Dressings and topical agents for preventing pressure ulcers (Protocol)

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[Intervention Protocol]

Dressings and topical agents for preventing pressure ulcers

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ABSTRACT

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

To evaluate the effects of dressings and topical agents on the prevention of pressure ulcers, in people of any age without existing pressure ulcers, but considered to be at risk of developing a pressure ulcer, in any care setting.

BACKGROUND

Description of the condition

A pressure ulcer is defined as localised injury to the skin, underlying tissue or both, usually over a bony prominence, as a result of pressure, or pressure in combination with shear (Appendix 1). A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated (EPUAP/NPUAP 2009). Pressure ulcers are generally graded 1, 2, 3 and 4, according to the depth of tissue damage, with grade 1 being the least severe and grade 4 indicating full-scale tissue destruction (Moore 2005) (Appendix 2).

Pressure ulcers occur in people who do not have the ability to reposition themselves in order to relieve pressure on bony prominences. This ability is often diminished in the very old, the malnourished and those with an acute illness (Robertson 1990). Pressure ulcer prevalence and incidence figures differ depending on the method of data collection and the classification used. Prevalence rates fluctuate from 8.8% to 53.2% (Davis 2001; Tannen 2006) and incidence rates vary from 7% to 71.6% (Scott 2006; Whittington 2004). The most common anatomical sites for pressure ulcers to occur are the sacrum and the heels, and the majority are grade 1 or grade 2 in severity (Gallagher 2008; Gethin 2005; Moore 2000). The variability in prevalence and incidence rates may be partly explained by the fact that the studies are not conducted in the same clinical settings, meaning that the participants will be not be homogenous. Studies also use different data collection methods, for example, self-reporting by staff (risking under-reporting of the problem) versus the use of research nurses to collect the data. Furthermore, some studies may only report pressure ulcers of grade 2 and above, whereas others report grades 1 to 4, resulting in different prevalence/incidence rates.

Demographic forecasts suggest that in the next 50 years there will be three times more older persons living in the world (U.S. Census Bureau 2004). Indeed, by the year 2050 it is estimated that older individuals will comprise almost 17% of the global population compared to 7% in 2002 (U.S. Census Bureau 2004). The older population appears to be at greater risk of pressure ulcer development due to the likelihood of underlying neurological and cardiovascular problems (Bliss 1990). Furthermore, as a consequence of ageing, the skin undergoes a number of pathological changes (Nixon 2004). These changes alter the elastin and collagen content of the skin, reducing its elasticity and resilience, which in turn lowers the skin's protective mechanism against the adverse effects of shear and friction forces (Defloor 1999). Friction occurs when two surfaces move across one another, for example when a patient slides from the bed onto a chair (Collier 2006). Shear is the mechanical stress acting parallel to a plane of interest, such as is seen when a patient sits up in bed and then begins to slide down the bed, but their skin remains in the same place because it sticks to the bed linen. It is suggested that in the presence of shear, less external pressure is required to cause tissue damage because the shearing forces stretch the microcirculation which may occlude the blood supply to the affected areas (Collier 2006). By having larger numbers of the population within the older age group there will be larger numbers that will be experiencing immobility as a result of age related/associated conditions and thus there will be an increase in the risk of pressure ulcers. Changing population demographics and the predicted rise in the number of older persons in the future suggests that there will be a corresponding increase in the number of people with pressure ulcers unless effective preventative measures are put in place.

Pressure ulcers impact negatively on the individual's quality of life. Indeed, the emotional, physical, mental and social domains of life are all profoundly affected (Spilsbury 2007). For for individuals with pressure ulcers pain is described as one of the most significant problems (Spilsbury 2007). Furthermore, pressure ulcers have been found to be malodorous, especially when there is a large amount of devitalised tissue amalgamated with the presence of anaerobic bacteria in the wound bed (Stotts 2001). Combined with this, pressure ulcers can exude profusely, especially during the early inflammatory phase (Iocono 1998), thereby requiring frequent dressing changes (Rolstad 2000). Importantly, many of the treatment regimens adopted exacerbate these adverse effects (Hopkins 2006). Thus, it is important to consider the impact of prevention and treatments strategies on the individual and to choose those that will reduce discomfort and enhance rehabilitation wherever possible (Gorecki 2009). Pressure ulcers are also associated with increased mortality (Kroger 2008). Whether this relates to the fact that pressure ulcers occur in a population that is for the most part debilitated, with a high incidence of co-morbidities, or whether it relates to the presence of a pressure ulcer alone, remains unclear (Brown 2003). However, the evidence suggests an almost two-fold increase in death among those with pressure ulcers when compared to their matched counterparts without pressure ulcers (Landi 2007).

Pressure ulcers impose a significant financial burden on healthcare systems, indeed Bennett 2004 suggests that the total annual cost for pressure ulcer management in the UK is GBP 1.4 to 2.1 billion annually, or 4% of the total UK healthcare expenditure. These costs were estimated with the assumption that the individuals were cared for either in an acute hospital or in a long-term care setting, although the pressure ulcer was not the primary reason for hospitalisation (Bennett 2004). The resources which were considered were: nurse time (for dressing changes, patient repositioning and risk assessment), dressings, antibiotics, diagnostic tests, support surfaces and inpatient days (where appropriate). Daily costs were estimated by ulcer grade for patients who heal normally, and for three of the most common sources of delayed healing: critical colonisation, cellulitis and osteomyelitis (Bennett 2004). Costs rose as the severity of the pressure ulcer increased: GBP 1064 (grade 1) to GBP 10,551 (grade 4) (Bennett 2004). In Australia, the mean hospital costs for pressure ulcers are estimated at AUD 296.05 million (Graves 2005). In the United States, hos-

pital costs for adults with a diagnosis of pressure ulcers totaled USD 11.0 billion in 2006 (Russo 2006). The concept that they are an expensive healthcare issue has also been noted in the Netherlands where they have been found to be the third most expensive disease (Haalboom 2000). This is not due to the cost of medication or surgical interventions, but prolonged hospitalisation and the intensive nursing care required. The length of hospital stay for those with a pressure ulcer is suggested to be two to three times greater (30.4 days compared to 12.8 days) than a typical case without pressure ulcers (Allman 1999). Further work supports this argument, where in a cohort of 2000 patients, having a pressure ulcer was found to contribute to a median excess length of stay of 4.31 days (Graves 2005a). Pressure ulcers are also associated with significantly higher mean unadjusted hospital costs (USD 37,288 versus USD 13,924, P = 0.0001) (Allman 1999).

The exact mechanisms by which externally applied mechanical forces (pressure and shear) result in pressure ulcer development are not clearly understood (Stekelenburg 2007) however, it is postulated that there are four mechanisms within three functional units which lead to pressure ulcer development. The functional units are the capillaries, the interstitial spaces and the cells (Nixon 2005). The mechanisms are local ischaemia (Appendix 1), reperfusion injury (Appendix 1), impaired interstitial fluid flow (Appendix 1) and lymphatic drainage (Appendix 1) and sustained deformity of cells (Stekelenburg 2007). Sustained unrelieved pressure causes local tissue ischaemia (Appendix 1) and irreversible cellular changes, resulting in tissue destruction and pressure ulcer development (Kosiak 1959). Reperfusion injury is defined as injury to cells as a result of the restoration of blood supply to tissues which have been previously devoid of blood (Tsuji 2005). Reperfusion causes harm due to the production of toxic oxygen-derived free radicals which exceed the ability of the free radical scavenging mechanisms (Appendix 1). The oxygen free radicals are cytotoxic (Appendix 1) to cells and this damage causes an initiation of the inflammatory process, the recruitment of monocytes (Appendix 1) and macrophages (Appendix 1), and occlusion of capillaries (Appendix 1) due to the presence of leucocytes (Appendix 1) (Peirce 2000). The balance between the production of interstitial fluid and the reabsorption of this fluid is important in order to maintain osmotic pressure and thereby the diffusion of substances to and from cells (Green 1977). Direct compression occludes the lymphatics thereby impeding lymph flow, furthermore occlusion of blood flow causes the release of hormones which affect lymphatic smooth muscle, thereby impeding lymphatic contraction and thus the movement of lymph fluid. Both factors result in an accumulation of waste products, proteins and enzymes which ultimately lead to tissue damage (Reddy 1981). The role of cell deformation in pressure ulcer development is a recent research hypothesis, emerging from the knowledge that muscles are more susceptible to the effects of mechanical loading compared to skin (Bouten 2003). Cell deformation causes immediate cell death, whereas ischaemia alone causes localised hypoxia, which is reversed upon restoration of blood supply (Gawlitta 2007). This is because sustained cell deformation causes the cell to rupture, eliminating the possibility of cell damage reversal (Gawlitta 2007). Furthermore, the longer the duration of compression, the greater the evidence of cell death, suggesting that the time under compression is an important variable (Gawlitta 2007). Fundamentally, however, none of the mechanisms described will have any relevance unless the individual is exposed to sustained external mechanical forces. Therefore, as pressure is the causative factor, reducing the amount and duration of pressure will decrease the likelihood of pressure ulcer development.

Description of the intervention

Pressure ulcer prevention is now a huge industry and involves a range of interventions, such as nutritional care, skin care, use of pressure redistribution surfaces and repositioning (EPUAP/NPUAP 2009). Selection of an appropriate topical therapy (i.e. those applied to the skin) is also believed to contribute to pressure ulcer prevention strategies, and such therapies are widely used within the clinical setting (Butcher 2009).

A topical agent is a cream or an ointment that is applied directly to the skin (Reddy 2006). Whereas a dressing is a therapeutic or protective material applied to a wound to promote healing, it may also be used to protect the skin from damage (Butcher 2009). Dressings are classified into groups depending on their characteristics (Moore 2006).

For the purposes of pressure ulcer prevention, the types of dressings used would primarily be those that afford protection to the skin, such as:

- semi-permeable film dressings (a thin polyurethane membrane coated with a layer of an acrylic adhesive);
- hydrocolloid dressings (a dressing containing a dispersion of gelatin, pectin and carboxy-methylcellulose together with other polymers and adhesives forming a flexible wafer); or
- foam dressings (an open cell, hydrophobic, polyurethane foam sheet) (Dressings.org 2010).

Topical agents may be used in isolation, however, are more likely to be impregnated into dressings, or used in combination with dressings.

How the intervention might work

The 2009 EPUAP/NPUAP guidelines suggest that use of film dressings may help to protect the skin against the adverse effects of friction. Furthermore, they suggest that use of foam dressings may protect parts of the body at risk of shear injury (EPUAP/NPUAP 2009). The application of topical agents directly to the skin is also suggested to protect against the adverse affects of friction (Reddy 2006). Both friction and shear are included as risk factors

for pressure ulcer development in the Braden pressure ulcer risk assessment scale (Bergstrom 1987).

Why it is important to do this review

The use of dressings in the prevention of pressure ulcers is alluded to in the literature and in international pressure ulcer prevention guidelines. To date, the level of evidence to support these recommendations has not been systematically assessed (Butcher 2009). The use of adjunct therapies as part of prevention strategies adds to the overall costs, therefore it is important to explore whether use of these therapies provides potential benefit to patients (Moore 2008).

OBJECTIVES

To evaluate the effects of dressings and topical agents on the prevention of pressure ulcers, in people of any age without existing pressure ulcers, but considered to be at risk of developing a pressure ulcer, in any care setting.

METHODS

Criteria for considering studies for this review

Types of studies

Studies that randomise individuals (randomised controlled trials (RCTs)) or that randomise by groups (cluster-RCTs), will be eligible for inclusion.

Types of participants

People of any age, both adults and children, without a pressure ulcer, but considered to be at risk of developing a pressure ulcer, in any care setting.

Types of interventions

The primary intervention will be any wound dressing or topical agent applied to the skin with the aim of preventing the development of a pressure ulcer. Any type of dressing will be considered, but they are likely to be semi-permeable film dressings, hydrocolloid dressings or foam dressings and may be used in combination with a topical agent. We will include RCTs comparing the use of dressings, topical agents, or topical agents with dressings, compared with a different dressing, topical agent, combined topical agent and dressing or no intervention or standard care, with the aim of preventing the development of a pressure ulcer.

Types of outcome measures

Primary outcomes

Pressure ulcer incidence (the proportion of participants developing any new pressure ulcer/s of any grade). For the purpose of this review a pressure ulcer is defined as a localised injury to the skin, underlying tissue or both, usually over a bony prominence, as a result of pressure, or pressure in combination with shear. A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated (EPUAP/NPUAP 2009). This review will include all grades of pressure ulcer damage, following the definition of the EPUAP/NPUAP (EPUAP/NPUAP 2009). We will accept the definition of the method of assessment of pressure ulcer damage as outlined by trial authors.

Secondary outcomes

- Stage of any new pressure ulcer/s.
- Time to ulcer development.
- Costs of interventions.
- Quality of life as measured by a validated scale.
- Pain at dressing change, measured using a validated scale.
- Acceptability of the intervention (or satisfaction) with respect to patient comfort.
- Adverse events.
- Patient length of hospital stay.

Search methods for identification of studies

We will seek all RCTs or cluster-RCTs which evaluate the use of dressings or topical agents for the prevention of pressure ulcers using the search strategy adopted by the Cochrane Wounds Group.

Electronic searches

We will search the following electronic databases for RCTs or cluster-RCTs which evaluate the use of dressings or topical agents for the prevention of pressure ulcers:

- the Cochrane Wounds Group Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) (latest issue);
- Ovid MEDLINE (1948 to present);
- Ovid EMBASE (1980 to present); and
- EBSCO CINAHL (1982 to present).

We will use the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Biological Dressings explode all trees
#2 MeSH descriptor Occlusive Dressings explode all trees
#3 MeSH descriptor Hydrogels explode all trees
#4 MeSH descriptor Alginates explode all trees

#5 dressing*:ti,ab,kw
#6 (hydrocolloid* or alginate* or hydrogel* or foam or bead or film
or films or tulle or gauze or non-adherent or non adherent):ti,ab,kw
#7 MeSH descriptor Anti-Bacterial Agents explode all trees
#8 MeSH descriptor Administration, Topical explode all trees
#9 (#7 AND #8)
#10 (topical NEAR/2 antibiotic*):ti,ab
#11 MeSH descriptor Anti-Infective Agents, Local explode all trees
#12 MeSH descriptor Anti-Inflammatory Agents explode all trees
#13 MeSH descriptor Glucocorticoids explode all trees
#14 (#12 OR #13)
#15 (#8 AND #14)
#16 (topical NEAR/2 (steroid* or corticosteroid* or glucocorticoid*)):ti,ab,kw
#17 MeSH descriptor Estrogens explode all trees
#18 (#8 AND #17)
#19 (topical NEAR/2 (oestrogen or estrogen)):ti,ab,kw
#20 MeSH descriptor Enzymes explode all trees
#21 (#8 AND #20)
#22 (topical NEAR/2 enzym*):ti,ab,kw
#23 MeSH descriptor Growth Substances explode all trees
#24 (#8 AND #23)
#25 (topical NEAR/2 growth factor*):ti,ab,kw
#26 MeSH descriptor Collagen explode all trees
#27 (#8 AND #26)
#28 (topical NEAR/2 collagen):ti,ab,kw
#29 (topical NEAR/2 silver):ti,ab
#30 MeSH descriptor Ointments explode all trees
#31 (ointment* or lotion* or cream*):ti,ab,kw
#32 MeSH descriptor Honey explode all trees
#33 honey.ti,ab,kw
#34 (topical NEXT (agent* or preparation* or therap* or treatment*)):ti,ab,kw
#35 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 OR #10 OR #11 OR #15 OR #16 OR #18 OR #19 OR #21 OR #22 OR #24 OR #25 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
#36 MeSH descriptor Pressure Ulcer explode all trees
#37 pressure NEXT (ulcer* OR sore*):ti,ab,kw
#38 decubitus NEXT (ulcer* OR sore*):ti,ab,kw
#39 (bed NEXT sore*) OR bedsore*:ti,ab,kw
#40 (#36 OR #37 OR #38 OR #39)
#41 (#35 AND #40)

We will adapt this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We will combine 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 will combine the EMBASE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2010). We will not restrict studies with respect to language, date of publication or study setting.

We will search the following clinical trials registries:

- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)

Searching other resources

We will search the 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 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, where available, abstracts of the studies identified by the search strategy against the eligibility criteria for inclusion in the review. We will obtain full versions of potentially relevant studies and two review authors will independently screen these against the inclusion criteria. Any differences in opinion will be resolved by discussion and, where necessary, reference to the Cochrane Wounds Group editorial base.

Data extraction and management

Two review authors will independently extract data from eligible studies using a data extraction sheet. Specifically, we will extract the following information:

- author, title, source;
- date of study, study's geographical location;
- care setting;
- inclusion/exclusion criteria;
- patient characteristics;
- balance of groups at baseline;
- study design details;
- method of randomisation;
- allocation concealment;
- sample size calculation and sample size;
- intervention details, concurrent interventions;
- type of dressing and frequency of dressing change;
- use of additional dressing materials;
- patient length of hospital stay;
- outcome measures;
- blinding (of the patient/outcome assessor);
- length of follow up;
- loss to follow up;
- results;

- intention-to-treat analysis; and
- conclusions as reported by the study authors.

Any differences in opinion will be resolved by discussion and, where necessary, with reference to the Cochrane Wounds Group editorial base. If data are missing from reports, we will make attempts to contact study authors to obtain the missing information.

Assessment of risk of bias in included studies

Two review authors will independently assess the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011a). This tool addresses six specific domains: namely, sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance) (see Appendix 3 for details of criteria on which the judgement will be based). We will assess blinding and completeness of outcome data for each outcome separately.

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 ulceration) 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 however, if scale data have finite upper and lower limits we will apply an easy rule of thumb in order to test for skewedness. 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 a be matter of judgement. If we find relevant data that are skewed we will presented the data in 'Other data' tables. In addition, some of our secondary outcomes may be measured using ordinal scales. For 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 (for example, quality of life and pain). 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

For cluster-RCTs, we will conduct the analysis at the same level as the allocation, using a summary measurement for each cluster. Thus, the sample size will be the number of clusters and analysis will proceed as though the trials were individually randomised, with the clusters being the individuals. Where results in primary studies are not adjusted for clustering we will conduct an approximate analysis by multiplying the standard errors of the estimates by the square root of the design effect; where the design effect is calculated as DEff = 1 + (m - 1)*ICC, where m is the average cluster size. We will use the generic inverse-variance method in RevMan (RevMan 2011) for any meta-analysis of cluster-randomised designs (Higgins 2011b).

Dealing with missing data

If there is evidence of missing data, we will contact the study authors to request the information. If data are considered to be missing at random, we will analyse the available information. If data are considered to be not missing at random, we will make explicit the assumptions of any methods used to cope with the missing data, for example that the missing values were assumed to indicate a poor outcome. We will perform a sensitivity analysis to assess how sensitive results are to reasonable changes to 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.

Assessment of heterogeneity

We will explore clinical heterogeneity by examining potentially influential factors, e.g. care setting or patient characteristics. We will assess statistical heterogeneity using the I^2 statistic (Higgins 2003). This examines the percentage of total variation across studies due to heterogeneity rather than to chance. Values of I^2 over 75% indicate a high level of heterogeneity. We will carry out statistical pooling on groups of studies which are considered to be sufficiently similar. Where heterogeneity is absent or low (I^2 = 0% to 25%) we will use a fixed-effect model; if there is evidence of heterogeneity (I^2 more than 25%), we will use a random-effects model. If heterogeneity is very high (I^2 over 75%) we will not pool the data (Higgins 2003).

Assessment of reporting biases

We will complete a 'Risk of bias' table for each eligible study and will present an assessment of risk of bias using a 'Risk of bias' summary figure which will present the judgements in a cross-tabulation. This display of internal validity indicates the weight the reader may give to the results of each study.

Data synthesis

Initially we will conduct a structured narrative summary of the studies reviewed. We will enter quantitative data into RevMan 5 (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.

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).

Sensitivity analysis

We will perform a sensitivity analysis by excluding studies of the lowest quality. 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.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary of terms

Cytotoxic: causes damage to cell structure or function
Free radical scavenging mechanisms: the ability to remove unwanted destructive fragments of oxygen
Impaired interstitial fluid flow: reducing the flow of tissue fluid, which is a solution that bathes and surrounds the cells
Ischaemia: the loss of blood flow to tissues, due to a blocked blood vessel
Leucocyte: blood cells that engulf and digest bacteria and fungi
Lymphatic drainage: drainage of fluid from the lymphatic system which is a network that carries a clear fluid called lymph
Macrophages: white blood cells within tissues produced from the division of monocytes
Monocytes: a type of white blood cell that changes into a macrophage
Occlusion of capillaries: blockage of fluid flow within the smallest of the body's blood vessels
Reperfusion injury: damage to tissue caused when blood supply returns to the tissue after a period of loss of blood
Shear strain: the distortion or deformation of tissue as a result of shear stress (the force per unit area exerted parallel to the plane of interest (EPUAP/NPUAP 2009)

Appendix 2. International NPUAP-EPUAP pressure ulcer classification system for ulcer grading

Category/Stage I: non-blanchable redness of intact skin
Intact skin with non-blanchable erythema of a localised area usually over a bony prominence. Discolouration of the skin, warmth, oedema, hardness or pain may also be present. Darkly pigmented skin may not have visible blanching. **Further description:** the area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category/Stage I may be difficult to detect in individuals with dark skin tones. May indicate 'at risk' persons.
Category/Stage II: partial thickness skin loss or blister
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. **Further description:** presents as a shiny or dry shallow ulcer without slough or bruising. This category/stage should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation.
Category/Stage III: full thickness skin loss (fat visible)
Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Some slough may be present. May include undermining and tunnelling. **Further description:** the depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure ulcers. Bone/tendon is not visible or directly palpable.
Category/Stage IV: full thickness tissue loss (muscle/bone visible)
Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often include undermining and tunnelling. **Further description:** the depth of a Category/Stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g. fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable.

Appendix 3. 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.

HISTORY

Protocol first published: Issue 10, 2011

CONTRIBUTIONS OF AUTHORS

Development of first draft of protocol: ZM

Comments on protocol: JW

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

Zena Moore, is a member of the medical advisory board of Systagenix Wound Management. Zena Moore, has received an honorarium for speaking at professional meetings for KCI, ConvaTec, Systagenix Wound Management, Fanin Health Care and Smith & Nephew.

Joan Webster: none

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