No eligible studies were obtained from the five commercial companies that were contacted. We are not aware of any relevant on-going studies (checked ISRCTN register 25 April 2013). The update search conducted in April 2013 yielded 116 citations of which two studies was obtained for further information: Turns 2012 (excluded) and Wang 2012 (awaiting assessment as requires translation from Chinese).

Included studies

We included five studies (446 participants) in this review (D'Hemecourt 1998; Jensen 1998; Markevich 2000; Vandeputte 1997; Whalley 2001): a summary is presented in Table 1. One study was single-centred (Jensen 1998) and three were multi-centred (D'Hemecourt 1998; Markevich 2000; Whalley 2001); the remaining study did not detail the number of centres. Two studies were undertaken in the USA (D'Hemecourt 1998; Jensen 1998); one in Belgium (Vandeputte 1997) and one study was multi-national, taking place in Spain, UK, Lithuania and Belgium (Whalley 2001). Markevich 2000 did not detail country(ies) of conduct.

All studies were undertaken in adults with diabetes, with one study including people with both type 1 or type 2 diabetes (D'Hemecourt 1998). This study also included participants with at least one ulcer of Wagner grade 3 or 4, where as Whalley 2001 included only ulcers that were Wagner grade 1 or 2 ulcers and Jensen 1998 only included Wagner grade 2 ulcers. One study only included participants with ulcers that were neuropathic (Whalley 2001). Vandeputte 1997 specified that it allowed entry to people with infected non-neuropathic and sloughy ulcers whereas Jensen 1998 only included participants with no signs of ulcer infection, and a documented blood supply consistent will the ability to heal (no further information or measures provided). In general it seems that a wide range of ulcer types were evaluated across these studies from potentially more complex wounds (D'Hemecourt 1998; Vandeputte 1997) to potentially less complex (Jensen 1998). The duration of trial follow up ranged from 10 days (Markevich 2000) to 20 weeks (D'Hemecourt 1998), details presented in Table 1. Of the five included studies, four were two-arm and one was three-arm (D'Hemecourt 1998). All studies reported the number of ulcers healed. Mean time to healing was reported in Jensen 1998 and D'Hemecourt 1998 (summary estimate not provided). Adverse event reporting did not appear systematic in most studies (potentially with the exception of D'Hemecourt 1998) although this was difficult to assess, particularly for Markevich 2000 and Whalley 2001 which were reported as conference abstracts only.

Excluded studies

We excluded 79 studies from the review (an additional exclude was added from the update search). The main reasons for exclusion were: the study was not randomised (n = 9), no single, identifiable dressing type was evaluated (n = 11); another intervention, not a dressing, differed between study groups (n = 26); the dressing(s) evaluated were not hydrogel (n = 26). Another reason was recorded for seven studies.

Risk of bias in included studies

We classified studies rated 'high risk' for any of three key domains: randomisation sequence, allocation concealment and blinded outcome assessment, as being at high risk of bias (Characteristics of included studies; Figure 1; Figure 2). We rated all five studies as being at unclear risk of bias due to poor reporting.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

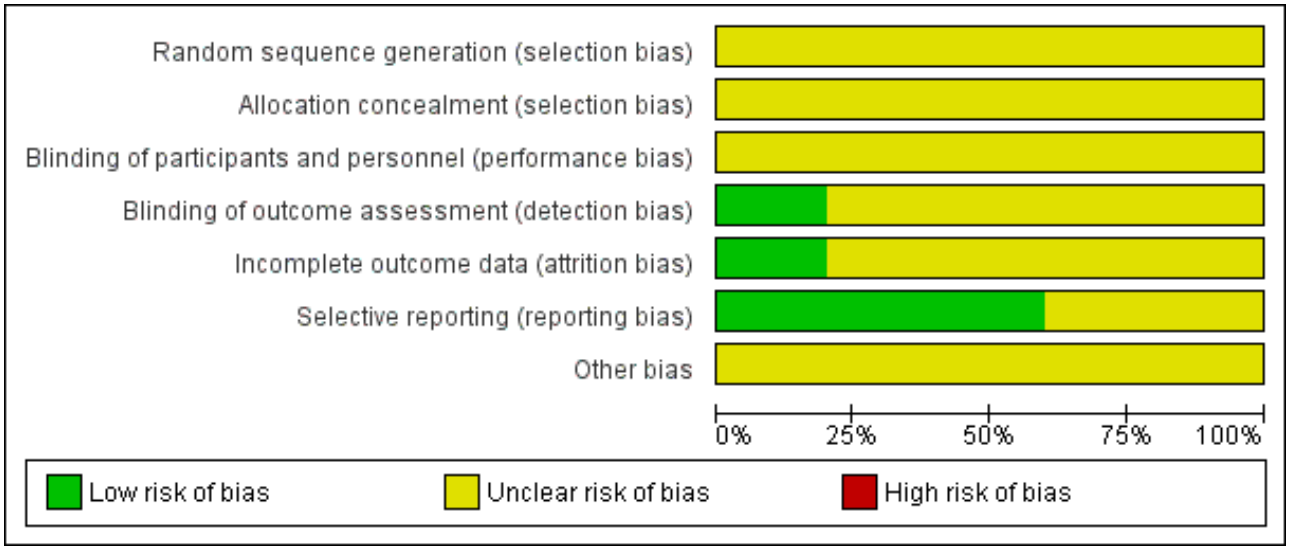
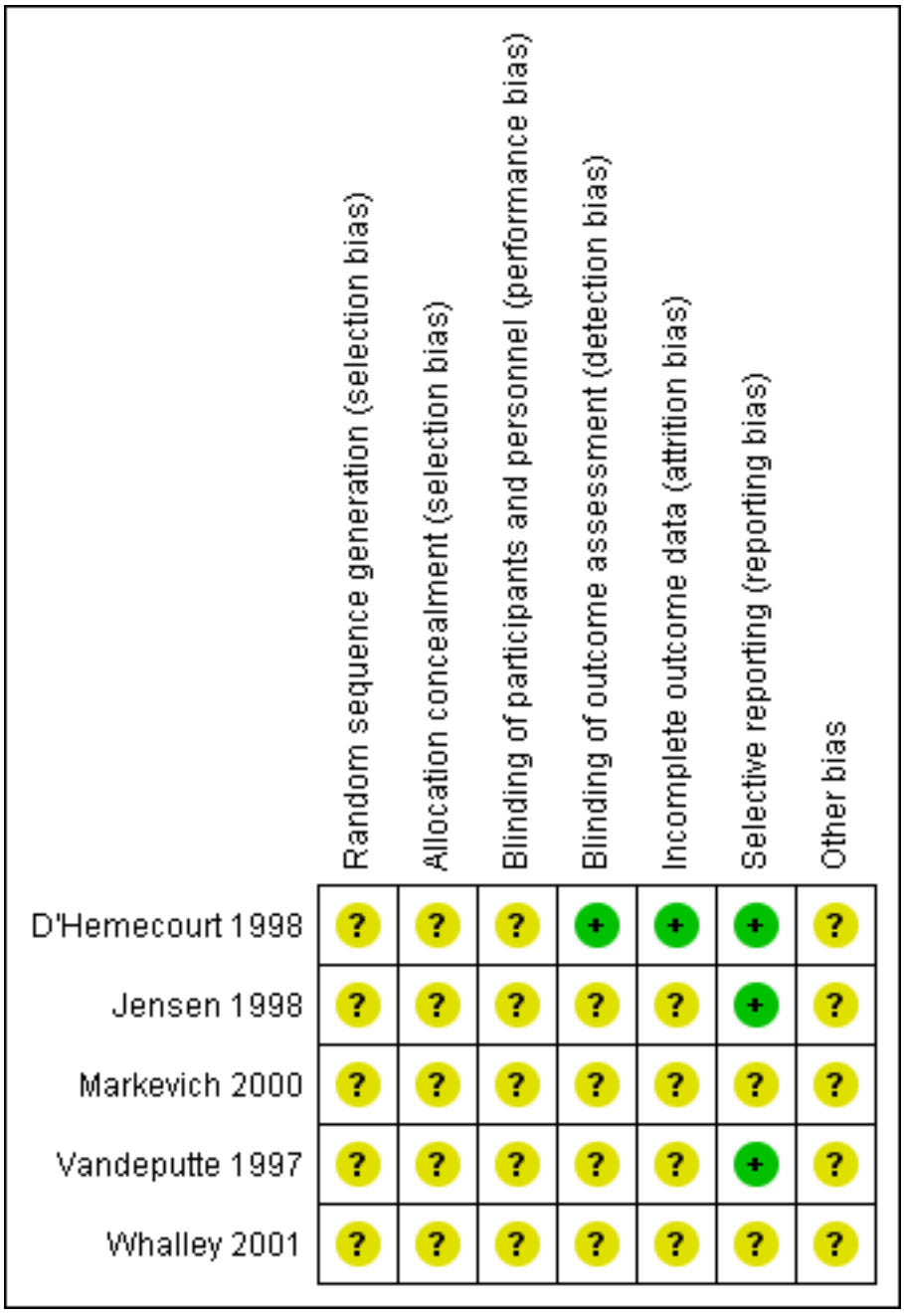


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Adequacy of randomisation process

All five studies were described as "randomised", however, none reported the method used to generate randomisation sequence and hence we judged all to be unclear for this domain.

Allocation concealment

None of the studies reported the allocation procedure such that we could assess the degree of concealment and hence we judged all trials to be unclear for this domain.

Blinding

Assessment of wound healing can be subjective and thus has the potential to be influenced if the outcome assessor is aware of the treatment allocation. In this review we focused on whether the studies had conducted blinded outcome assessment. We judged D'Hemecourt 1998 to be at low risk of bias and the other studies to be unclear for this domain.

Incomplete outcome data

Whilst D'Hemecourt 1998 reported some trial loss to follow up it stated that "analysis of efficacy was based on the intention to treat population, which included patients who were randomised

to treatment, received at least one treatment and had any post-baseline data". All numbers presented in the analysis matched the number of participants randomised it was deemed that an intention-to-treat (ITT) analysis had been conducted and the study was judged to be at low risk of bias for this domain. Jensen 1998 reported that five participants of 31(16%) were excluded post-randomisation; it seems that the authors conducted an ITT analysis but this is not clear. Likewise the remaining studies did not report enough information to make a judgement about ITT analysis and so were classed as unclear.

Selective reporting

All studies reported outcomes adequately and we deemed them to be at unclear or low risk of bias. However, it is important to note that judgement for this domain may be of limited value given it was made at face value based on the reporting of outcomes in the results that were described in the methods. Study reports were not compared to study protocols, which were not actively sought.

Other potential sources of bias

One study was funded by a commercial organisation (Jensen 1998). Funding for the remaining four studies was unclear. All included studies reported no or limited baseline data thus the potential for imbalance was unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Hydrogel dressings compared to basic wound contact dressings for foot ulcers in people with diabetes; **Summary of findings 2** Hydrogel dressings compared to Larval therapy for foot ulcers in people with diabetes; **Summary of findings 3** Hydrogel dressing compared to platelet-derived growth factor for foot ulcers in people with diabetes; **Summary of findings 4** Purilon hydrogel compared to Intrasite hydrogel for foot ulcers in people with diabetes

Dressing compared with non-dressing

Dressing compared with larval therapy

Comparison 1: hydrogel dressing compared with larval therapy (one trial; 140 participants)

Markevich 2000 was a two-arm study with 140 participants that compared a hydrogel dressing with the application of the larvae of the green-bottle fly *Lucilia sericata* (larval therapy) (Table 1).

Primary outcome: ulcer healing

Markevich 2000 had a follow-up period of 10 days, suggesting that the primary outcome was debridement rather than complete healing (the study also measured number of wounds with granulation tissue covering 50% of the wound); explaining the low numbers of healing events in this study. There was no statistically significant difference in the number of ulcers healed in the hydrogel-dressed group (2/70; 3%) compared with the larval therapy-treated group (5/70; 7%): risk ratio (RR) 0.40, 95% confidence interval (CI) 0.08 to 1.99 (Analysis 1.1). The proportion of participants with more than a 50% reduction in wound area was 27% in the hydrogel-dressed group and 51% in the larval therapy-treated group (values and standard deviation (SD) not reported; attempts to contact author unsuccessful).

Secondary outcomes: not reported

Summary: hydrogel dressing compared with larval therapy

Limited data from one small study with a very short follow up period found no difference in numbers of ulcers healed between larval therapy-treated ulcers and hydrogel-dressed ulcers.

Dressing compared with platelet-derived growth factor

Comparison 2: hydrogel dressing compared with platelet-derived growth factor (one trial; 104 participants)

D'Hemecourt 1998 was a three-arm study (two groups relevant to this comparison) with a maximum follow up of 20 weeks. The two relevant arms contained 104 participants and compared a hydrogel dressing with a platelet-derived growth factor (becaplermin gel, 100 µg/g). There was no statistically significant difference in the number of ulcers healed in the hydrogel-dressed ulcers (25/70; 36%) compared with the growth-factor-treated ulcers (15/34; 44%): RR 0.81, 95% CI 0.50 to 1.32 (Analysis 2.1).

Summary: hydrogel dressing compared with platelet-derived growth factor

There was no statistically significant difference in healing between ulcers treated with hydrogel and platelet-derived growth factors.

Dressing compared with dressing

Advanced wound dressing compared with basic wound contact dressing

Comparison 3: hydrogel dressing compared with basic wound contact dressing (three trials; 198 participants)

Three studies (D'Hemecourt 1998; Jensen 1998; Vandeputte 1997) compared a hydrogel with a basic wound contact dressing (Table 1). D'Hemecourt 1998 was a three-arm study, with two arms relevant to this comparison that contained 138 participants and compared a hydrogel with a wet-to-moist saline dressing. Jensen 1998 was a two-arm study with 31 participants that compared a hydrogel dressing with gauze pad soaked in sterile saline. Vandeputte 1997 was a two-arm study with 29 participants that compared a hydrogel dressing (elasto gel with 65% glycerol, 17.5% water and 17.5% polyacrylamide) with dry gauze.

Primary outcome: ulcer healing

D'Hemecourt 1998 had a maximum follow-up of 20 weeks . There was no statistically significant difference in the number of ulcers healed in the hydrogel-dressed group (25/70; 36%) compared with the basic wound contact dressed group (15/68; 22%): RR 1.62, 95% CI 0.94 to 2.80 (Analysis 3.1). This study undertook blinded outcome assessment. Additionally, whilst 41 (24%) of study participants were reported as withdrawn, the report confirms that the intention-to-treat population was the primary population for analysis.

Jensen 1998 had a maximum follow-up of 16 weeks. Significantly more ulcers healed in the hydrogel-dressed group (11/14; 79%) compared with the basic wound contact dressed-group (6/17; 35%): RR 2.23, 95% CI 1.11 to 4.48 (Analysis 3.1). Five participants were not included in the analysis with one participant lost from the hydrogel-dressed group and four from the basic wound contact-dressed group. As explained earlier, we have included these participants in our analysis as denominators but not numerators (i.e. assumed not to have healed). The mean time to healing was reported as 10.3 weeks in the hydrogel-dressed group compared with 11.69 weeks in

the basic wound contact-dressed group. In general median and not mean time to healing is the best time to healing summary estimate. The use of mean vales can result in biased estimates - since to calculate mean time to healing either all participants must have healed and/or assumptions need to be made about the shape of the survival curve.

Vandeputte 1997 had a follow-up of 12 weeks. Significantly more ulcers healed in the hydrogel-dressed group (14/15; 93%) compared with the basic wound contact-dressed group (7/14; 50%): RR 1.87, 95% CI 1.09 to 3.21 (Analysis 3.1).

We pooled ulcer healed data from these three studies (D'Hemecourt 1998; Jensen 1998; Vandeputte 1997) with a total of 198 participants using a fixed-effect model (Chi^2: P = 0.77; I^2 = 0%) (Analysis 3.1). Significantly more ulcers healed in the hydrogel-dressed groups compared with the basic wound contact-dressed groups: RR 1.80, 95% 1.27 to 2.56. However, we stress that the baseline ulcer grade was different in these trials: D'Hemecourt 1998 (grade 3 and 4), Jensen 1998 (grade 2) and Vandeputte 1997 (not specific about grade but did include more severe ulcers), as was trial follow-up time. These differences may partly explain the difference in overall ulcer healing that is observed in these studies (29% over 20 weeks in D'Hemecourt 1998 and 55% over 16 weeks in Jensen 1998).

Secondary outcomes:

D'Hemecourt 1998: reported the number of wound-related adverse events. There was no statistically significant difference in number of adverse events between the hydrogel-dressed group (19/70; 27%) and the basic wound contact-dressed group (25/68; 37%): RR 0.74, 95% CI 0.45 to 1.21 (Analysis 3.2). Neither was there a statistically significant difference in number of participants reporting pain as an adverse event between the groups (11/70; 16% in the hydrogel-treated group compared with 10/68; 15%): RR 1.07, 95% CI 0.49 to 2.35 (Analysis 3.3).

Jensen 1998: there were no amputations in the hydrogel-dressed group compared with one amputation in the basic wound contract-dressed group. Adverse events recording was minimal with three specific adverse events being reported for the hydrogel-dressed group compared with four for the basic wound contact-dressed group. The average cost per day of treatment in US Dollars was USD 7.01 in the hydrogel-dressed group and USD 12.28 in the basic wound contact-dressed group. However, these costs were not collected or compared as part of a full economic evaluation.

Vandeputte 1997: reported the number of infection related complications in each study group. There was no statistically significant difference in number of events between the hydrogel-dressed group (1/15; 7%) compared with the basic wound contact-dressed group (7/14; 50%): RR 0.14, 95% 0.02 to 1.01. It is important to remember that this study did not have blinded outcome assessment and neither were the mechanisms for reporting adverse events clearly detailed.

Given the lack of methodological detail regarding the collection of adverse event data and the differences in the type of data presented, we did not pool these data.

Summary: hydrogel dressings compared with basic wound contact dressing

Data from three studies (n=198) found a statistically significant increase in the healing of diabetic foot ulcers in hydrogel-treated ulcers compared with those treated with basic wound contact dressings. This difference is driven by two small trials of unclear risk of bias.

Advanced dressing compared with advanced dressing

Comparison 4: hydrogel dressing compared with hydrogel dressing (one trial; 74 participants)

Primary outcome: ulcer healing

Whalley 2001 recruited 74 participants and compared one type of hydrogel (Purilon) with another (Intrasite) for a maximum of 10 weeks. Data were only available from conference abstracts.

Whilst 74 participants were randomised, data were only presented for 66 of these. The study reports that 35% of ulcers achieved complete healing in the Purilon group compared with 19% in the Intrasite group. The numbers of people in each group were not reported in the abstract (attempts to contact author unsuccessful), nor was the baseline comparability of the participants by treatment group which makes the data impossible to interpret with confidence,

Secondary outcomes:

The direct cost of wound treatments to reach a 75% reduction in wound area were reported to be 32% lower for the Purilon hydrogel. However, no further details are presented and we must stress that this is a very limited analysis that should not be interpreted as an economic evaluation.

Summary: hydrogel dressing compared with hydrogel dressing

There was no evidence that more ulcers dressed with a Purilon hydrogel healed within 10 weeks compared with Intrasite-dressed ulcers.

Summary of Findings Table

We have included a Summary of Findings table (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4): this aims to give a concise overview and synthesis of the volume and quality of the evidence for this comparison. The Summary of Findings table confirm our conclusion that the quality of evidence is of moderate quality where hydrogel is compared with basic wound contact dressings: we note that according to the GRADE definition this still means that "*Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.*" We also note that the three studies in this comparison had limited details reported to inform the individual risk of bias assessments. We did not downgrade the evidence under the GRADE risk of bias for this comparison (as there were no domains assessed at high risk of bias) - however, a large number were unclear and this must be acknowledged. The quality of estimates for other comparisons is considered low.

DISCUSSION

Summary of main results

This review has identified, appraised and presented all available RCT evidence (five studies) regarding the clinical effectiveness of

hydrogel wound dressings in the treatment of diabetic foot ulcers. When data from three studies (20, 16 and 12 weeks follow-up; n = 198) were pooled there was a statistically significant increase in ulcer healing with hydrogel compared with basic wound contact dressings. All studies were at unclear risk of bias due to poor reporting of trial methods. It is important to note that included ulcers in D'Hemecourt 1998 were predominantly grade 3, where as Jensen 1998 only included grade 2 ulcers. Ulcer grade was not specified in Vandeputte 1997 but based on the inclusion criteria there was the potential for more serious ulcers to be included. The different ulcer grades may explain why study healing was lower in D'Hemecourt 1998 compared to Jensen 1998 even though D'Hemecourt 1998 had a longer follow-up time. There is no evidence to inform clinicians as to how hydrogel compares with other advanced dressings in terms of clinical and/or cost-effectiveness.

There was no evidence of any difference between hydrogel and larval therapy or platelet derived growth factor, nor between different brands of hydrogel in terms of ulcer healing.

Quality of the evidence

We deemed all studies to be at unclear risk of bias given the lack of methodological detail reported. Many included studies did not follow good practice conduct and reporting guidelines, e.g. CONSORT (Schulz 2010). Key areas of good practice are the robust generation of a randomisation sequence, for example, computer-generated, robust allocation concealment, for example the use of a telephone randomisation service, and blinded outcome assessment where possible. All this information should be clearly stated in the study report as all trial authors should anticipate the inclusion of their trials in systematic reviews. In terms of analysis, where possible, data from all participants should be included, that is an intention-to-treat analysis is conducted. Steps should be taken during trial conduct to prevent missing data as far as is possible. Where missing data is an issue, imputation methods should be considered and clearly reported when implemented. Finally, where possible, robust economic data should be collected.

Potential biases in the review process

The review considered as much evidence as it was possible to obtain, including studies that were not published in English-language journals. We contacted relevant pharmaceutical companies but did not receive any relevant RCT data from them. There is the potential for publication bias. It is also important to note that three studies are awaiting assessment and may be included in future reviews. However, we anticipate this is unlikely for the majority of these studies.

Agreements and disagreements with other studies or reviews

Prior to this systematic review, the most recent and relevant review regarding the healing of diabetic foot ulcers (Hinchliffe 2008) included one RCT (Jensen 1998 also included here) that compared a hydrogel dressing in the treatment of diabetic foot ulcers. No conclusions were made regarding the results of this study. However, our review included and pooled data from the same three studies (D'Hemecourt 1998; Jensen 1998; Vandeputte 1997) as another Cochrane Review (Edwards 2010), which had the primary aim of assessing the debridement of diabetic foot ulcers. Thus Edwards 2010 also suggested that hydrogel may be more effective than basic contact wound dressings in the treatment of diabetic foot ulcers. However, caution must be advised in changing clinical practice on the basis of findings informed largely by small trials of unknown risk of bias. Clinicians should also be aware of the types of ulcers that were included in each trial.

AUTHORS' CONCLUSIONS

Implications for practice

Based on a comprehensive review of current evidence hydrogel dressings may be better than basic contact wound dressings at healing non-complex diabetic foot ulcers. However, any potential change in practice regarding the use of hydrogels would need to be informed by clinical experience and acknowledge the uncertainty around this decision due to the quality of data used to inform these analyses. It is also important to note that this review was unable to present information on how hydrogel dressings compare with other advanced wound dressings. Thus, practitioners may elect to consider other characteristics such as cost and symptom management properties when choosing between alternatives

Implications for research

Current evidence suggests that hydrogel may be better than basic contact wound dressings at healing diabetic foot ulcers, although there is some uncertainty around this decision. There is no available evidence regarding the effectiveness of hydrogel with other advanced dressing types, thus further research may be warranted. Given the large number of dressing options, the design of future trials should be driven by the questions of high priority to patients and other decision-makers. It is also important for research to ensure that the outcomes that are collected in research studies are those that matter to patients, carers and health professionals. It may be that dressings should be viewed as management tools and that other treatments that address patient lifestyle issues merit the main focus in terms of future research. Where trials are conducted, good practice guidelines must be followed in their design, implementation and reporting. Further reviews are being conducted to synthesise evidence regarding the effect of other dressings on the treatment of diabetic foot ulcers. It would then be useful to conduct further evidence synthesis (overview of reviews, mixed treatment comparisons or both) to aid decision-making regarding the choice of dressings for diabetic foot ulcers across all available options.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

D'Hemecourt 1998

Methods	Multi-centred (10 sites), 3-arm RCT comparing good wound care with good wound care and sodium carboxymethylcellulose aqueous hydrogel (NaCMC hydrogel) and good wound care and becaplermin gel; undertaken in USA Duration of follow up: until wound healing or 20 weeks if not healed
Participants	172 patients Inclusion criteria: patients of 19 years of age or older with type 1 or type 2 diabetes mellitus. Patients with at least one full thickness (stage 3 or 4), chronic diabetic foot ulcer present for at least 8 weeks prior to the study. A target area between 1.0 and 10 cm^2 was required. Transcutaneous oxygen tension (TcPO2) on the limb with the target ulcer had to be ≥ 30 mm Hg. Exclusion criteria: osteomyelitis affecting the area of the target ulcer was present. After debridement, the target ulcer area measured was < 1 cm^2 or > 10 cm^2. Patients having more than 3 chronic ulcers present at baseline. Patients with ulcers resulting from any cause other than diabetes or patients with cancer at the time of enrolment were excluded. Patients on concomitant medications known to affect wound healing. Women who were pregnant or nursing, or of childbearing potential and not using an acceptable method of birth control were also excluded.
Interventions	Group A (n = 70): good wound care (daily wet-to-moist saline dressing changes every 12 hours, sharp debridement of the ulcer when deemed necessary by the investigator, systemic control of infection if present, and off-loading of pressure) and NaCMC hydrogel. A thin layer was applied daily for morning dressing change for 20 weeks or until ulcers healed. Group B (n = 68): good wound care Group C (n = 34): good wound care and becaplermin gel (100 µg/g). A thin layer was applied daily for morning dressing change for 20 weeks or until ulcers healed Co-intervention: off-loading and systemic control of infection No brand details provided for any intervention
Outcomes	Primary outcome: ulcer healing (number of ulcers healed; time to complete healing) Secondary outcomes: adverse events (wound-related; pain reported as adverse event) Health-related quality of life; amputation; costs and ulcer recurrence not reported
Notes	Trial data: Analysis 4.1 Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

D'Hemecourt 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned in a 2:2:1 ratio to one of three treatment groups." Comment: method of generation of random schedule not reported
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "both the NaCMC gel and becaplermin gel treatment groups were conducted in double blind fashion; the group receiving good wound care alone was blinded to the investigator by a third party." Comment: insufficient information to judge if the participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "evaluator blinded" Comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "...41 (24%) of study participants withdrawn from the study..." "The intention to treat population was the primary population for analysis" Comment: the presentation of data and the methods outlined suggest that an ITT analysis was done considering all randomised participants in the denominator
Selective reporting (reporting bias)	Low risk	Comment: based on paper only, protocol not obtained
Other bias	Unclear risk	Comment: some baseline differences in groups of interest for ulcer depth and duration. However, these baseline data were only presented for 24 participants so risk has been classed unclear. Funding source was not reported

Jensen 1998

Methods	Single-centre, 2-arm RCT comparing a hydrogel dressing with a standard wet-to-moist saline dressing undertaken in the USA. Duration of follow up: until ulcer healing or up to 16 weeks if healing did not occur.
Participants	31 participants Inclusion criteria: no signs of infection in the ulcer or the peri-wound tissue. Diabetic foot ulcer measuring at least 1 cm diameter, diabetic patients with foot ulcers of Wagner grade 2 defined as full thickness into subcutaneous tissue but not involving tendon, joint capsule or bone, having palpable pulse and willingness to comply to the treatment. Documented blood supply consistent with the ability to heal (no further information or measures provided), willingness to comply with protocol instructions. Exclusion criteria: not reported
Interventions	Group A (n = 14): hydrogel dressing (Carrington Laboratories, Inc). An 1/8 to 1/4 inch layer of hydrogel dressing applied over the entire surface of wound Group B (n = 17): gauze pad soaked in sterile saline. The saline-moist gauze was moistened as needed In both groups the wound was cleansed with ULTRAKLENZ wound cleanser, and the trial dressings were covered with a gauze pad, wrapped with a Kling bandage and secured with tape. Dressings were bandaged daily. Co-intervention: all participants were initially treated with sharp debridement to remove all non-viable tissue in and around the ulcer. All received custom made healing sandals. Instructions were given on the importance of weight distribution and offloading of the ulcer.

Jensen 1998 *(Continued)*

Outcomes	Primary outcome: ulcer healing (number of ulcers healed; average time to close) Secondary outcomes: amputation; adverse events; costs Health-related quality of life and ulcer recurrence not reported
Notes	Trial data: Analysis 4.1 Funding source: Carrington Laboratories, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were then randomised to receive one of the following daily protocols for the study period of up to 16 weeks." Comment: method of generation of random schedule not reported
Allocation concealment (selection bias)	Unclear risk	Comment: the process of randomising participants, including who did this is not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no mention of blinding in study report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no mention of blinding in study report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: in total 5 patients (of the total 31, 16%) were excluded post-randomisation. However, it is unclear from the study report what data were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: based on study report, protocol not obtained
Other bias	Unclear risk	Comment: funded by commercial organisation. No baseline data reported. The report states that "wound chronicity could not be adequately determined for all patients, where data were available the average ulcer duration was longer in the hydrogel group (8.9 months) than in the saline control group (3 months)". It is important to note that these data are NOT complete and so can not be used to inform the interpretation of findings.

Markevich 2000

Methods	Multi-centred, 2-arm RCT comparing a hydrogel dressing with the use of larval therapy. The study was of 30 months duration but patient follow up was reported as 10 days.
Participants	140 patients Inclusion and exclusion criteria not stated. Mean age reported as 53.6 +/- 15.4 years. Group A: 15.14 cm^2 Group B: 14.9 cm^2
Interventions	Group A (n = 70): hydrogel (no data on brand of hydrogel or on frequency of dressing change)

Markevich 2000 *(Continued)*

	Group B (n = 70): larvae of the green-bottle fly *Lucilia sericata* (larval therapy) for 72 hrs. Absorbent dressings were used over the larvae and were changed as required.
Outcomes	Primary outcome: ulcer healing (number of ulcers healed at 10 days; % patients with granulation tissue covering over 50% of wound; proportion of patients with more than a 50% reduction in wound area) Secondary outcomes: not reported
Notes	Trial data: Analysis 4.1 Very short follow-up data presented Conference abstract only Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: published abstract only - method of generation of random schedule not reported. Does however state that patients were "randomly assigned" to treatment with maggots or hydrogel.
Allocation concealment (selection bias)	Unclear risk	Comment: published abstract only - no details in the text
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: reported as double-blind but no details in the published abstract to judge if the participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: reported as double-blind but no details in the published abstract to judge if the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: published abstract only - unable to assess incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: published abstract only - unable to assess selective outcome reporting
Other bias	Unclear risk	Comment: published abstract only. Baseline measures were reported as being balanced at baseline but only baseline mean surfaces areas were reported.

Vandeputte 1997

Methods	Two-arm RCT, comparing hydrogel dressing with dry gauze undertaken in Belgium. The maximum duration of follow up was 12 weeks (3 months).
Participants	29 participants (30 wounds) Inclusion criteria: any patient who was diabetic and had wound on his foot (neuropathic or not) was included in the trial Necrotic and infected wounds and patients who already had amputated toe were not excluded Exclusion criteria: patients receiving systemic antibiotics

Vandeputte 1997 *(Continued)*

Interventions	Group A (n = 15): hydrogel dressing (Elasto gel with 65% glycerol, 17.5% water and 17.5% polyacrylamide) and wounds cleansed with a dermal wound cleanser Group B (n = 14): dry gauze change twice a day and irrigated with chlorhexidine (0.05% solution) We assumed that the dermal cleanser noted was also chlorhexidine
Outcomes	Primary outcome: ulcer healing (number of ulcers healed) Secondary outcomes: adverse events (infective complications) Health-related quality of life; amputation; costs; and ulcer recurrence not reported
Notes	Trial data: Analysis 4.1 Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were allocated to treatment groups according to a pre-prepared randomisation listing." Comment: method of generation of random schedule not reported
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "At each dressing change, the state of the ulcer and surrounding skin was assessed and the nurse also observed the ease of removal and application of dressing. The wounds were photographed every four weeks" Comment: Not clear who assessed the wounds for healing..
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Methods and Results sections report control group as n = 14. Results section states: "two patients in the control group died?" Comment: information insufficient to judge concerning patients death in control group
Selective reporting (reporting bias)	Low risk	Nine parameters pre-specified in the Methods section were reported in results
Other bias	Unclear risk	Comment: baseline data like mean ulcer area not reported. Hence, insufficient information to assess if any important source of bias exists. Unclear if participant with more than one wound that was followed without taking this lack of independence into account in the analysis.

Whalley 2001

Methods	Multi-centred, 2-arm RCT comparing the effectiveness of two hydrogels Purilon gel and IntraSite gel undertaken in multiple countries: Spain, UK, Lithuania and Belgium. The duration of follow up was for a minimum of 4 weeks until healing or for a maximum 10 weeks.
Participants	74 patients; (66 patients evaluated) no further data available

Whalley 2001 *(Continued)*

	Inclusion criteria: neuropathic foot ulcer, Wagner grade 1 or 2 Exclusion criteria: not stated
Interventions	Group A: Purilon gel (Coloplast A/S) Group B: IntraSite gel (Smith & Nephew) Co-intervention: dressings changed every second day. All patients had appropriate off-loading. Weekly assessment of ulcer area, peri-ulcer skin reactions, inflammation/infection of peri-ulcer skin and patient comfort. Biatain non-adhesive dressing used as a secondary dressing.
Outcomes	Primary outcome: ulcer healing (% ulcers healed at 10 weeks; change in mean wound area; average time to 75% reduction in wound area) Secondary outcomes: costs (description) Amputation; adverse events; health-related quality of life and ulcer recurrence not reported
Notes	Trial data: Analysis 4.1 Conference abstract only Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: published abstract only. Method of generation of random schedule not reported. The abstract does state that participants were 'recruited and randomised to Purilon Gel or Intrasite...'
Allocation concealment (selection bias)	Unclear risk	Comment: published abstract only - no details in the text
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: published abstract only - blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: published abstract only - blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: reports that "66 patients were evaluated out of 74 randomised". Not clear if intention-to-treat analysis conducted.
Selective reporting (reporting bias)	Unclear risk	Comment: published abstract only - unable to assess incomplete outcome data
Other bias	Unclear risk	Comment: published abstract only - unable to assess other risk of bias

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

Study	Reason for exclusion
Agas 2006	Study did not randomise participants
Ahroni 1993	The dressing groups evaluated in this study were not hydrogel dressings
Altman 1993	No single, identifiable dressing type evaluated
Alvarez 2003	The dressing groups evaluated in this study were not hydrogel dressings
Apelqvist 1990	Relevant outcome data are not reported: study outcome was limited to change in size of necrotic material on the wound. Study authors were unable to provide the original healing outcome data.
Apelqvist 1996	No single, identifiable dressing type evaluated
Apelqvist 2004	No single, identifiable dressing type evaluated
Armstrong 2004	No single, identifiable dressing type evaluated
Baker 1993	The dressing groups evaluated in this study were not hydrogel dressings
Belcaro 2010	The dressing groups evaluated in this study were not hydrogel dressings
Blackman 1994	The dressing groups evaluated in this study were not hydrogel dressings
Bogaert 2004	Study did not randomise participants
Bradshaw 1989	Trial stopped after recruiting six participants. No data presented. Authors not contacted for healing data.
Caravaggi 2003	Other intervention, not dressings, differs between trial arms
Chang 2000	Study did not include diabetic foot ulcers
Chauhan 2003	Other intervention, not dressings, differ between trial arms
Chirwa 2010	Study did not randomise participants
Clever 1995	The dressing groups evaluated in this study were not hydrogel dressings
Cuevas 2007	No single, identifiable dressing type evaluated
Dash 2009	Other intervention, not dressings, differ between trial arms
Diehm 2005	Study did not randomise participants
Donaghue 1998	The dressing groups evaluated in this study were not hydrogel dressings
Driver 2006	Other intervention, not dressings, differs between trial arms
Edmonds 2009	Other intervention, not dressings, differs between trial arms
Eginton 2003	No single, identifiable dressing type evaluated
Etoz 2003	Study did not randomise participants
Farac 1999	Author contacted: study not suitable for inclusion due to data quality issues

Study	Reason for exclusion
Foo 2004	The dressing groups evaluated in this study were not hydrogel dressings
Foster 1994	The dressing groups evaluated in this study were not hydrogel dressings
Foster 1999	Other intervention, not dressings, differs between trial arms
Gao 2007	Other intervention, not dressings, differs between trial arms
Gentzkow 1996	Other intervention, not dressings, differs between trial arms
Gottrup 2011	The dressing groups evaluated in this study were not hydrogel dressings
Hanft 2002	Other intervention, not dressings, differs between trial arms
Jeffcoate 2009	The dressing groups evaluated in this study were not hydrogel dressings
Jeffery 2008	Study did not randomise participants
Jude 2007	The dressing groups evaluated in this study were not hydrogel dressings
Kordestani 2008	The dressing groups evaluated in this study were not hydrogel dressings
Lalau 2002	The dressing groups evaluated in this study were not hydrogel dressings
Landsman 2010	Other intervention, not dressings, differs between trial arms
Lazaro-Martinez 2007	No single, identifiable dressing type evaluated
Lipkin 2003	Other intervention, not dressings, differs between trial arms
Marston 2001	Other intervention, not dressings, differs between trial arms
Mazzone 1993	The dressing groups evaluated in this study were not hydrogel dressings
McCallon 2000	Study did not randomise participants
Mody 2008	Study did not include diabetic foot ulcers
Moretti 2009	Other intervention, not dressings, differs between trial arms
Mueller 1989	Other intervention, not dressings, differs between trial arms
Mulder 1994	Required further data specific to diabetic foot ulcers. Unablet o obtain.
Munter 2006	The dressing groups evaluated in this study were not hydrogel dressings
Novinscak 2010	No homogenous dressing group evaluated
Ogce 2007	The dressing groups evaluated in this study were not hydrogel dressings
Palao i Domenech 2008	The dressing groups evaluated in this study were not hydrogel dressings
Parish 2009	Other intervention, not dressings, differs between trial arms
Pham 1999	Other intervention, not dressings, differs between trial arms

Study	Reason for exclusion
Piaggesi 1997	Study did not randomise participants
Piaggesi 2001	The dressing groups evaluated in this study were not hydrogel dressings
Reyzelman 2009	No single, identifiable dressing type evaluated
Roberts 2001	The dressing groups evaluated in this study were not hydrogel dressings
Robson 2005	Other intervention, not dressings, differs between trial arms
Robson 2009	Study did not include diabetic foot ulcers
Sabolinski 2000	Other intervention, not dressings, differs between trial arms
Sabolinski 2001	Other intervention, not dressings, differs between trial arms
Shaw 2010	Other intervention, not dressings, differs between trial arms
Shukrimi 2008	Other intervention, not dressings, differs between trial arms
Sibbald 2011	The dressing groups evaluated in this study were not hydrogel dressings
Solway 2011	Study did not randomise participants
Steed 1992	Other intervention, not dressings, differs between trial arms
Steed 1995	Other intervention, not dressings, differs between trial arms
Steed 1996	Other intervention, not dressings, differs between trial arms
Subrahmanyam 1993	The dressing groups evaluated in this study were not hydrogel dressings
Trial 2010	The dressing groups evaluated in this study were not hydrogel dressings
Turns 2012	Other intervention, not dressings
Urbaneie 1999	No homogenous dressing group evaluated
Varma 2006	No homogenous dressing group evaluated
Veves 2001	Other intervention, not dressings, differs between trial arms
Veves 2002	The dressing groups evaluated in this study were not hydrogel dressings
Woo 2010	The dressing groups evaluated in this study were not hydrogel dressings
Yao 2007	Other intervention, not dressings, differs between trial arms
Zimny 2003	Other intervention, not dressings, differs between trial arms

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

Wang 2012

Methods	RCT?
Participants	People with diabetes and foot ulcers
Interventions	Topical bismuth subgallate/borneol (Suile) dressing compared with hydrogel
Outcomes	Unsure
Notes	Awaiting retrieval and translation

DATA AND ANALYSES

Comparison 1. Hydrogel dressing compared with larval therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Hydrogel dressing compared with larval therapy, Outcome 1 Number of ulcers healed.

Study or subgroup	Hydrogel dressing n/N	Larval therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Markevich 2000	2/70	5/70		0%	0.4[0.08,1.99]

Favours larval therapy 0.01 0.1 1 10 100 Favours hydrogel dressing

Comparison 2. Hydrogel dressing compared with platelet-derived growth factor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2 Hydrogel dressing compared with platelet-derived growth factor, Outcome 1 Number of ulcers healed.

Study or subgroup	Hydrogel n/N	Growth factor n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Hemecourt 1998	25/70	15/34		0%	0.81[0.5,1.32]

Favours growth factor 0.01 0.1 1 10 100 Favours hydrogel

Comparison 3. Hydrogel dressing compared with basic wound contact dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	3	198	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.27, 2.56]
2 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Quality of life	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3 Hydrogel dressing compared with basic wound contact dressing, Outcome 1 Number of ulcers healed.

Study or subgroup	Hydrogel n/N	Basic wound contact n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Hemecourt 1998	25/70	15/68		54.59%	1.62[0.94,2.8]
Jensen 1998	11/14	6/17		19.44%	2.23[1.11,4.48]
Vandeputte 1997	14/15	7/14		25.98%	1.87[1.09,3.21]
Total (95% CI)	**99**	**99**		**100%**	**1.8[1.27,2.56]**
Total events: 50 (Hydrogel), 28 (Basic wound contact)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=2(P=0.77); I^2=0%					
Test for overall effect: Z=3.29(P=0)					

Favours basic wound — Favours hydrogel

Analysis 3.2. Comparison 3 Hydrogel dressing compared with basic wound contact dressing, Outcome 2 Adverse events.

Study or subgroup	Hydrogel n/N	Basic wound contact n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vandeputte 1997	1/14	7/14		0%	0.14[0.02,1.01]
D'Hemecourt 1998	19/70	25/68		0%	0.74[0.45,1.21]

Favours hydrogel — Favours basic wound

Analysis 3.3. Comparison 3 Hydrogel dressing compared with basic wound contact dressing, Outcome 3 Quality of life.

Study or subgroup	Hydrogel n/N	Basic wound contact n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Hemecourt 1998	11/70	10/68		0%	1.07[0.49,2.35]

Favours hydrogel — Favours basic wound

Comparison 4. Trial data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trial data			Other data	No numeric data

Analysis 4.1. Comparison 4 Trial data, Outcome 1 Trial data.

		Trial data					
Study	Groups	Primary outcome: ulcer healing	Secondary: health-related quality of life	Number and level of amputations	Adverse events, including pain	Cost	Ulcer recurrence
D'Hemecourt 1998	Group A (n = 70): good wound care and NaCMC gel Group B (n = 68): good wound care Group C (n = 34): good wound care and becaplermin gel (100 µg/g)	*Number of ulcers healed:* Group A: 25/70 Group B: 15/68 Group C: 15/34 *Time to complete healing (days):* Group A: 98* Group B: 141* Group C: 85* *It is unclear if these are mean or median times to healing. Although a life plot table presented suggests that median time to healing was not reached in any group. Explained by the very short follow-up time of this trial - 10 days.	n/r	n/r	*Wound related:* Group A: 19/70 Group B: 25/68 Group C: 7/34 *Pain reported as adverse event:* Group A: 11/70 Group B: 10/68 Group C: 2/34	n/r	n/r
Jensen 1998	Group A (n = 14): hydrogel dressing Group B (n = 17): gauze pad soaked in sterile saline	*Number of ulcers healed:* Group A: 11 Group B: 6 *Average time to close (weeks):* Group A: 10.30 Group B: 11.69	n/r	Amputation: Group A: 0 Group B: 1	Group A: cellulitis = 2; hospitalised for non study-related dehydration = 1 Group B: partial amputation = 1; increased eschar formation = 2; cellulitis = 1	*Cost in US dollars/day/group including nursing time and cost of products used, it is not clear if this is per patient)*: Group A: $7.01 per day Group B: $12.28 per day	n/r
Markevich 2000	Group A (n = 70): hydrogel (no data on brand) Group B (n = 70): larvae of the green-bottle fly *Lucilia sericata* (larval therapy)	*Number of ulcers healed at 10 days:* Group A: 2/70 Group B: 5/70 *Proportion of patients with granulation tissue covering over 50% of wound (numbers not supplied)* Group A: 34% Group B : 60% *Proportion of patients with more than a 50% reduction in wound area (numbers not supplied)*	n/r	n/r	n/r	n/r	n/r

Study	Groups	Trial data					
		Primary outcome: ulcer healing	Secondary: health-related quality of life	Number and level of amputations	Adverse events, including pain	Cost	Ulcer recurrence
		Group A: 27% Group B : 51%					
Vandeputte 1997	Group A (n = 15): hydrogel dressing (Elasto gel with 65% glycerol, 17.5% water and 17.5% polyacrylamide) and wounds cleansed with a dermal wound cleanser Group B (n = 14): dry gauze change twice a day and irrigated with chlorhexidine (0.05% solution)	*Number of ulcers healed:* Group A: 14/15 Group B: 7/14	n/r	n/r	*Infective complications* Group A: 1/15 Group B: 7/14 Two participants in the control group died	n/r	n/r
Whalley 2001	Group A: Purilion gel Group B: IntraSite gel	*Percentage of ulcers healed at 10 weeks (numbers not presented):* Group A: 35% Group B: 19% *Change in mean wound area* Group A: 2.5 cm^2 (SD 3.2) to 0.6 cm^2 (SD 1.1) Group B: 2.4 cm^2 (SD 2.9) to 1.0 cm^2 (SD 1.8) *Average time to 75% reduction in wound area (days):* Group A: 35 days Group B: 46 days				Direct cost associated with wound treatment to reach 75% reduction in wound area was 32% lower for patients treated with Purilion gel	

ADDITIONAL TABLES

Table 1. Summary of studies

First author	Group A	Group B	Group C	Duration of follow up	% healed data
D'Hemecourt 1998	Good wound care and NaCMC gel; a thin layer was applied daily for morning dressing change for 20 weeks or until ulcers healed No brand information	Good wound care (daily wet-to-moist saline dressing changes every 12 hours, sharp debridement of the ulcer when deemed necessary by the investigator, systemic control of infection if present, and off-loading of pressure) No brand information	Good wound care and becaplermin gel (100 µg/g)	20 weeks	Yes
Jensen 1998	Hydrogel dressing (Carrington Laboratories, Inc)	Gauze pad soaked in sterile saline		16 weeks	Yes

Table 1. Summary of studies *(Continued)*

Markevich 2000	Hydrogel (no data on brand of hydrogel)	Larvae of the green-bottle fly *Lucilia sericata* (larval therapy). Absorbent dressings were used over the larvae and were changed as required.	10 days	Yes
Vandeputte 1997	Hydrogel dressing (Elasto gel with 65% glycerol, 17.5% water and 17.5% polyacrylamide)	Dry gauze twice a day	12 weeks	Yes
Whalley 2001	Purilon gel (Coloplast A/S)	IntraSite Gel (S&N Hlth)	10 weeks	Yes

APPENDICES

Appendix 1. Search methods used in the original version of this review - June 2011

Electronic searches

We searched the following databases:

- the Cochrane Wounds Group Specialised Register (searched 10 June 2011);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2);
- Ovid MEDLINE (1950 to June Week 1 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, June 8, 2011);
- Ovid EMBASE (1980 to 2011 Week 22); and
- EBSCO CINAHL (1982 to 3 June 2011).

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following exploded MeSH headings and keywords:

#1 MeSH descriptor Occlusive Dressings explode all trees
#2 MeSH descriptor Biological Dressings explode all trees
#3 MeSH descriptor Alginates explode all trees
#4 MeSH descriptor Hydrogels explode all trees
#5 MeSH descriptor Silver explode all trees
#6 MeSH descriptor Honey explode all trees
#7 (dressing* or alginate* or hydrogel* or "foam" or "bead" or "film" or "films" or tulle or gauze or non-adherent or "non adherent" or silver or honey or matrix):ti,ab,kw
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Foot Ulcer explode all trees
#10 MeSH descriptor Diabetic Foot explode all trees
#11 diabet* NEAR/3 ulcer*:ti,ab,kw
#12 diabet* NEAR/3 (foot or feet):ti,ab,kw
#13 diabet* NEAR/3 wound*:ti,ab,kw
#14 (#9 OR #10 OR #11 OR #12 OR #13)
#15 (#8 AND #14)

We adapted this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision). We combined the EMBASE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network. There were no restrictions on the basis of date or language of publication.

Searching other resources

We attempted to contact researchers to obtain any unpublished data when needed. We also searched the reference lists of the included studies and previous systematic reviews. We contacted appropriate manufacturers (Smith & Nephew, Convatec Ltd, Mölnlycke Health Care, 3M Healthcare, Coloplast Ltd) for details of any unpublished studies. We also checked for ongoing studies in the ISRCTN register.

Appendix 2. Risk of bias criteria

1. Was the allocation sequence randomly generated?

Low risk of bias

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

High risk of bias

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

Unclear

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

2. Was the treatment allocation adequately concealed?

Low risk of bias

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

High risk of bias

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

Unclear

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

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

Low risk of bias

Any one of the following.

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

High risk of bias

Any one of the following.

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

Unclear

Any one of the following.

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

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

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

High risk of bias

Any one of the following.

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

Unclear

Any one of the following.

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

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

Low risk of bias

Any of the following.

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

High risk of bias

Any one of the following.

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

Unclear

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

6. Other sources of potential bias

Low risk of bias

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

High risk of bias

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

- had a potential source of bias related to the specific study design used; or
- 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
25 June 2013	New search has been performed	First update, new search, no new trials identified.
25 June 2013	New citation required but conclusions have not changed	Summary of findings table included, conclusions not changed.

CONTRIBUTIONS OF AUTHORS

Jo Dumville developed the review and co-ordinated development, completed the first draft of the protocol, made an intellectual contribution, approved the final version prior to submission and is the guarantor of the review and the update.
Susan O'Meara edited the review, made an intellectual contribution and approved the final version of the review and the update prior to submission.
Sohan Deshpande completed the first draft of the review, made an intellectual contribution and approved the final version of the review prior to submission.
Katharine Speak made an intellectual contribution to the review, advised on the review and approved the final version prior to submission.

Contributions of editorial base:

Nicky Cullum: edited the protocol and review; advised on methodology, interpretation and content. Approved the final review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited and copy edited the review and the update.
Ruth Foxlee: designed the search strategy and edited the search methods section.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Bandages, Hydrocolloid; *Wound Healing; Diabetic Foot [*drug therapy]; Hydrogel, Polyethylene Glycol Dimethacrylate [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans