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Hydrocolloid dressings for treating pressure ulcers.
Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD010364.
DOI: 10.1002/14651858.CD010364.

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[Intervention Protocol]

Hydrocolloid dressings for treating pressure ulcers

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Editorial group: Cochrane Wounds Group.
Publication status and date: New, published in Issue 2, 2013.

Citation: Keogh SJ, Nelson EA, Webster J, Jolly J, Ullman AJ, Chaboyer WP. Hydrocolloid dressings for treating pressure ulcers. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD010364. DOI: 10.1002/14651858.CD010364.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of hydrocolloid wound dressings for healing pressure ulcers in people in any care setting.

BACKGROUND

Description of the condition

Pressure ulcers are an internationally recognised patient safety problem, estimated to affect 2.5 million people annually (House 2011). The development of pressure ulcers in any patient is a serious complication resulting in pain, decreased quality of life and significant expenditure of both time and money for the healthcare industry (VanGilder 2009). Also known as pressure injury, pressure sores, decubitus ulcers, or bedsores, pressure ulcers are a localised injury to the skin, underlying tissue, or both, usually occurring over a bony prominence, as a result of pressure, or pressure in combination with shear stress (EPUAP/NPUAP 2009).

The main factors associated with the development of pressure ulcers are exposure of the skin to excessive pressure, and a reduced tolerance of the skin to pressure. Pressure is exerted on the skin, soft tissue, muscle, and bone by the weight of an individual or a device applied against the surface. Tissue tolerance is the ability of the skin and its supporting structures to tolerate the effects of pressure by distributing it (cushioning) and by the transfer of pressure loads from the skin surface to the skeleton (AWMA 2012). Tissues are capable of withstanding enormous pressures briefly, but prolonged exposure to pressure initiates a series of events that potentially leads to necrosis and ulceration of tissue.

Factors that increase pressure on the skin include impairments in mobility, activity or sensory perception, because then the pressure is not relieved by movement or changes to body position. Intrinsic risk factors for the development of pressure ulcers include advancing age, poor nutrition, poor perfusion and oxygenation, whereas, extrinsic risk factors include increased moisture, shear and friction. Shear forces and friction aggravate the effects of pressure upon tissue and are important components of the mechanism of injury. The combination of pressure, shear forces, and friction causes mi-

crocirculatory occlusion, resulting in ischemia and tissue anoxia (lack of oxygen) and stimulation of inflammatory processes, which may lead to necrotic cell death, and ulceration. Irreversible tissue damage may occur in a vulnerable patient with as little as 30 minutes of uninterrupted pressure (Kirman 2008). In addition, excessive contact of the skin to fluids impairs its barrier function, causes maceration and an increased risk of the development of pressure ulcers.

Global prevalence rate of pressure ulcers ranges from 8% to 30%, depending on patient factors and treatment setting. Prevalence surveys in European acute care settings found an overall prevalence of 18.1%, with individual countries reporting prevalence of between 8.3% to 23% (Vanderwee 2007). A recent US study estimated pressure ulcer prevalences of approximately 13.3% in acute care settings and 29% to 30% in long-term care settings (VanGilder 2009). Within Australia, pressure ulcer prevalence is currently estimated at between 5% to 15% in acute care settings and between 13% and 37% in aged care (DoH 2006). These international studies of prevalence illustrate the extent of the burden of all grades of pressure ulcers, however, variability in prevalence in similar settings suggests pressure ulcers are amenable to intervention, with substantial potential for improvement in patient and financial outcomes.

A number of systems for describing the amount of tissue damage exist, but pressure ulcers are generally graded 1, 2, 3 and 4, according to the depth of tissue damage, with category/stage 1 being the least severe, and category/stage 4 indicating complete tissue destruction (Moore 2005), as illustrated in Table 1 (EPUAP/NPUAP 2009). The majority of pressure ulcers occur on the sacrum or heel, but they also occur frequently over the elbow, hip, ischium, shoulder, spinous process, ankle, toe, head or face (Lahmann 2006; Shanin 2008; Vanderwee 2007).

Internationally, substantial investment has occurred over recent decades in monitoring, preventing and treating pressure ulcers. For example, it is estimated that the annual cost of treating pressure ulcers in Australia is between AUD 300-350 million with the cost of treating a stage 4 ulcer at nearly AUD 22, 000 (AUD) (Graves 2005; Young 1997). The total annual cost for pressure ulcer management in the UK has been estimated to be approximately GBP 1.4 to 2.1 billion annually. This equates to 4% of the total UK healthcare expenditure (Bennett 2004). The main costs incurred for the treatment and management of pressure ulcers are due to prolonged hospitalisation and the extent of nursing care required. The average length of acute hospital stay for a patient with a pressure ulcer is 12 days. In comparison, the average length of stay for patients without a pressure ulcer is 4.6 days (VanGilder 2009). Furthermore, discomfort and pain, increased time spent in hospital, increased risk of mortality, altered body image and reduced quality of life, together with the potential cost associated with litigation, compounds the cost to health services and the burden upon the patient with the pressure ulcer (VQC 2004).

In spite of the level of investment in prevention and monitoring of pressure ulcers, many people continue to develop them. This is the case particularly in acute care settings where people may present with an increased number of high risk factors such as decreased mobility, impaired perfusion, poor nutrition, and fluctuating patient status. Pressure ulcer treatment strategies can be costly and complex.

Description of the intervention

Treatment of pressure ulcers is primarily two-fold involving the relief of pressure allied with wound management. Other general strategies include patient education, pain management, optimising circulation/perfusion, optimising nutrition and the treatment of clinical infection (AWMA 2012). Wound management may involve surgical or chemical debridement (removal of dead tissue) and dressings to protect the wound and promote healing. Dressings can be divided into four main categories, namely, basic wound dressings, advanced wound dressings, anti-microbial dressings and specialist dressings. Classification of a dressing depends on its purpose and the key material used. Key attributes of a dressing have been described (BNF 2010), and include:

- the ability of the dressing to absorb and contain exudate without leakage or strike-through (saturation);
- lack of particulate contaminants left in the wound;
- thermal insulation;
- level of 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;
- comfort.

The focus of this review is hydrocolloid dressings, the properties of which are described below. However, as hydrocolloid dressings are likely to be evaluated against one of the many wound dressings available, a description of potential comparators has been categorised, according to the British National Formulary (BNF 2010). These are listed alphabetically below, by their generic names and, where possible with their corresponding trade names and manufacturers. Dressing names, manufactures and distributors may vary between countries.

Absorbent dressings are applied directly to the wound and may be 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).

Alginate dressings are highly absorbent fabrics/yarns that 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; this can be lifted off at dressing removal, or rinsed away with sterile saline. Bonding to a secondary viscose pad increases absorbency. Examples include: 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 include: Advadraw (Advancis) and Vacutex (Protex).

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

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

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

Honey-impregnated dressings contain medical-grade honey that is purported to have antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. It is important to note that, when such dressings are used on patients with diabetes, the patients should be monitored for changes in blood-glucose concentrations. Examples include: Medihoney (Medihoney) and Activon Tulle (Advancis).

Hydrocolloid dressings are usually composed of an absorbent hydrocolloid matrix on a vapour-permeable film or foam backing. Examples include: Granuflex (ConvaTec) and NU DERM (Systagenix). Fibrous alternatives have been developed that resemble alginates and are not occlusive: Aquacel (ConvaTec).

Hydrogel dressings consist of a starch polymer and up to 96% water. These dressings can 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 include: ActiformCool (Activa) and Aquaflo (Covidien).

Iodine-impregnated dressings release free iodine, which is thought to act as a wound antiseptic, when exposed to wound exudate. Examples include Iodoflex (Smith & Nephew) and Iodozyme (Insense).

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

Odour-absorbent dressings contain charcoal and are used to absorb wound odour. Often this type of wound dressing is used in conjunction with a secondary dressing to improve absorbency. An example is CarboFLEX (ConvaTec).

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

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

Silver-impregnated dressings are 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 include: Acticoat (Smith & Nephew) and Urgosorb Silver (Urgo).

The diversity of dressings available to clinicians (including variation within each type listed above) makes evidence-based decision-making difficult when determining the treatment regime for the patient. Some dressings are formulated with an 'active' ingredient such as silver that is promoted as a dressing treatment option to reduce infection and possibly to promote healing. With increasingly sophisticated technology being applied to wound care, practitioners need to know how effective these, often expensive, dressings are compared with more traditional, and usually less costly, dressings. However, far from providing critical evaluation of dressing types for clinical use, studies have shown wide variation in practice and wound (pressure ulcer) care knowledge (Maylor 1997; Pieper 1995).

How the intervention might work

The principle of moist wound healing governs wound care practice today. This is optimised through the application of occlusive or semi-occlusive dressings and preparation of the wound bed (AWMA 2012). Animal experiments performed 50 years ago suggested that acute wounds healed more quickly when their surface was kept moist, rather than being left to dry and to scab (Winter 1962; Winter 1963a; Winter 1963b). Winter 1962 examined the rate of epithelialisation in experimental wounds cut into the skin of healthy pigs, comparing wounds with a natural scab exposed to the air against wounds that were covered with polythene film. He found that epithelialisation occurred more quickly in the latter.

Wounds exposed to the air lose water vapour, the upper dermis dries and healing takes place beneath a dry scab. Covering a wound with an occlusive dressing prevents scab formation and radically alters the pattern of epidermal wound healing. Winter's (1962) research focused only on acute, superficial wounds, but the results have been used to generate a theory of moist wound healing for all types of wound of varying aetiologies. However, the theory of moist wound healing may not provide a basis for satisfactory management of every type of wound encountered. Whilst a moist environment at the wound site has been shown to aid the rate of epithelialisation in superficial wounds, excess moisture at the wound site can cause maceration of the peri wound (surrounding) skin (Cutting 2002). Some early studies also suggested that keeping wounds moist might predispose them to infection (Hutchinson 1991). It is not entirely clear which type(s) of wound should be kept moist, how much moisture is required, when it should be applied, and in what combination with other factors it actually

confers benefit. However, Bishop and colleagues have proposed a general principle of *moisture balance* (Bishop 2003), that is, that dressings must absorb exudate away from the wound surface, while ensuring that the wound surface remains moist. Despite a plethora of research into wound care, the optimal level of exudate to promote wound healing has yet to be established.

The principle of moist wound healing has led to the development of several commercially available wound dressings to support optimal healing processes. These have revolutionised wound management (Benbow 2005); products include hydrogels that retain moisture in contact with the wound, hydrocolloids that absorb small amounts of excess moisture without drying the wound bed, absorbent foams, alginates, adhesive dressings, non-adhesive dressings and silicone-based low-adherent dressings. Hydrocolloid dressings (the subject of this review) are composed of a layer of sodium carboxymethylcellulose (or similar material that forms a gel when wet) bonded onto a vapour-permeable film or foam pad. These occlusive dressings absorb exudate whilst maintaining a moist wound environment. Fibrous hydrocolloids are a sub-set of dressings that are designed for use in wounds with heavy exudate in lieu of alternate dressing types such as alginates (BNF 2010; Pan Pacific Clinical Guidelines 2011).

Why it is important to do this review

Pressure ulcer prevention and management is a significant burden to all healthcare systems. It is an internationally recognised patient safety problem and serves as a clinical indicator of the standard of care provided. Pressure ulcers are the second most reported incident that leads to patient harm in the health system, and are a significant source of suffering for patients and their care givers (PSC 2009; Reddy 2008). Over recent decades significant investment has been placed in strategies aimed at pressure ulcer prevention. Treatment strategies for pressure ulcers can also be costly and complex, and there is a large range of wound care products available. Despite a growing amount of literature concerned with wound care interventions, relatively few research studies have used clinical trial methodology to evaluate clinical effectiveness. The complexity of suggested interventions, and range of options available suggests that the evidence requires evaluation and presentation to the clinician to assist with effective decision making. This review is part of a suite of reviews investigating the use of individual dressing types in the treatment of pressure ulcers. Each review will focus on a particular dressing type. These reviews will then be summarised in an overview of reviews which will draw together all existing Cochrane review evidence regarding the use of dressing treatments for pressure ulcers.

There is a plethora of wound care products available, however, the evidence base to support use of some of these products remains incomplete. Thus, there is a clear need to provide clinicians with a reliable evidence base with which to make sound decisions for the treatment of pressure ulcers, if we are to reduce their prevalence and burden.

OBJECTIVES

To assess the effects of hydrocolloid wound dressings for healing pressure ulcers in people in any care setting.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and controlled clinical trials (CCTs) that have evaluated the effects of any hydrocolloid wound dressing compared with any other dressing-based intervention for treatment of pressure ulcers of grade/category 2 or above, irrespective of publication status or language. CCTs are quasi-randomised studies where, although the trial involves testing an intervention and control, concurrent enrolment and follow-up of test intervention- and control-treated groups, the method of allocation is not considered strictly random (Lefebvre 2011). Crossover trials will be excluded.

Types of participants

People of any age with a pressure ulcer of grade/category 2 or above in any care setting.

Types of interventions

The primary intervention under investigation is any hydrocolloid wound dressing used for treating pressure ulcers. We will include any trial in which the presence or absence of a hydrocolloid dressing is the only systematic difference between treatment groups. This is likely to lead to a comparison of the effects of hydrocolloid dressings with other dressing treatments or no dressing treatment.

Types of outcome measures

Primary outcomes

- Incidence of healed pressure ulcers (proportion of participants in whom a pressure ulcer healed);
- time to complete healing; and
- adverse events.

Secondary outcomes

- Reduction in ulcer size;
- cost (including measurements of resource use such as number of dressing changes and nurse time);
- quality of life (measured using any validated tool);
- patient satisfaction/acceptability measured using any tool; and
- ulcer recurrence.

Search methods for identification of studies

Electronic searches

We will search the following trials databases:

- the Cochrane Wounds Group Specialised Register (latest);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (latest issue);
- Ovid MEDLINE (1946 to present);
- Ovid EMBASE (1974 to present);
- EBSCO CINAHL (1982 to present).

We will search 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: [Silver Sulfadiazine] explode all trees
#7 MeSH descriptor: [Honey] explode all trees
#8 MeSH descriptor: [Bandages, Hydrocolloid] explode all trees
#9 (dressing* or alginate* or hydrogel* or hydrocolloid* 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
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #9
#11 MeSH descriptor: [Pressure Ulcer] explode all trees
#12 (pressure next (ulcer* or sore* or injur*)):ti,ab,kw
#13 (decubitus next (ulcer* or sore*)):ti,ab,kw
#14 ((bed next sore*) or bedsore):ti,ab,kw
#15 #11 or #12 or #13 or #14
#16 #10 and #15
The search strategy will be adapted to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We will combine the Ovid MEDLINE search with the Cochrane Highly Senstive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the MEDLINE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2012). The EMBASE search will be combined with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). There will be no restrictions on the basis of date, or language or publication.
We will search the following Ongoing Trials registers to identify ongoing or recently completed studies:

- the metaRegister of Controlled Trials (www.controlled-trials.com);
- the U.S. National Institutes of Health ongoing trials register (www.clinicaltrials.gov);
- the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch)

Searching other resources

We will search bibliographies of all retrieved and relevant publications identified by these strategies for further studies. We will contact manufacturers of dressings used in the prevention of pressure ulcers (e.g. 3M, Hollister, Kendall, ConvaTec, Smith & Nephew), and experts in the field, to ask for information relevant to this review.

Data collection and analysis

Selection of studies

Two review authors will independently assess titles and abstracts of all citations retrieved by the search for relevance against the inclusion criteria. After this initial assessment, full versions of all potentially eligible studies will be retrieved. The same two review authors will then independently check the full papers for eligibility. Discrepancies between review authors will be resolved through discussion and, where required, a third independent review author will be consulted (Higgins 2011a). A list of studies that were excluded from the review, for which full trial reports were retrieved, and the reasons for their exclusion will be published for transparency. A Preferred Reporting Items of SYstematic reviews and Meta-Analyses (PRISMA) flowchart will also be completed.

Data extraction and management

Details from eligible studies will be extracted and summarised using a data extraction sheet. Two review authors will extract data independently and then perform a cross check for accuracy and agreement. Any discrepancies will be resolved though discussion and arbitration by a third review author, if necessary. Studies that have been published in duplicate will only be included once. If there are any data missing from the papers, then attempts will be made to contact study authors to retrieve the missing information. The following data will be extracted:

- country of origin;

- type/grade/category of pressure ulcer;
- location of pressure ulcer;
- unit of investigation (per patient) - single injury versus multiple injuries per patient;
- care setting;
- eligibility criteria and key baseline participant data;
- number of patients randomised to each trial arm;
- 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);
- source of funding.

Assessment of risk of bias in included studies

Two review authors will independently assess each eligible study for risk of bias using the Cochrane Collaboration 'Risk of bias assessment tool'. The tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues which may potentially bias the study (Higgins 2011b). A 'Risk of bias' table will be completed for each eligible study. A separate assessment of blinding and completeness of outcome data will be conducted for each outcome. Discrepancies between review authors will be resolved through discussion. Findings will be presented using the 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry. We will classify trials as being at high risk of bias if they are rated 'high' for any of three key criteria, namely, randomisation sequence, allocation concealment and blinded outcome assessment.

Measures of treatment effect

For dichotomous outcomes, we will calculate risk ratio (RR) plus 95% confidence intervals (CI). For continuous outcomes, we will calculate mean difference (MD) plus 95% confidence intervals. We will analyse time-to-event data (e.g. time to healing) as survival data, using the appropriate analytical method (as per the Cochrane Handbook for Systematic Reviews of Interventions version 5) (Deeks 2011). We will not analyse time-to-event data, incorrectly presented as continuous data, but present the data in a narrative format in the review. Skewed data are difficult to enter into a meta-analysis unless 'normalised' by log transformation. If scale data, however, have finite upper and lower limits, we will apply an easy rule of thumb in order to test for skewness. If the standard deviation, when doubled, is greater than the mean, it is unlikely that the mean is the centre of the distribution and will not be entered into the meta-analysis (Altman 1996). Where continuous data have less obvious finite boundaries, the situation is more problematic and may be a matter of judgement. If we find relevant data that are skewed, we will present this data in 'Other data' tables. In addition, some of our secondary outcomes may be measured using ordinal scales. For the sake of simplicity we will assume that these are continuous, and analyse data with the standardised mean difference (SMD). It is also possible that different tools may be used to measure the same outcome (e.g. quality of life). We will collect data only from those studies where scales have been validated and are self-reported, or completed by an independent rater or relative (not the therapist or investigator). We will use the standardised mean difference as the summary statistic in any meta-analysis of such data (Deeks 2011).

Unit of analysis issues

In this type of trial, it is likely that patients will have more than one pressure ulcer and trialists have commonly separately randomised multiple wounds on a patient. As a part of the 'Risk of bias' assessment we will record how individual pressure ulcers were studied and analysed. This will include the grading of ulcers, location of ulcers, number of ulcers per patient, and whether they have (incorrectly) been treated as independent in the study, rather than applying a within-patient analysis. If the unit of analysis is the ulcer and not the person, we will describe and address unit of analysis issues in the text.

Dealing with missing data

If there is evidence of missing data, attempts will be made to contact the study authors to request the missing information. If we consider that data are missing at random, we will analyse the available information. If we consider that data are not missing at random, we will assume that the missing values indicate a poor outcome. We will perform a sensitivity analysis to assess how sensitive the results are to reasonable changes in the assumptions that are made. We will also address the potential impact of the missing data on the findings of the review in the discussion section.

Assessment of heterogeneity

Both clinical and statistical heterogeneity will be considered. If appropriate, data will be pooled using meta-analysis with RevMan 5.1 (RevMan 2011). Heterogeneity of selected studies will be assessed visually and by using the chi-squared test with significance being set at P value less than 0.10.This assesses whether observed differences in results are compatible with chance alone. In addition, the degree of heterogeneity will be investigated by calculating the I^2 statistic (an equation combining the chi-squared statistic relative to its degree of freedom) (Higgins 2002).

Assessment of reporting biases

We will explore reporting bias using visual asymmetry on the funnel plot which will be constructed if at least 10 studies are available for the meta analysis of a primary outcome (Sterne 2011).

Data synthesis

Initially we will conduct a structured narrative summary of the studies reviewed. We will enter quantitative data into RevMan 5.1 (RevMan 2011), and analyse the data using the RevMan analysis software. For dichotomous outcomes, we will calculate RR plus 95% CI. For continuous outcomes, we will calculate MD plus 95% CI. The decision to pool data in a meta-analysis will depend upon the availability of outcome data and assessment of between-trial heterogeneity. If evidence of significant heterogeneity is identified (i.e. greater than 50%), potential causes will be explored, and a random-effects approach to the analysis used, otherwise a fixed-effect method will be used.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available we will undertake the following subgroup analysis:

- type of setting (community, hospital, inpatient, outpatient), and
- grade/category of ulcer.

Sensitivity analysis

We will perform a sensitivity analysis by excluding studies at high risk of bias In this sensitivity analysis, we will only include studies that are assessed as having a low risk of bias in all key domains, namely adequate generation of the randomisation sequence, adequate allocation concealment and blinding of outcome assessor, for the estimates of treatment effect.

'Summary of findings' table

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Schunemann 2011b). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. Quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables:

- time to complete ulcer healing;
- number of ulcers healed during the trial period;
- adverse events; and
- health-related quality of life.

ACKNOWLEDGEMENTS

The authors are grateful to the following peer reviewers for their time and comments: Andrew Jull, Debra Fayter, Gill Worthy, Sonya Osborne and Sylvia Stanway. The authors would like to acknowledge the contribution of Elizabeth Royle, copy editor.

The NHMRC has provided funding for this review from its Centre of Research Excellence Scheme, which funds one or more of the authors.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. ***National Pressure Ulcer Advisory Panel (NPUAP)/European Pressure Ulcer Advisory Panel (EPUAP) classification system*** **(2009)**

Category/Stage	Definition
Category/Stage 1	Intact skin with non-blanchable redness of a localised area usually over a bony prominence Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area The area may be painful, firm, soft, warmer or cooler compared to adjacent tissue May be difficult to detect in individuals with dark skin tones May indicate "at risk" persons.
Category/Stage 2	Partial thickness loss of dermis presenting as a shallow open ulcer with a red-pink wound bed, without slough May also present as an intact or open/ruptured serum-filled or sero-sanguinous filled blister Presenting as a shiny or dry shallow ulcer without slough or bruising Stage II should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation
Category/Stage 3	Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle is *not* exposed. Slough may be present but does not obscure the depth of tissue loss. *May* include undermining and tunnelling. The depth varies according to anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and stage III pressure ulcers (PUs) can be shallow. In contrast, areas of significant adiposity can develop extremely deep stage III PUs. Bone or tendon is not visible or directly palpable.
Category/Stage 4	Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed The depth of a stage IV pressure injury varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and these PUs can be shallow. Stage IV PUs can extend into muscle and/or supporting structures (e.g. fascia, tendon or joint capsule) making osteomyelitis possible.

Table 1. ***National Pressure Ulcer Advisory Panel (NPUAP)/European Pressure Ulcer Advisory Panel (EPUAP) classification system*** **(2009)** (*Continued*)

	Exposed bone or tendon is visible or directly palpable.

APPENDICES

Appendix 1. 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 used without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

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

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

Low risk of bias

Any one of the following:

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

High risk of bias

Any one of the following:

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

Unclear

Either of the following:

- Insufficient information 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

Either 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 are 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
13 November 2013	Amended	Acknowledgement added to the funders

CONTRIBUTIONS OF AUTHORS

Samantha Keogh developed the protocol and co-ordinated development, completed the first draft of the protocol, co-ordinated edits of subsequent drafts, made an intellectual contribution, approved the final version prior to submission and is the guarantor of the protocol.

Amanda Ullmann completed the first draft of the protocol, made an intellectual contribution to and approved the final version of the protocol prior to submission.

E Andrea Nelson, Joan Webster, Jim Jolly and Wendy Chaboyer all edited the protocol, made an intellectual contribution and approved the final version of the protocol prior to submission.

Contributions of editorial base:

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

DECLARATIONS OF INTEREST

None to declare.

SOURCES OF SUPPORT

Internal sources

- Griffith University NHMRC Centre for Research Excellence in Nursing, Not specified.
In-kind (time and overheads).

External sources

- NIHR/Department of Health (England), (Cochrane Wounds Group), UK.