Aloe vera for treating acute and chronic wounds

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Aloe vera for treating acute and chronic wounds (Review)

Dat AD, Poon F, Pham KBT, Doust J

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Aloe vera for treating acute and chronic wounds

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ABSTRACT

Background

Aloe vera is a cactus-like perennial succulent belonging to the Liliaceae Family that is commonly grown in tropical climates. Animal studies have suggested that Aloe vera may help accelerate the wound healing process.

Objectives

To determine the effects of Aloe vera-derived products (for example dressings and topical gels) on the healing of acute wounds (for example lacerations, surgical incisions and burns) and chronic wounds (for example infected wounds, arterial and venous ulcers).

Search methods

We searched the Cochrane Wounds Group Specialised Register (9 September 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 3), Ovid MEDLINE (2005 to August Week 5 2011), Ovid MEDLINE (In-Process & Other Non-Indexed Citations 8 September 2011), Ovid EMBASE (2007 to 2010 Week 35), Ovid AMED (1985 to September 2011) and EBSCO CINAHL (1982 to 9 September 2011). We did not apply date or language restrictions.

Selection criteria

We included all randomised controlled trials that evaluated the effectiveness of Aloe vera, aloe-derived products and a combination of Aloe vera and other dressings as a treatment for acute or chronic wounds. There was no restriction in terms of source, date of publication or language. An objective measure of wound healing (either proportion of completely healed wounds or time to complete healing) was the primary endpoint.

Data collection and analysis

Two review authors independently carried out trial selection, data extraction and risk of bias assessment, checked by a third review author.

Main results

Seven trials were eligible for inclusion, comprising a total of 347 participants. Five trials in people with acute wounds evaluated the effects of Aloe vera on burns, haemorrhoidectomy patients and skin biopsies. Aloe vera mucilage did not increase burn healing compared with silver sulfadiazine (risk ratio (RR) 1.41, 95% confidence interval (CI) 0.70 to 2.85). A reduction in healing time with Aloe vera was noted after haemorrhoidectomy (RR 16.33 days, 95% CI 3.46 to 77.15) and there was no difference in the proportion of patients...
completely healed at follow up after skin biopsies. In people with chronic wounds, one trial found no statistically significant difference in pressure ulcer healing with Aloe vera (RR 0.10, 95% CI -1.59 to 1.79) and in a trial of surgical wounds healing by secondary intention Aloe vera significantly delayed healing (mean difference 30 days, 95% CI 7.59 to 52.41). Clinical heterogeneity precluded meta-analysis. The poor quality of the included trials indicates that the trial results must be viewed with extreme caution as they have a high risk of bias.

Authors’ conclusions

There is currently an absence of high quality clinical trial evidence to support the use of Aloe vera topical agents or Aloe vera dressings as treatments for acute and chronic wounds.

PLAIN LANGUAGE SUMMARY

Aloe vera for treating acute and chronic wounds

Aloe vera is a cactus-like, succulent plant which grows in tropical climates. Aloe vera is widely used in a variety of cosmetics including creams and toiletries. Some studies conducted in animals have suggested that Aloe vera may help wound healing. Aloe vera can be applied topically as a cream or gel, or can be impregnated into a dressing and applied to the wound.

The authors of this Cochrane Review wanted to find evidence on whether Aloe vera encourages wound healing in people with acute wounds (for example lacerations, surgical incisions and burns) and chronic wounds (for example infected wounds, arterial and venous ulcers). The review found that there was not enough research evidence to answer this question.

BACKGROUND

Description of the condition

Wound healing is a complex biological process where the main goal of clinical intervention is the promotion of tissue restoration (Mendonca 2009). Wounds can result from many conditions including burns, arterial disease, surgery and trauma, and can be classified as acute or chronic. Acute wounds are wounds that follow a predictable and timely repair process which results in the restoration of sufficient anatomical and functional integrity if healing proceeds normally (Lazarus 1994). This predictable sequence of events can be broken down to initial inflammation, collagen and fibroblast deposition (scar tissue formation), angiogenesis (new blood vessel formation), wound contraction and scar remodeling. Chronic wounds, however, are wounds where the repair process has been disrupted (e.g. infection, immunosuppression) and healing has been subsequently delayed.

Description of the intervention

Aloe vera (also known as Aloe barbadensis Mill., Aloe indica Royle, Aloe perfoliata L. var. vera and A. vulgaris Lam) is a plant belonging to the Liliaceae family, of which there are over 360 known species (Vogler 1999). They are cactus-like perennial succulents and are characterised by stem less, large, thick, fleshy leaves that are lance-shaped and have a sharp apex and a spiny margin (Steenkamp 2007). The plant provides two distinct products: the yellow latex, which is referred to as aloe juice, and the leaf pulp which is the innermost portion of the leaf and is composed of the parenchyma cells whose baseline function is for storage of food and nutrients that contain the Aloe vera gel. The raw pulp contains about 98.5% water with the remaining 1.5% containing a range of compounds including water-soluble and fat-soluble vitamins, minerals, enzymes, polysaccharides, phenolic compounds and organic acids (Hamman 2008). The leaf pulp is commonly delivered as a topical ointment on wounds in a gel, cream or mucilage form (the mucilage being the thick, glue-like gel substance that is derived from the leaf pulp of the Aloe vera plant).

Aloe vera has been used in wound healing since ancient times, with evidence suggesting it was well-known to the ancient Egyptian, Greek and Indian cultures. The use of Aloe vera was mentioned in the Ebers papyrus, widely considered as an important medical document of ancient Egypt and dating back 1550 BC (Atherton 1998). In 330 BC, the famous Greek king Alexander the Great was said to be persuaded by his mentor Aristotle to capture the island of Socotra (now part of modern day Yemen) in the Indian Ocean, famed for its supply of aloe which he needed to heal his...
wounded soldiers (Atherton 1998).

How the intervention might work
Evidence from animal studies has highlighted the possible effects of Aloe vera in wound healing (Chithra 1998; Mendonca 2009; Takzare 2009). Prostaglandin and bradykinin hydrolysing enzymes in Aloe vera, including carboxypeptidase and bradykinase, are hypothesised to reduce pain and inflammation (Steenkamp 2007; Takzare 2009). Aloe-derived polysaccharides such as mannose-6-phosphate have been postulated to be active growth substances, especially in epithelialisation (Davis 1994; Boudreau 2006; Steenkamp 2007). Davis 1994 hypothesised that the binding of mannose-6-phosphate to fibroblast receptors induces fibroblastic proliferation, which ultimately helps promote collagen deposition and tissue reorganisation. Acemannan, another polysaccharide, has been shown to up-regulate white blood cell activity in the wound healing process (Boudreau 2006; Tamura 2009). Similarly, Kuzuya 2001 suggested that the antibacterial properties of anthraquinones, an organic compound responsible for the natural pigment of Aloe vera, is beneficial in minimising infection (Tamura 2009).

Why it is important to do this review
Aloe vera enjoys a great degree of popularity (Steenkamp 2007) and is used in a wide variety of products including cosmetics, creams and toiletries. The goal of this review is to summarise trials investigating the effects of Aloe vera as a treatment for wounds (e.g. burns, lacerations, post-surgical) and provide health practitioners and consumers with evidence about the effects of Aloe vera to assist them with their clinical decision-making.

OBJECTIVES
To determine the effects of Aloe vera-derived products (for example dressings and topical gels) on the healing of acute (for example lacerations, surgical and burns) and chronic wounds (for example infected wounds, arterial and venous ulcers).

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCTs), published or unpublished, in any language.

Types of participants
Trials involving participants of any age and disease state with acute or chronic wounds were included. An acute wound was considered to be any one of the following: surgical wounds, burns, lacerations and other skin injuries resulting from trauma. We considered a chronic wound as any one of the following: skin ulcers, infected wounds, surgical wounds healing by secondary intention, pressure ulcers, arterial and venous ulcers.

Types of interventions
Trials comparing the effects of wound treatment containing Aloe vera, aloe-derived products and a combination of Aloe vera and other dressings compared with placebo, standard wound care or other wound healing interventions.

Types of outcome measures

Primary outcomes
- Time to complete wound healing.
- Proportion of participants to have a completely healed wound.

Secondary outcomes
- Change in wound size.
- Cosmetic appearance of wound healing.
- Incidence of adverse events.
- Incidence of infection.
- Financial cost of wound healing.
- Quality of life.

Search methods for identification of studies

Electronic searches
We searched the following electronic databases:
- the Cochrane Wounds Group Specialised Register (searched 9 September 2011);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 3);
- Ovid MEDLINE (2005 to August Week 5 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations 8 September 2011);
- Ovid EMBASE (2008 to 2011 Week 35);
Ovid AMED (1985 to September 2011);
EBSCO CINAHL (1982 to 9 September 2011)

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following search string:
#1 MeSH descriptor Aloe explode all trees
#2 aloe*:ti,ab,kw
#3 (#1 OR #2)
The search strategies for Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL and Ovid AMED can be found in Appendix 1; Appendix 2, Appendix 3 and Appendix 4 respectively. 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); Ovid format (Lefebvre 2011). We combined the Ovid EMBASE and EBSCO CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2010). There were no restrictions on the basis of date or language of publication.

Search other resources
We searched the bibliographies of all retrieved and relevant publications identified by the above strategies for further studies.

Data collection and analysis

Selection of studies
Two review authors (FP and KP) screened the title and abstract of each potential study identified from the electronic searches. Each author decided on trial inclusion using pre-determined eligibility criteria. Disagreement among authors was resolved by discussion with a third review author (JD) when necessary.

Data extraction and management
Two review authors (AD and KP) extracted data onto a data extraction sheet.
We extracted the following data:
- country of origin;
- trial setting;
- type of wound;
- unit of investigation (per patient or wound);
- eligibility criteria and key baseline participant data;
- number of participants randomised to each trial arm;
- details of the treatment regimen received by each group;
- 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); and
- risk of bias criteria.

If any data were missing from trial reports, we attempted to contact the study authors and acquire the data. We only included studies that were published in duplicate once but considered all versions for maximal data extraction. Any disagreement was to be resolved by discussion amongst the authors.

Assessment of risk of bias in included studies
Two review authors (FP and KP) independently assessed the eligible studies for bias according to the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011). This tool identifies six distinct domains including sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity (see Appendix 5).

Measures of treatment effect
For dichotomous data, we extracted counts to enable the calculation of the risk ratio (RR) for Aloe vera relative to the comparator. For continuous outcomes, we extracted mean difference (MD) and standard deviations (SD) to enable the calculation of the mean difference. We planned that if data were available on time to wound healing using time-to-event analyses and it was judged that a pooled analysis would be appropriate, we would combine data using the general inverse variance method using both fixed and random-effects models, with estimates of log rank estimates converted to log hazard ratios and standard errors and combined with estimates of log hazard ratios from Cox proportional models.

Unit of analysis issues
The healing of multiple wounds from an individual patient cannot be considered as independent events, therefore the correct unit of randomisation to assess the healing of wounds is the individual patient. We analysed measures of effect, such as counts of events or time to events, based on the individual patient wherever possible.

Dealing with missing data
Any studies identified which likely had missing data, we made attempts to contact the study authors for additional information.

Assessment of heterogeneity
Where it was judged that the studies were sufficiently clinically homogeneous to estimate a pooled estimate of treatment effects, we planned to combine the studies in a meta-analysis. A priori, we judged that the two most likely sources of clinical heterogeneity
would be the type of wound (for example surgical, lacerations and infected wounds etc) and the Aloe vera formulation. We planned to investigate heterogeneity using the Chi² test and I² statistic. We did not intend to pool study results in a meta analysis where there was evidence of substantial heterogeneity (I² statistic greater than 60% or P value of the Chi² <0.10).

Assessment of reporting biases
We planned to investigate possible publication bias by constructing a funnel plot of precision (SE of the log OR) against ORs for the primary endpoints of proportion of patients with a completely healed wound.

Data synthesis
Where we undertook meta analysis we planned to use both a fixed and random-effects model to calculate a pooled risk ratio for dichotomous data and to calculate a weighted mean difference for continuous data.

Subgroup analysis and investigation of heterogeneity
We determined that the following analyses by subgroup would be investigated for possible sources of heterogeneity:
- type of wound;
- Aloe vera formulation.

Sensitivity analysis
We planned to perform a sensitivity analysis excluding studies of the lowest quality. In the sensitivity analysis, we planned to only include studies that were 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.

RESULTS

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

Results of the search
The search identified 178 possibly relevant studies, of which 10 were still considered potentially relevant after the first screening. Two review authors (AD and KP) independently obtained and screened abstracts or full-text articles against the inclusion and exclusion criteria. Any disagreements were discussed with a third review author (JD).

Included studies
Seven studies met the inclusion criteria (see Characteristics of included studies table). The included trials were conducted in India (Akhtar 1996), Iran (Khorasani 2009; Eshghi 2010), Thailand (Thamlikitkul 1991) and the USA (Schmidt 1991; Phillips 1995; Thomas 1998). Five of the studies focused on people with acute wounds: burns (Thamlikitkul 1991; Akhtar 1996; Khorasani 2009), post-haemorrhoidectomy wounds (Eshghi 2010) and shave biopsies of skin (Phillips 1995). Two studies recruited patients with chronic wounds; pressure ulcers (Thomas 1998) and post-gynaecological surgical wounds healing by secondary intention (Schmidt 1991). We could only obtain the abstract for Akhtar 1996 although we made attempts to contact the author. The studies utilised various topical formulations of Aloe vera. Three studies used Aloe vera cream (Akhtar 1996; Khorasani 2009; Eshghi 2010), one study evaluated Aloe vera mucilage (Thamlikitkul 1991), two studies used a commercial Aloe vera gel dressing (Phillips 1995; Thomas 1998) and one study used Aloe vera gel (Schmidt 1991). Khorasani 2009 was the only study to use the body part (specifically the hands and feet) as the unit of randomisation. The other six studies used the individual person as the unit of randomisation. The studies varied with regards to the settings in which the patients were treated. In two trials patients were hospitalised for the duration of treatment (Thamlikitkul 1991; Khorasani 2009). In three trials patients were initially treated in hospital (Schmidt 1991; Phillips 1995; Eshghi 2010) followed by discharge to the community and self care (Phillips 1995; Eshghi 2010) or nursing care (Schmidt 1991). One study treated patients in community care settings (nursing facilities or home healthcare agencies) with initial treatment being carried out by healthcare staff, after which patients were instructed to self-treat (Thomas 1998).

Excluded studies
Three studies did not meet the inclusion criteria and were excluded from the review (see Characteristics of excluded studies table). Fulton 1990 and Visuthikosol 1995 were controlled clinical trials and Sun 1994 could not be obtained for assessment.

Risk of bias in included studies
We appraised the quality of each study using the Cochrane Collaboration’s tool for assessing risk of bias. Many studies failed to describe sufficiently the methodology and study design therefore most studies were judged to be at moderate to high risk of bias (Figure 1). Akhtar 1996 was particularly difficult to assess as it was only available as an abstract.
Figure 1. ‘Risk of bias’ summary: review authors’ judgements about each risk of bias item for each included study.

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<th>Allocation concealment (selection bias)</th>
<th>Blinding (performance bias and detection bias)</th>
<th>Blinding (performance bias and detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Free of other bias?</th>
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<td>+</td>
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<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Thamlikkul 1991</td>
<td>+</td>
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<td>+</td>
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Allocation

Sequence generation
Three studies (Thomas 1998; Khorasani 2009; Eshghi 2010) did not describe the method of sequence generation. For the remaining studies, sequence generation was achieved by block randomisation (Akhtar 1996), computer generation (Schmidt 1991; Phillips 1995) and stratified randomisation (Thamlikitkul 1991). In Schmidt 1991, the patients were initially stratified by the type of surgical incision (vertical or transverse) and then randomised using a random number sequence generated by a computer program.

Allocation concealment
Whilst the reports of all seven studies stated that allocation was random, none provided a clear description of the method of allocation so we could not judge the adequacy of concealment.

Blinding
The studies had varying levels of blinding. One study reported blinding of patients and nursing staff who applied the topical interventions (Eshghi 2010) but did not describe whether assessors were also blinded. One study (Phillips 1995) reporting using blinded wound assessors; another did not attempt a blinded study as no placebo was available and the study authors reported that the wounds treated with Aloe vera gel had a distinctive visual appearance (Schmidt 1991). Akhtar 1996 mentioned the use of blinding but provided no more information whilst the two remaining trials (Thamlikitkul 1991; Thomas 1998; Khorasani 2009) did not state whether blinding was employed. Whilst difficulties in blinding patients and nursing staff can be perceived it should be possible to blind outcome assessors or at least have independent, blinded verification from photographs.

Incomplete outcome data
Thomas 1998 reported a loss of 11 patients from a sample size of 41 representing a drop out rate of 25%. Schmidt 1991 reported a significant loss of 19 patients from a sample size of 41, with no reasons given; this loss represents a 47.5% drop out rate. These significant drop out rates suggested that randomisation and trial maintenance was not able to be established and the studies must be judged at high risk of bias for this domain. Eshghi 2010 did not state the proportion of participants with completely healed wounds at the conclusion of the study (28 days), however the proportion of participants completely healed at the halfway stage (14 days) was reported, conceivably because this is when there was a significant difference. Akhtar 1996 had insufficient information to determine loss to follow up. The remaining studies reported no loss to follow up (Thamlikitkul 1991; Phillips 1995; Khorasani 2009).

Selective reporting
No protocols were available for any of the studies. Eshghi 2010 was at risk of selective reporting bias as they only reported data and follow-up midway through their study (14 days) instead of the end of the study (28 days). It is highly likely that there was no significant difference at 28 days and that is why they chose to report their statistically significant results at 14 days.

Other potential sources of bias
One study was terminated early due to an observed delay in healing within the experimental group (Schmidt 1991). Only the abstract was available for the Akhtar 1996 study and therefore both these studies were judged to be at high risk of bias for this domain. Baseline characteristics were similar in the control and intervention groups in all trials.

Effects of interventions
A total of seven trials involving 347 participants was included in this review. The results of the Aloe vera interventions have been presented under subgroups of acute or chronic wounds.

1. Acute wounds

1.1 Burns
Three trials (n = 168) recruited patients with burns (Thamlikitkul 1991; Akhtar 1996; Khorasani 2009). Two trials were conducted in single centres (Akhtar 1996; Khorasani 2009) while Thamlikitkul 1991 was a multi-centred trial. Two trials recruited participants with either first or second-degree burns (Thamlikitkul 1991; Akhtar 1996) whilst the third recruited participants with second-degree burns only (Khorasani 2009). The studies investigated the following interventions: Aloe vera cream compared with framycetin cream (Akhtar 1996), Aloe vera cream compared with silver sulfadiazine cream (Khorasani 2009) and Aloe vera mucilage compared with silver sulfadiazine cream (Thamlikitkul 1991).

1.1.1 Aloe vera cream compared with framycetin cream
Akhtar 1996 (n = 100) compared Aloe vera cream with framycetin cream. Framycetin is an aminoglycoside antibiotic that primarily works by disrupting bacterial protein synthesis. Baseline characteristics were similar in both groups. Mean days to healing were reported however the standard deviations were not. We made attempts to contact the author to obtain missing data but no reply was received. Mean time to healing was 18 days for the Aloe vera cream group and 30.9 days in the framycetin cream group. The mean difference was -12.9 days favouring the Aloe vera group.

Secondary outcomes: none reported.

1.1.2 Aloe vera cream compared with silver sulfadiazine cream
One trial compared Aloe vera cream containing Aloe vera gel powder 0.5% with silver sulfadiazine 1% cream (Khorasani 2009). Thirty participants were recruited with each participant having two body parts with burns (e.g. two hands). One body part was randomised to the Aloe vera group whilst the other body part was randomised to the silver sulfadiazine group. Khorasani 2009 was the only included trial to use the individual body part as the unit of randomisation. The trial reported on the proportion of patients with a completely healed wound at 19 days. Of the Aloe vera group, 30/30 (100%) recorded a completely healed wound at 19 days compared with 24/30 (80%) of the silver sulfadiazine group at the same time interval (risk ratio (RR) 1.24, 95% CI 1.03 to 1.50 without correction for correlation) (Analysis 1.1). The mean wound healing time was also measured by the trial. The mean time to wound healing was 15.9 ± 2 days in the Aloe vera group and 18.73 ± 2.65 days in the silver sulfadiazine group. It was not appropriate for the study to analyse time-to-event data (time to complete wound healing) using methods for continuous outcomes (e.g. using mean times-to-event) as the relevant times are only known for the subset of participants who have had the event (participants who fully healed). Those participants who did not heal must be excluded, which almost certainly will introduce bias. The most appropriate way of summarising time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio. Secondary outcomes: the trial tested the incidence of infection on days three, seven and 13 by swabbing the wound site: no infection was reported at all during the trial. No other secondary outcomes were reported.

### 1.1.3 Aloe vera mucilage compared with silver sulfadiazine cream

One trial (n = 38) compared Aloe vera mucilage with silver sulfadiazine cream (Thamlikitkul 1991). The mucilage is the thick, glue-like gel substance that is derived from the leaf pulp of the Aloe vera plant. In this trial, patients of any age with thermal first or second-degree burns of less than 30% of the body surface area and within 24 hours of admission were included. The Aloe vera mucilage and silver sulfadiazine cream was applied twice daily. Baseline characteristics were similar in both groups. The study recorded the proportion of participants with a completely healed wound, but did not state the duration of follow up. There was no statistically significant difference in the proportion of participants with a completely healed wound between the groups: 11/20 (55%) healed in the Aloe vera group compared with 7/18 (39%) in the silver sulfadiazine group; RR 1.41, 95% CI 0.70 to 2.85 (Analysis 2.1). Secondary outcomes: the trial measured the incidence of treatment side effects, specifically skin itching and irritation. Of the Aloe vera group 8/20 (40%) recorded itching and skin irritation compared with 8/18 (44%) in the silver sulfadiazine group.

### 1.2 Acute surgical wounds

One trial (n = 49) allocated patients who had recently undergone a haemorrhoidectomy to Aloe vera cream (with 0.5% Aloe vera gel powder) or placebo group (Eshghi 2010). The placebo cream was a mixture of liquid white paraffin, sterile alcohol, cetyl alcohol, solid white paraffin and propylene paraben and it was deemed to have no healing properties. Baseline characteristics between the control and intervention groups were similar. Data on the proportion of participants with completely healed wound at the conclusion of the study (28 days) were not given, although the authors that state that the difference between both groups was ‘not statistically significant’. We made an attempt to contact the study authors to clarify the results however did not receive a reply. The trial reported the proportion of participants with a completely healed wound at 14 days (or halfway through the study): 24/24 (100%) of the Aloe vera group completely healed at 14 days compared with 1/24 (4%) of the placebo group (RR 16.33 days, 95% CI 3.46 to 77.15 (Analysis 3.1) and this difference was statistically significant in favour of Aloe vera. Secondary outcomes: none reported.

### 1.3 Skin biopsy

One trial (n = 49) recruited patients who had recently undergone a shave biopsy excision for suspected skin cancers (Phillips 1995). Participants were allocated to receive either an Aloe vera derivative gel dressing (Carrasyn® hydrogel) or conventional therapy (initial cleansing of the wound with hydrogen peroxide followed by the application of antibiotic ointment and an adhesive dressing). Dressings in both groups were changed daily. There was no difference in the proportion of participants with a completely healed wound at 14 days: 26/26 (100%) were healed in the Aloe vera group compared with 23/23 (100%) in the conventional therapy group (Analysis 4.1). Secondary outcomes: the trial reported that there was no infection recorded in either the Aloe vera group or conventional therapy group. In terms of adverse events, contact dermatitis to the adhesive dressing occurred in 6/26 (23%) participants who used the Aloe vera and 6/23 (26%) in the conventional therapy group.

### 2. Chronic wounds

#### 2.1 Pressure ulcers

One trial (n = 41) recruited patients with stage II, III or IV pressure ulcers with an area greater than or equal to 1 cm² (Thomas 1998). The participants were allocated to receive an amorphous hydrogel dressing derived from Aloe vera (Carrasyn® gel wound dressing) or a saline gauze dressing. The dressings were applied on a daily basis. Eleven participants failed to complete the study and were not included in the statistical analysis (high risk of attrition bias).
Of the 30 participants included in the statistical analysis, 16 were from the Carrasyn® group and 14 were from the saline gauze group. Of participants in the Carrasyn® group 10/16 (63%) had a completely healed ulcer at 10 weeks while 9/14 (64%) of the participants with a saline gauze dressing had a completely healed ulcer. The trial reported that there was no difference between the experimental and control groups for risk of healing (RR 0.97, 95% CI 0.56 to 1.68) (Analysis 5.1). The trial also measured the mean time to wound healing. In the wounds that did heal, those treated with the Aloe vera dressing healed in a mean of 5.3 ± 2.3 weeks, while those treated with a saline gauze healed in a mean of 5.2 ± 2.4 weeks, as not all participants were included in the final analysis we have not plotted these data as they are presented as continuous data and not survival data. Again, time to complete wound healing is time-to-event data and the most appropriate way of summarizing time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio. It is not appropriate to analyse time-to-event data using methods for continuous outcomes (e.g. using mean times-to-event) as the relevant times are only known for the subset of participants who have had the event.

Secondary outcomes: none reported.

2.2 Postoperative wound healing by secondary intention

One trial (n = 40) recruited outpatients with surgical wounds healing by secondary intention after either caesarean section or laparotomy for gynaecologic surgery (Schmidt 1991). The patients were allocated to receive standard wound care plus Aloe vera dermal gel or standard wound care alone. Standard wound care was a wet-to-dry dressing that was applied using a solution with equal parts of saline and sodium hypochlorite 0.025%. Almost half of the participants (19) dropped out of the study and were not included in the statistical analysis increasing the risk of bias of this study. Of the 21 participants included in the final analysis, 10 were from the Aloe vera group and 11 were from the standard care group. The mean healing time was 83 ± 28 days in the Aloe vera group and 53 ± 24 days for those who received standard care, as not all participants were included in the final analysis we have not plotted these data as they are presented as continuous and not survival data and therefore are reported inappropriately as explained previously. Secondary outcomes: none reported.

D I S C U S S I O N

This systematic review summarises the best available evidence regarding the effectiveness of Aloe vera in patients with both acute and chronic wounds. After an extensive search of the literature, we found seven RCTs with most at moderate to high risk of bias due to their poor methodology. The trial at lowest risk of bias was Phillips 1995, but this was a small study (n = 49) and so a treatment effect cannot be ruled out due to the lack of statistical power. All the included studies were small, with a mean sample size of 50 (range 30 to 100).

The strength of a systematic review is the ability to summarise or pool data from several trials to make an overall conclusion or estimate of effect. We could not undertake meta-analysis in this review due to a lack of replication of trials with the same wound type and intervention. The variation in comparator treatments (ranging from framycetin cream to silver sulfadiazine cream) also contributed to the inability to perform a meta-analysis. A lack of consistency in the primary outcome measures was also another key reason why data pooling was not possible. Finally healing was variously measured as proportion of wounds completely healed and time to healing and three studies (Schmidt 1991; Thomas 1998; Khorasani 2009) wrongly analysed time to healing as if it were a continuous variable.

The evidence on wound healing was contradictory at best. Some studies in patients with burns (Thamlikitkul 1991; Akhtar 1996; Khorasani 2009) and post-haemorrhoidectomy (Eshghi 2010) reported an improvement in wound healing with Aloe vera but again these were small studies at high risk of bias. Thomas 1998, on the other hand, found no difference between Aloe vera and the comparator. It was, however, a small study with a significant dropout rate. Schmidt 1991 reported that Aloe vera gel delayed wound healing in patients healing by secondary intention post-gynaecological surgery, however it was a flawed trial as there was no blinding of the study participants or study assessors. The high dropout rate, with no subsequent explanation of the reasons behind the dropout, was also a major cause of concern for this trial. Thus, the results of this trial along with every other included trial must be interpreted with a great deal of caution.

In terms of secondary outcomes, the financial cost of wound healing, quality of life measures and adverse events rates were generally not well reported in most trials. In fact, Akhtar 1996 and Thomas 1998 had no clear report on the incidence of adverse effects or infections. Schmidt 1991 reported treatment withdrawals but did not specify the reasoning behind those withdrawals. Considering that treatment compliance is closely linked with the treatment itself, it is likely that these withdrawals may have been due to the treatment adverse effect. No trial reported adverse effects in accordance to the Item 19 of the CONSORT statement which clarifies the reporting of harms in RCTs (Ioannidis 2004). In brief, the statement concludes that if data on adverse events were collected, events should be listed and defined, with reference to standardised criteria where appropriate. The authors should also provide a balanced discussion of benefits and harms (Ioannidis 2004). Future research into Aloe vera as a treatment for wounds may benefit from a quality of life analysis and economic evaluation as it may provide information on treatment compliance.
The results of this review are similar to previous Aloe vera reviews (Vogler 1999; Maenthaisong 2007) on wounds and burns respectively. Collectively, we conclude that there is little high-level evidence to support the use of Aloe vera topical agents or aloe-derived dressings in the treatment of acute and chronic wounds.

Limitations of the review
Incomplete reporting of some trials (Akhtar 1996; Eshghi 2010) made it difficult for us to assess the risk of bias of these trials. Although we made attempts to contact the authors to obtain additional data, no response was forthcoming and this lack of information was reflected in the review.

AUTHORS’ CONCLUSIONS

Implications for practice
There is currently insufficient clinical trial evidence available regarding the effects of Aloe vera topical agents or Aloe vera dressings as treatments for acute and chronic wounds. This is primarily due to the lack of high quality trials with adequate methodology.

Implications for research
This systematic review has highlighted the need for future high quality research into Aloe vera and its effects on acute and chronic wounds. We make the following recommendations based on our analysis of the current data:

- Properly designed randomised controlled trials with stringent trial methodology are suggested for any future research into the effects of Aloe vera on wound healing. These trials need to have the following attributes: clear inclusion and exclusion criteria, true randomisation, adequate allocation concealment, blinded outcome assessment and participants, adequate sample size, intention-to-treat analysis and baseline comparability of groups. Specifically, the trials should be reported according to the guidelines set out in the CONSORT statement to enable readers to determine the validity and reliability of the results (Begg 1996).

- These trials should also assess the incidence of infection and adverse effects of Aloe vera. Quality of life issues surrounding the routine use of Aloe vera topical solutions or dressings should also be investigated in order to determine whether sufficient compliance can be maintained amongst patients.

- An economic evaluation should also be conducted to determine if the costs of Aloe vera topical preparations and Aloe vera dressings justify their potential benefits.

ACKNOWLEDGEMENTS

The authors would like to thank Sally Bell-Syer, Ruth Foxlee and Nicola Thomis (Cochrane Wounds Group) for their assistance with literature searching and the preparation of this review. We would like to acknowledge the contribution of the Wound Group Editors (Nicky Cullum, Mieke Flour, Elizabeth McInnes and Gill Worthy) and Copy Editor (Jenny Bellorini). We would also like to thank the following referees: Una Adderley, Britt Ebbeskog, Emma Maund, Catriona Mcdaid, Jane Nadel and Sylvia Stanway for contributions at both protocol and review stage.

REFERENCES

References to studies included in this review

Akhtar 1996  [published data only]

Eshghi 2010  [published data only]

Khorasani 2009  [published data only]

Phillips 1995  [published data only]

Schmidt 1991  [published data only]

Thamlikitkul 1991  [published data only]

Thomas 1998  [published data only]
* Thomas D, Goode P, LaMaster K, Tennyson T. Acemannan hydrogel dressing versus saline dressing for

Thomas DR, Goode PS. Acemannan hydrogel versus saline dressings for pressure ulcers: a randomized controlled trial. *Journal of Investigative Medicine* 1998;46(7):283A.

References to studies excluded from this review

Fulton 1990 *(published data only)*


Sun 1994 *(published data only (unpublished sought but not used))*


Visuthikosol 1995 *(published data only)*


Additional references

Atherton 1998


Begg 1996


Boudreau 2006


Chithra 1998


Davis 1994


Hamman 2008


Higgins 2011


Ioannidis 2004


Kuzuya 2001


Lazarus 1994


Lefebvre 2011


Maenthaisong 2007


Mendonça 2009


SIGN 2010


Steenkamp 2007


Takzare 2009


Tamura 2009

Tamura N, Yoshida T, Miyaji K, Sugita-Konishi Y, Hartori M. Inhibition of infectious diseases by components from...

**Vogler 1999**


* Indicates the major publication for the study
### Characteristics of Studies

**Characteristics of included studies** (ordered by study ID)

#### Akhtar 1996

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single-centre RCT</th>
</tr>
</thead>
</table>
| Participants | Country: India  
100 participants who had first or second degree burns to 10% to 40% of total body surface area  
Exclusion criteria: electrical, chemical and radiation burns, 3rd and 4th degree burns, patients with systemic diseases like diabetes, malignancy or on immunosuppressants or vitamin deficient |
| Interventions | 1) Aloe vera cream applied every third day (n = 50)  
2) Framycetin cream applied every third day (n = 50)  
Duration: until fully healed |
| Outcomes | Mean wound healing time (no standard deviation was stated)  
1) 18 days  
2) 30.9 days |
| Notes | |

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Method of randomisation: block size of 8. “Allocation to intervention was done by block randomisation of 8 subjects”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes - participants blinded</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes - caregivers blinded</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes - outcome assessors blinded</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes - levels of attrition reported and acceptable</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Selective reporting (reporting bias) | Unclear risk | No protocol was available for the study and there was insufficient information to permit a clear judgement. The study report was available in abstract form only
---|---|---
Free of other bias? - as specified in the description | Unclear risk | This could not be assessed as the study report was available in abstract form only

### Eshghi 2010

**Methods**

Single-centre RCT

**Participants**

Country: Iran

49 participants who had symptomatic III and IV degree haemorrhoidal disease and underwent surgical haemorrhoidectomy

Exclusion criteria: pregnancy, anal fissure, heart and liver disease

**Interventions**

1. Aloe vera cream (with 0.5% Aloe vera gel powder) applied 12 hours post-haemorrhoidectomy and 3 times a day up to 28 days post-operation (n = 24)
2. Placebo cream applied 12 hours post-haemorrhoidectomy and 3 times a day up to 28 days post-operation (n = 25)

Duration: 28 days

**Outcomes**

Proportion of participants with completely healed wound at 14 days classified by Grade 3 wound (completed layer of epithelial covering on wound)

1. 24/24 (100%)
2. 1/24 (4%)

**Notes**

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method of randomisation not reported although the study was referred to as a &quot;prospective, randomized, double-blind placebo-controlled trial&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
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<td>Patients blinded to treatment allocation, “both the nurse and patients were blinded”</td>
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<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Care givers (nurses) blinded to treatment allocation, “both the nurse and patients were blinded”</td>
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<td>All outcomes - caregivers blinded</td>
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</table>
### Eshghi 2010  
*(Continued)*

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>All outcomes - outcome assessors blinded</td>
<td></td>
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</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Data on the proportion of participants with completely healed wound at the conclusion of the study (28 days) were not given</td>
</tr>
<tr>
<td>All outcomes - levels of attrition reported and acceptable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No protocol was available for the study and there was insufficient information to permit a clear judgement</td>
</tr>
<tr>
<td>Free of other bias? - as specified in the description</td>
<td>Low risk</td>
<td>Baseline characteristics were comparable. Trial not stopped early</td>
</tr>
</tbody>
</table>

### Khorasani 2009

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single-centre RCT</th>
</tr>
</thead>
</table>
| Participants | Country: Iran  
30 patients with 60 second degree-burns  
Inclusion criteria: the burn had to have occurred within 24 hours before the initiation of treatment; the patient had to have 2 same site burns, which only were the feet or hands; the burns had to be of second degree with respect to depth and similar burned surface areas in 2 different parts of the body; and the patients had to have less than 40% total burn surface area (TBSA) burns  
Exclusion criteria: patients with diabetes, immunodeficiency, pregnancy and kidney diseases. Also excluded were patients with electrical and chemical burns |
| Interventions | 1) Aloe vera cream (0.5% aloe vera gel powder), twice daily (n = 30)  
2) Silver sulfadiazine 1% cream, twice daily (n = 30)  
Duration: until healed |
| Outcomes | Mean wound healing time  
1) 15.9 days (SD 2)  
2) 18.73 days (SD 2.65)  
Also reported the proportion of patients with a completely healed wound at 19 weeks  
1) 30/30 (100%)  
2) 24/30 (80%) |
| Notes | Risk of bias |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Method of randomisation was not reported, however the paper states "randomised controlled study" |
Khorasani 2009  (Continued)

| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding (performance bias and detection bias) | Unclear risk | Not reported |
| All outcomes - participants blinded | | |
| Blinding (performance bias and detection bias) | Unclear risk | Not reported |
| All outcomes - caregivers blinded | | |
| Blinding (performance bias and detection bias) | Unclear risk | Not reported |
| All outcomes - outcome assessors blinded | | |
| Incomplete outcome data (attrition bias) | Low risk | All the participants’ results were accounted for at the end of the study |
| All outcomes - levels of attrition reported and acceptable | | |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available for the study and there was insufficient information to permit a clear judgement |
| Free of other bias? - as specified in the description | Low risk | Baseline characteristics were comparable. Trial not stopped early |

Phillips 1995

Methods  Single-centre RCT

Participants  Country: United States of America
49 patients who recently underwent shave biopsies to remove benign skin tumours
Exclusion criteria: patients were excluded if their shave biopsies showed malignant carcinoma

Interventions  1) Aloe vera derivative gel dressing containing acemannan (Carrasyn hydrogel), changed twice daily (n = 26)
2) Conventional therapy (hydrogen peroxide, antibiotic ointment (bacitracin) and adhesive dressing), changed twice daily (n = 23)
Duration: 2 weeks

Outcomes  Proportion of participants with a completely healed wound
1) 26/26 (100%)
2) 23/23 (100%)

Notes
### Phillips 1995

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
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<td>Random sequence generation (selection bias)</td>
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<td>“Computer generated”</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
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<tr>
<td>All outcomes - participants blinded</td>
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<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
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<tr>
<td>All outcomes - caregivers blinded</td>
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<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>“The observer was blinded”</td>
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<td>All outcomes - outcome assessors blinded</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All the participants’ results were accounted for</td>
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<tr>
<td>All outcomes - levels of attrition reported and acceptable</td>
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</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol was available for the study and there was insufficient information to permit a clear judgement</td>
</tr>
<tr>
<td>Free of other bias? - as specified in the description</td>
<td>Low risk</td>
<td>Baseline characteristics were comparable. Trial not stopped early</td>
</tr>
</tbody>
</table>

### Schmidt 1991

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single-centre RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Country: United States of America</td>
<td>40 women with complications of wound healing after gynaecological surgery</td>
</tr>
<tr>
<td>Exclusion criteria: diabetes mellitus, cancer, required treatment with glucocorticoids or immunosuppressive drugs, history of abdominal irradiation or chronic debilitating disease</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
</tr>
<tr>
<td>1) Standard wound care plus Aloe vera dermal gel, given every 8 to 12 hours (n = 10)</td>
<td></td>
</tr>
<tr>
<td>2) Standard wound care (wet-to-dry dressing was applied using a solution with equal parts of saline and sodium hypochlorite 0.025%) (n = 11)</td>
<td></td>
</tr>
<tr>
<td>Duration: until healed</td>
<td></td>
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<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Mean wound healing time</td>
<td></td>
</tr>
<tr>
<td>1) 83 days (SD 28)</td>
<td></td>
</tr>
<tr>
<td>2) 53 days (SD 24)</td>
<td></td>
</tr>
</tbody>
</table>
Schmidt 1991  (Continued)

<table>
<thead>
<tr>
<th>Notes</th>
<th>19 participants dropped out of the study and were not accounted for in the final analysis</th>
</tr>
</thead>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>“random number sequence generated by a computer program”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
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<td>High risk</td>
<td>“The study was not blinded”</td>
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<tr>
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<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>“The study was not blinded”</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Reported a significant loss of 19 patients from a sample size of 41, with no reasons given; this loss represents a 47.5% dropout rate</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
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<td>No protocol was available for the study and there was insufficient information to permit a clear judgement</td>
</tr>
<tr>
<td>Free of other bias? - as specified in the description</td>
<td>High risk</td>
<td>“terminated early due to an observed delay in healing within the experimental group”</td>
</tr>
</tbody>
</table>

Thamlikitkul 1991

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multi-centre RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Thailand 38 patients with minor burns  Inclusion criteria: patients of any age with thermal first or second-degree burns of less than 30% of the body surface area and within 24 hours of admission. Patients must have also not yet received any antibiotics or topical treatment.  Exclusion criteria: patients with diabetes mellitus or those in a moribund state</td>
</tr>
<tr>
<td>Interventions</td>
<td>1) Aloe vera mucilage applied twice daily (n = 20)  2) Silver sulfadiazine cream applied twice daily (n = 18)  Duration: until burns healed or patient had to leave the hospital</td>
</tr>
</tbody>
</table>
### Outcomes

Proportion of participants with a completely healed wound (no standard deviation was stated)

1) 11/20 (55%)
2) 7/18 (39%)

### Notes

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>All outcomes - caregivers blinded</td>
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<td>Not reported</td>
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<td>All outcomes - outcome assessors blinded</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants’ results were accounted for at the end of the trial</td>
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<td>All outcomes - levels of attrition reported and acceptable</td>
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<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol was available for the study and there was insufficient information to permit a clear judgement</td>
</tr>
<tr>
<td>Free of other bias? - as specified in the description</td>
<td>Low risk</td>
<td>Baseline characteristics were comparable. Trial not stopped early</td>
</tr>
</tbody>
</table>

### Thomas 1998

Methods

Multi-centre RCT

Participants

Country: United States of America
41 patients with pressure ulcers were enrolled
Inclusion criteria: patients who had a stage II, III or IV pressure ulcer with an area of greater or equal to 1 cm²
Excluded criteria: ulcers resulting from venous or arterial insufficiency of other non-pressure aetiology (e.g. vasculitis or diabetic ulcer) were excluded. Wounds with sinus
tracts and/or undermining greater than 1 cm were also excluded. Clinically infected wounds were also excluded. Concomitant use of other topical medications to the study ulcer or steroids was not allowed. Patients with a severe generalised medical condition and estimate survival of less than 6 months were excluded. Patients who were HIV-positive, currently abusing alcohol or drugs, pregnant, breast feeding, not on acceptable means of contraception in perimenopausal women, had a current diagnosis of cancer or were receiving chemotherapy were also excluded.

| Interventions | 1) Acemannan hydrogel dressing derived from the aloe plant, applied daily (n = 16)  
2) Saline gauze dressing, applied daily (n = 14)  
Duration: 10 weeks, unless the wounds healed earlier |
|-----------------|------------------------------------------------|

| Outcomes | Mean wound healing time  
1) 5.3 weeks (SD 2.3)  
2) 5.2 weeks (SD 2.4)  
Also reported the percentage of participants to be fully healed at 10 weeks  
1) 10/16 (63%)  
2) 9/14 (64%) |
|-----------------|------------------------------------------------|

<table>
<thead>
<tr>
<th>Notes</th>
<th>11 patients (6 from the control group and 5 from the experimental group) failed to complete the study and were not included in the statistical analysis</th>
</tr>
</thead>
</table>

**Risk of bias**

| Bias | Authors' judgement | Support for judgement |
|-----------------|------------------------------------------------|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding (performance bias and detection bias) | Unclear risk | Not reported |
| All outcomes - participants blinded | | |
| Blinding (performance bias and detection bias) | Unclear risk | Not reported |
| All outcomes - caregivers blinded | | |
| Blinding (performance bias and detection bias) | Unclear risk | Not reported |
| All outcomes - outcome assessors blinded | | |
| Incomplete outcome data (attrition bias) | High risk | Even though all participants’ results were accounted for at the end of the study, there was a significant loss to follow up (25% drop out rate) |
| All outcomes - levels of attrition reported and acceptable | | |
Thomas 1998  (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>No protocol was available for the study and there was insufficient information to permit a clear judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of other bias? - as specified in the description</td>
<td>Low risk</td>
<td>Baseline characteristics were similar</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; SD: standard deviation

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulton 1990</td>
<td>Study design - controlled clinical trial</td>
</tr>
<tr>
<td>Sun 1994</td>
<td>Article could not be obtained for assessment</td>
</tr>
<tr>
<td>Visuthikosol 1995</td>
<td>Study design - controlled clinical trial</td>
</tr>
</tbody>
</table>
### Comparison 1. Burns: Aloe vera cream versus silver sulfadiazine cream

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with a completely healed wound</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Comparison 2. Burns: Aloe vera mucilage versus silver sulfadiazine cream

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with a completely healed wound</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Comparison 3. Acute surgical wound: Aloe vera cream versus placebo cream

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with a completely healed wound</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Comparison 4. Skin biopsy: Aloe vera gel dressing versus conventional therapy

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with a completely healed wound</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Comparison 5. Pressure ulcer: Aloe vera dressing versus saline gauze dressing

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Proportion of patients with a completely healed wound</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

---

**Analysis 1.1. Comparison 1 Burns: Aloe vera cream versus silver sulfadiazine cream, Outcome 1 Proportion of patients with a completely healed wound.**

Review: Aloe vera for treating acute and chronic wounds

Comparison: 1 Burns: Aloe vera cream versus silver sulfadiazine cream

Outcome: 1 Proportion of patients with a completely healed wound

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aloe vera cream</th>
<th>SSD</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khorasani 2009</td>
<td>30/30</td>
<td>24/30</td>
<td>1.24 [1.03, 1.50]</td>
<td></td>
</tr>
</tbody>
</table>

0.05 0.2 1 5 20

Favours SSD Favours Aloe vera

---

**Analysis 2.1. Comparison 2 Burns: Aloe vera mucilage versus silver sulfadiazine cream, Outcome 1 Proportion of patients with a completely healed wound.**

Review: Aloe vera for treating acute and chronic wounds

Comparison: 2 Burns: Aloe vera mucilage versus silver sulfadiazine cream

Outcome: 1 Proportion of patients with a completely healed wound

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aloe vera mucilage</th>
<th>Silver sulfadiazine cream</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thamlikitkul 1991</td>
<td>11/20</td>
<td>7/18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.01 0.1 1 10 100

Favours silver Favours Aloe vera
**Analysis 3.1. Comparison 3 Acute surgical wound: Aloe vera cream versus placebo cream, Outcome 1**

Proportion of patients with a completely healed wound.

**Review:** Aloe vera for treating acute and chronic wounds

**Comparison:** 3 Acute surgical wound: Aloe vera cream versus placebo cream

**Outcome:** 1 Proportion of patients with a completely healed wound

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aloe vera gel dressing</th>
<th>Placebo cream</th>
<th>Risk Ratio M-H, Random 95% CI</th>
<th>Risk Ratio M-H, Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eshghi 2010</td>
<td>24/24</td>
<td>1/24</td>
<td>16.33 [3.46, 77.15]</td>
<td></td>
</tr>
</tbody>
</table>

Favours placebo cream

Favours Aloe vera gel

**Analysis 4.1. Comparison 4 Skin biopsy: Aloe vera gel dressing versus conventional therapy, Outcome 1**

Proportion of patients with a completely healed wound.

**Review:** Aloe vera for treating acute and chronic wounds

**Comparison:** 4 Skin biopsy: Aloe vera gel dressing versus conventional therapy

**Outcome:** 1 Proportion of patients with a completely healed wound

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aloe vera gel dressing</th>
<th>Conventional therapy</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips 1995</td>
<td>26/26</td>
<td>23/23</td>
<td>1.00 [0.92, 1.08]</td>
<td></td>
</tr>
</tbody>
</table>

Favours conventional

Favours Aloe vera gel
### Analysis 5.1. Comparison 5 Pressure ulcer: Aloe vera dressing versus saline gauze dressing, Outcome 1
Proportion of patients with a completely healed wound.

**Review:** Aloe vera for treating acute and chronic wounds

**Comparison:** 5 Pressure ulcer: Aloe vera dressing versus saline gauze dressing

**Outcome:** 1 Proportion of patients with a completely healed wound

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aloe vera dressing</th>
<th>Saline gauze dressing</th>
<th>Risk Ratio M-H Random 95% CI</th>
<th>Risk Ratio M-H Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas 1998</td>
<td>10/16</td>
<td>9/14</td>
<td>0.97 [0.56, 1.68]</td>
<td></td>
</tr>
</tbody>
</table>

0.005 0.1 1 10 200
Favours Aloe vera Favours saline gauze

**APPENDICES**

**Appendix 1. Ovid MEDLINE search strategy**

1 exp Aloe/
2 aloe*.ti,ab.
3 or/1-2

**Appendix 2. Ovid EMBASE search strategy**

1 exp Aloe/
2 exp Aloe barbadensis extract/
3 exp Aloe vera/
4 exp Aloe vera extract/
5 aloe*.tw.
6 or/1-5

**Appendix 3. EBSCO CINAHL search strategy**

S3 S1 or S2
S2 TI aloe* or AB aloe*
S1 (MH "Aloe")
Appendix 4. Ovid AMED search strategy

1 exp Aloe/
2 aloe*.ti,ab.
3 or/1-2

Appendix 5. The Cochrane Collaboration’s tool for assessing risk of bias

1. Was the allocation sequence randomly generated?

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

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

Unclear
Insufficient information 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 un Concealed 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
- stopped early due to some data-dependent process (including a formal-stopping rule); or
- had extreme baseline imbalance; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear
There may be a risk of bias, but there is either:
- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.
HISTORY

Protocol first published: Issue 10, 2010
Review first published: Issue 2, 2012

CONTRIBUTIONS OF AUTHORS

Anthony Dat conceived, designed, coordinated the review and extracted data, checked the quality of data extraction, undertook quality assessment, analysed or interpreted data, checked quality assessment, performed statistical analysis, checked quality of statistical analysis, completed the first draft of the review, performed part of the writing or editing of the review, wrote to study authors/experts/companies and approved the final review prior to submission.

Flora Poon designed the review, extracted data, checked quality of data extraction and undertook and checked quality assessment, analysed or interpreted data, checked quality of data analysis, performed and checked quality of statistical analysis, completed the first draft of the review, performed part of the writing or editing of the review, wrote to study authors/experts/companies and approved the final review prior to submission.

Kim B T Pham extracted data and checked the quality of data extraction, undertook quality assessment, analysed or interpreted data, checked quality assessment, performed statistical analysis and checked quality of statistical analysis, completed first draft of the review, performed part of the writing or editing of the review, and approved the final review prior to submission.

Jenny Doust designed the review, checked the quality of the data extraction, analysed or interpreted data and checked quality assessment, performed and checked quality of statistical analysis, performed part of writing or editing the review, and approved the final review prior to submission.

Contributions of editorial base:

Nicky Cullum: edited the review, advised on methodology, interpretation and review 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.
Ruth Foxlee: designed the search strategy, ran the searches and edited the search methods section.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied
External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Aloe; *Bandages; Acute Disease; Anti-Infective Agents, Local [therapeutic use]; Biopsy; Burns [drug therapy]; Chronic Disease; Framycetin [therapeutic use]; Gels; Hemorrhoids [surgery]; Phytotherapy [*methods]; Pressure Ulcer [drug therapy]; Randomized Controlled Trials as Topic; Silver Sulfadiazine [therapeutic use]; Skin [pathology]; Time Factors; Wound Healing [*drug effects]; Wounds and Injuries [drug therapy]

MeSH check words

Humans