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Topical silver for preventing wound infection

Review

Intervention

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Abstract

English

Background

Silver-containing treatments are popular and used in wound treatments to combat a broad spectrum of pathogens, but evidence of their effectiveness in preventing wound infection or promoting healing is lacking.

Objectives

To establish the effects of silver-containing wound dressings and topical agents in preventing wound infection and healing of wounds.

Search methods

We searched the Cochrane Wounds Group Specialised Register (6 May 2009); The Cochrane Central Register of Controlled Trials (CENTRAL) (2009 Issue 2); Ovid MEDLINE (1950 to April Week 4 2009); Ovid EMBASE (1980 to 2009 Week 18); EBSCO CINAHL (1982 to April Week 4 2009) and Digital Dissertations (to May 2009) for relevant trials. We contacted manufacturers and distributors.

Selection criteria

Randomised controlled trials (RCTs) comparing silver-containing wound dressings and topical agents with silver-containing and non silver-containing comparators on uninfected wounds.

Data collection and analysis

Two authors independently selected trials, assessed risk of bias, and extracted data.

Main results

We identified 26 RCTs (2066 patients). Heterogeneity of treatments and outcomes precluded meta-analysis. We grouped results according to wound type, and silver preparation.

Burns

Thirteen trials compared topical silver (in a variety of formulations - including silver sulphadiazine (SSD) cream) with non-silver dressings. One trial showed fewer infections with silver nitrate when compared with a non-silver dressing, but three trials showed significantly more infection with SSD than with the non-silver dressing.

Six trials compared SSD cream with silver-containing dressings. One showed significantly fewer infections with the silver-containing dressing (Hydron AgSD) compared with SSD, the remaining five found no evidence of a difference.

One trial compared two silver-containing dressings, and showed a significantly lower infection rate with silver-coated gauze (Acticoat®) than with silver nitrate gauze.

Other wounds

Six trials compared SSD/silver-containing dressings with non-silver dressings (nine dressings in total). Most comparisons (seven) found no significant differences in infection rates; one trial in a variety of wounds exhibited significantly fewer infections with SSD/hydrocolloid, but another, in acute wounds, found significantly more infections with SSD. Only one comparison showed a significant reduction in healing time associated with a silver-containing hydrofibre dressing in diabetic foot ulcers.

Authors' conclusions

There is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection; some poor quality evidence for SSD suggests the opposite.

摘要

背景

銀的局部性使用對於傷口感染的預防

含銀敷料和藥膏廣泛使用於傷口以對抗多種致病源。但是其對於預防感染的證據仍十分薄弱。

目標

了解含銀敷料和藥膏對於感染預防以及傷口癒合的效果。

搜尋策略

我們找尋了以下資料庫：Cochrane Wounds Group Specialised Register (6 May 2009); The Cochrane Central Register of Controlled Trials (CENTRAL) (2009 Issue 2); Ovid MEDLINE (1950 to April Week 4 2009); Ovid EMBASE (1980 to 2009 Week 18); EBSCO CINAHL (1982 to April Week 4 2009) 以及 Digital Dissertations (to May 2009) 我們還聯絡了製造商和經銷商。

選擇標準

隨機對照試驗　比較含銀敷料,含銀藥膏和未含銀藥膏對於未感染的傷口的作用

資料收集與分析

兩位作者各自選擇試驗，評估研究偏差的風險以及汲取資料。

主要結論

我們找到了26項隨機對照試驗 (2066位病患), 但因為治療方法和結果的不同，無法進行整合分析 (meta　analysis) 。我們依據傷口種類和含銀敷料的不同進行分類。BurnsThirteen trials 比較了含銀藥膏 (包括磺胺銀軟膏SSD cream) 和不含銀敷料的不同。有一個試驗顯示硝酸銀會降低感染的機會，但是有三個試驗顯示用磺胺銀軟膏 (SSD cream) 和用不含銀敷料相比，大幅增加了感染的機會。有六個試驗比較了硝酸銀藥膏和含銀敷料：其中一個顯示含銀敷料 (Hydron AgSD) 和SSD相比降低了感染的機會，但另外五個試驗顯示兩者並沒有不同。有一個試驗顯示浸銀紗布 (Acticoat) 比起硝酸銀紗布明顯降低感染的機會。Other woundsSix trials則比較了硝酸銀藥膏/含銀敷料 和 不含銀敷料 (總共九種) 。大部分 (七個) 顯示感染率沒有明顯差別；有一個包含種不同傷口的試驗顯示硝酸銀藥膏/水狀膠質明顯降低感染率，但是另一個試驗則顯示急性傷口使用硝酸銀藥膏其感染率明顯增加。只有一個比較顯示在糖尿病足潰瘍中含銀水狀膠質敷料能明顯降低傷口恢復時間。

作者結論

沒有足夠證據顯示含銀敷料或含銀藥膏能促進傷口癒合或預防感染；一些品質不佳的證據顯示硝酸銀藥膏反而會造成反效果。

翻譯人

本摘要由羅東博愛醫院洪綱翻譯。

此翻譯計畫由臺灣國家衛生研究院 (National Health Research Institutes, Taiwan) 統籌。

總結

含銀敷料或藥膏可能並不能預防傷口感染或促進癒合：含銀敷料或藥膏目前正被廣泛使用。它們可能能促進傷口癒合或預防傷口感染，但是真相如何有待商榷。這篇回顧找到了26篇臨床試

驗 (包含了2066位病患)，比較了含銀和不含銀的敷料或藥膏。其中有20個試驗是針對燒傷傷口，其他則是各式各樣的傷口。大部分的研究規模都不大，而且品質低落。檢視之後，作者認為沒有足夠證據來支持含銀藥膏或敷料在臨床上的使用。有一小部份低品質的研究顯示硝酸銀藥膏對於部分增厚的燒傷傷口，不但不能促進傷口癒合或防止感染，它還會延緩傷口的恢復。

Résumé scientifique

Argent topique pour prévenir l'infection d'une plaie

Contexte

Les traitements contenant de l'argent sont courants, ils sont utilisés pour traiter les plaies et combattre un large spectre d'agents pathogènes, mais il n'y a pas suffisamment de données relatives à leur efficacité pour prévenir l'infection des plaies ou favoriser leur cicatrisation.

Objectifs

Etablir les effets des pansements et des agents topiques à base d'argent pour prévenir l'infection des plaies et favoriser leur cicatrisation.

Stratégie de recherche documentaire

Nous avons effectué une recherche dans le registre spécialisé du groupe Cochrane sur les plaies et les contusions (06.05.2009) ; le registre Cochrane des essais contrôlés (CENTRAL) (2009, Numéro 2) ; Ovid MEDLINE (de 1950 à Semaine 4 d'avril 2009) ; Ovid EMBASE (de 1980 à semaine 18 2009) ; EBSCO CINAHL (de 1982 à Semaine 4 d'avril 2009) et Digital Dissertations (jusqu'en mai 2009) pour trouver des essais pertinents. Nous avons contacté les fabricants et les distributeurs.

Critères de sélection

Les essais contrôlés randomisés (ECR) comparant les pansements et les agents topiques contenant de l'argent à des comparateurs contenant ou non de l'argent sur des plaies non infectées.

Recueil et analyse des données

Deux auteurs ont sélectionné les essais, évalué leurs risques de biais et extrait les données de façon indépendante.

Résultats principaux

Nous avons trouvé 26 ECR (2066 patients). L'hétérogénéité des traitements et des critères de jugement empêchait une méta-analyse. Nous avons regroupé les résultats en fonction du type de plaie et de la préparation d'argent.

Brûlures

Treize essais comparaient l'argent topique (dans une multitude de formulations - y compris la crème à base de sulfadiazine d'argent (SSD) aux pansements sans argent. Un essai a montré moins d'infections avec le nitrate d'argent par rapport à un pansement sans argent, mais trois essais ont montré qu'il y avait beaucoup plus d'infections avec le sulfadiazine d'argent qu'avec les pansements sans argent.

Six essais comparaient une crème à base de sulfadiazine d'argent à des pansements contenant de l'argent. Une essai a montré qu'il y avait un peu moins d'infections avec le pansement contenant de l'argent (Hydron AgSD) par rapport au sulfadiazine d'argent, les cinq essais restants n'ont montré aucune différence.

Un essai comparait deux pansements contenant de l'argent, et a démontré un taux d'infection sensiblement inférieur avec les compresses à base d'argent (Acticoat®) par rapport aux compresses à base de nitrate d'argent.

Autres plaies

Six essais comparaient le sulfadiazine d'argent/les pansements contenant de l'argent aux pansements sans argent (neuf pansements au total). La plupart des comparaisons (sept) n'ont montré aucune différence significative dans les taux d'infection ; un essai portant sur une multitude de plaies a montré qu'il y avait bien moins d'infections avec le sulfadiazine d'argent/hydrocolloïde, mais un autre, sur les plaies aigues, a montré qu'il y avait bien plus d'infections avec le sulfadiazine d'argent. Seulement une comparaison a démontré une diminution significative du temps de cicatrisation associé à un pansement hydrofibre contenant de l'argent pour les ulcères du pied diabétique.

Conclusions des auteurs

Il n'existe pas suffisamment de données permettant d'établir si les pansements ou les agents topiques contenant de l'argent favorisent la cicatrisation ou préviennent l'infection des plaies ; certaines données de qualité médiocre sur le sulfadiazine d'argent suggèrent le contraire.

Plain language summary

English

Probable that silver-containing dressings and creams do not prevent wound infection or promote healing

Wound dressings and creams containing silver are widely used. It is thought that silver may help wounds to heal faster and prevent infection, but we did not know if this was true. This review identified 26 trials (involving 2066 participants) comparing silver-containing dressings or creams against dressings or creams that did not contain silver. Twenty of the trials were on burn wounds, while the other trials were on a mixture of wound types. Most studies were small and of poor quality. After examining them all, the authors concluded that there is not enough evidence to support the use of silver-containing dressings or creams, as generally these treatments did not promote wound healing or prevent wound infections. Some evidence from a number of small, poor-quality studies suggested that one silver-containing compound (silver sulphadiazine) has no

effect on infection, and actually slows down healing in patients with partial-thickness burns.

Résumé simplifié

Il est probable que les pansements et les crèmes contenant de l'argent ne préviennent pas l'infection d'une plaie ou ne favorisent pas la guérison.

Les pansements et les crèmes contenant de l'argent sont largement utilisés. On pense que l'argent peut aider les plaies à cicatriser plus rapidement et empêche l'infection, mais nous ne savons pas si cela est réellement vrai. Cette revue a identifié 26 essais (totalisant 2066 participants) comparant les pansements ou les crèmes contenant de l'argent aux pansements ou crèmes n'en contenant pas. Vingt essais portaient sur les brûlures, alors que les autres traitaient de plusieurs types de plaies. La plupart des études étaient de petite taille et de qualité généralement médiocre. Après les avoir toutes examinées, les auteurs ont conclu qu'il n'existait pas suffisamment de données permettant de soutenir l'utilisation des pansements ou des crèmes à base d'argent, car ces traitements ne favorisent généralement pas la cicatrisation des plaies et n'empêchent pas les infections. Certaines données issues de plusieurs études de petite taille et de qualité médiocre suggéraient qu'un composant contenant de l'argent (sulfadiazine d'argent) n'avait aucun effet sur l'infection et de fait ralentissait la cicatrisation chez les patients présentant des brûlures de second degré.

Notes de traduction

Traduit par: French Cochrane Centre 15th April, 2013
Traduction financée par: Pour la France : Minist&#xfffd;re de la Sant&#xfffd;. Pour le Canada : Instituts de recherche en sant&#xfffd; du Canada, minist&#xfffd;re de la Sant&#xfffd; du Qu&#xfffd;bec, Fonds de recherche de Qu&#xfffd;bec-Sant&#xfffd; et Institut national d'excellence en sant&#xfffd; et en services sociaux.

Background

Description of the condition

Wounds are a prevalent clinical problem and a burden to many patients, resulting in pain, discomfort, longer hospital stay, and considerable economic costs for the healthcare system. Wounds are either acute or chronic, and can result from venous or arterial insufficiency, diabetes, burns, trauma, chronic pressure or surgery (O'Meara 2001; O'Meara 2008). If wounds become contaminated with bacteria or clinically infected, wound healing is likely to be impaired (Ovington 2003). This holds true for both acute and chronic wounds. In addition, wound infection is one of the most common surgical complications (Wilson 2004), and leads to significant mortality and morbidity. The focus in wound care, therefore, is to prevent wound infection and to promote wound healing.

Prevention of wound infection has always been a challenge. It was not until the late eighteenth century that micro-organisms were recognised as the cause of infectious diseases, and the principles of asepsis and hygiene began to be more fully understood (germ theory, as developed by Pasteur during the period 1860 to 1863, and Lister's development of

antiseptic surgery) (Abedon 1998). Good hygiene and use of antiseptics were initially considered effective strategies for the prevention of infection, including wound infection. Nurses developed stringent hygiene rules for dressing changes (Arrowsmith 2001; Fernandez 2008; Lethaby 2008; Moore 2005), and physicians experimented with various antiseptics. Some of these preventative actions have been investigated for their effectiveness in various types of wounds, including aseptic dressing techniques (Lawson 2003; Stotts 1997), hand-rubbing (Kac 2005; Moralejo 2003; Rossoff 1995; Rotter 1997; Tanner 2008), sterile gloving (Adeyemo 2005; Perelman 2004), shaving (Balthazar 1982; Tang 2001; Tanner 2006), and skin disinfection (Edwards 2004).

Description of the intervention

Several antiseptic dressings or agents are available, each claiming advantages regarding wound healing or prevention of wound infection. The effectiveness of antiseptics such as povidone iodine, chlorhexidine, alcohol, and silver-based compounds against microorganisms has been studied in vitro as well as in vivo (Brooks 2001; Kucan 1981; Lammers 1990; Nagl 2003; Vogt 2001; Wilson 1986). In particular, silver-based compounds (e.g. silver sulphadiazine cream (SSD)) have been widely used on burns since the 1960s in an attempt to overcome the problem of wound infection (Hartford 1981), and increasingly, silver-containing dressings and topical applications are being used to prevent infection in non-burn wounds such as leg ulcers (Karlsmark 2003), diabetic foot ulcers (Bergin 2006), fingertips (Jakobsen 1993), and pressure ulcers (Dowsett 2004). There is a growing number of silver-containing dressings and topical agents available for the treatment of skin wounds, including creams such as SSD, silver salts such as silver nitrate, alginates (e.g. Silvercel®), foams (e.g. Avance, Contreet Ag), hydrofibres (e.g. Aquacel® Ag), hydrocolloids (e.g. SSD/hydrocolloid, Contreet Ag) and polymeric films and meshes (e.g. Arglaes), including metallic, nanocrystalline (e.g. Acticoat®) or ionic silver (Aquacel® Ag).

How the intervention might work

Silver ions bind to the DNA of bacteria and bacterial spores, thus reducing their ability to replicate (Ballard 2002; Cooper 2004). Furthermore, silver is reported to be effective against all known bacteria, fungi and some viruses (Ovington 2001). Few bacteria have been shown to develop resistance to silver (resistance is a major problem associated with use of antibiotics). Silver has also been described as effective against malodour (Münter 2006). The various silver-containing dressings differ in the way the Ag^+ ions are released. Mostly, Ag^+ ions are released from the dressing through oxidation when the silver atoms come into contact with fluid. The silver can be incorporated as complex silver molecules in creams, ointments, hydrocolloids, hydrogels or foam dressings, which regulate the speed of delivery. Recent products have been produced in an attempt to ensure a more controlled and prolonged release of small (nanocrystalline) silver particles into the wound area. This nanocrystalline form releases silver ions faster than the normal silver materials, and, therefore, is claimed to have increased antimicrobial activity (Dunn 2004).

Why it is important to do this review

Silver-containing dressings have become popular despite the absence of a robust summary of the evidence for their role in preventing wound infection, and encouraging wound healing (Brett 2006). The effect of silver-containing wound dressings and topical applications as treatments for infected wounds is the subject of a related review (Vermeulen 2007), which identified little evidence of effectiveness. It is timely, therefore, to conduct a systematic review of the effects of silver-containing dressings and topical agents for the prevention of wound infection and the promotion of wound healing in uninfected wounds.

Objectives

To summarise the evidence for the effects of silver-containing dressings and topical agents compared with non-silver dressings and topical agents in terms of preventing of wound infections and/or promoting wound healing.

Methods

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials (RCTs), both published and unpublished, that evaluated the effects of silver-containing dressings and topical agents (used alone or in combination with other dressings/agents), in preventing infection or promoting the healing, or both, of uninfected wounds of any aetiology (cause) and in any care setting.

Types of participants

Men and women aged 18 years and over with any type of wound (not diagnosed as infected at baseline) in any care setting.

Types of interventions

Wound dressings and topical applications containing silver.

Eligible comparisons were:

1. topical silver-containing agents compared with topical agents without silver;
2. dressings containing silver compared with any dressings without silver (including dressings containing other antiseptics);
3. comparisons between alternative topical preparations of silver (e.g. SSD cream);
4. comparisons between alternative silver-containing dressings, including dose comparisons.

Types of outcome measures

Primary outcomes

1. Wound infection rate (Cutting 2005; Mangram 1999; McLaws 2000): infection was defined as localised pain and swelling, spreading erythema (redness), appearance of a purulent exudate, odour, and the presence of a positive bacterial culture with more than 10^5 colony-forming units per mm^3 tissue (Mangram 1999). Trial authors' definitions of infection (e.g. critical colonisation) were also accepted.
2. Wound healing: this was measured as time to complete healing, rate of change in wound area or volume, or both, or time to skin grafting.

We decided to promote the outcome of wound healing from a secondary to a primary outcome after publication of the review protocol, since it is the most important outcome for patients.

The outcome of time to skin grafting was also added post-protocol. Although the appropriateness of a wound for skin graft is a subjective judgement, skin grafting is only undertaken on clean and granulating wounds. We judged these post-protocol changes to be unlikely to introduce bias to the review.

Secondary outcomes

- Adverse events;
- rate of use of systemic antibiotics;
- pain;
- patient satisfaction;
- health related quality of life (HRQoL);
- length of hospital stay (LOS);
- costs.

Search methods for identification of studies

Electronic searches

The following electronic databases were searched:

1. Cochrane Wounds Group Specialised Register (Searched 6 May 2009);
2. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2009);
3. Ovid MEDLINE (1950 to April Week 4 2009);
4. Ovid EMBASE (1980 to 2009 Week 18);

5. EBSCO CINAHL (1982 to April Week 4 2009);
6. Digital dissertations at http://www.umi.com (to October 2008).

The following search strategy was used in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Wound Infection explode all trees
#2 (wound* NEAR/5 infect*):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Skin Ulcer explode all trees
#5 MeSH descriptor Diabetic Foot explode all trees
#6 MeSH descriptor Pressure Ulcer explode all trees
#7 MeSH descriptor Wounds, Penetrating explode all trees
#8 MeSH descriptor Lacerations explode all trees
#9 MeSH descriptor Burns explode all trees
#10 MeSH descriptor Bites and Stings explode all trees
#11 MeSH descriptor Surgical Wound Dehiscence explode all trees
#12 MeSH descriptor Wound Healing explode all trees
#13 (skin NEXT ulcer*) or (foot NEXT ulcer*) or (feet NEAR/5 ulcer*) or (diabetic NEXT foot) or (diabetic NEXT ulcer*) or (leg NEXT ulcer*) or (varicose NEXT ulcer*) or (varicose NEAR/5 wound*) or (venous NEXT ulcer*) or (stasis NEXT ulcer*) or (arterial NEXT ulcer*):ti,ab,kw
#14 ((ischaemic or ischemic) NEXT (wound* or ulcer*)):ti,ab,kw
#15 (bed NEXT sore*) or (pressure NEXT sore*) or (pressure NEXT ulcer*) or (decubitus NEXT ulcer*):ti,ab,kw
#16 (surgical NEXT wound*):ti,ab,kw
#17 ("gun" or guns or gunshot):ti,ab,kw
#18 ("stab" or stabs or stabbing):ti,ab,kw
#19 (burn or burns or scald*):ti,ab,kw
#20 (bite or bites or biting):ti,ab,kw
#21 laceration*:ti,ab,kw
#22 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23 (infect* or swell* or swollen or erythema* or odour or odor or hypertherm* or coloni* or contamin* or inflamm* or purulent or exudat* or devital*):ti,ab,kw
#24 (positive NEAR/5 culture*):ti,ab,kw
#25 (pain* NEAR/5 wound*):ti,ab,kw
#26 (dirty NEAR/5 wound*):ti,ab,kw
#27 (#23 OR #24 OR #25 OR #26)
#28 MeSH descriptor Silver explode all trees
#29 MeSH descriptor Silver Sulfadiazine explode all trees
#30 (silver* or contreet or acticoat or aquacel or avance or argent* or CuNova or urgotul or actisorb or arglaes or efodil or gyrosan or Nova-T or sulphadiazine or sulfadiazine or nanocrystalline or hydron or katomed or katoxyn or simanite or silverlon or sildimac or dimac or silvadene or agsd or ssd or flammazine or flamazine or flammacerium or sulplata or sulfaplata or silvazine or siax or oligorhine or ultradina):ti,ab,kw
#31 (#28 OR #29 OR #30)

#32 (#22 AND #27 AND #31)
#33 (#3 AND #31)
#34 (#32 OR #33)

The Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL search strategies can be found in Appendix 1, Appendix 2 and Appendix 3 respectively. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE (the sensitivity- and precision-maximising version (2008 revision)) Ovid format (**Lefebvre 2008**). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (**SIGN 2008**). No date or language restrictions were applied.

Searching other resources

We also contacted companies, manufacturers and distributors of silver dressings for details of unpublished and ongoing trials and scrutinised citations within all obtained trials and major review articles to identify any additional trials.

Data collection and analysis

Selection of studies

Two review authors (HV and DU) independently assessed the titles and abstracts of studies identified from the search in terms of their relevance and design. Full text versions of articles were obtained if, from the initial assessment, it was suggested they might meet the inclusion criteria. Another review author (either CV or MS) assessed those studies where there was disagreement.

Data extraction and management

Details of selected trials were extracted and summarised using a data extraction sheet. Data from trials published in duplicate were included only once. Data extraction was undertaken by one review author (CV), and checked for accuracy by a second (MS). Any discrepancy was resolved by discussion.

We extracted the following data.

- Characteristics of the trial (method of randomisation, setting, location of care, country, source of funding).
- Participants (number, type of wound(s), definition used to determine infection, wound size, duration of wound, length of follow-up, co-morbidities).
- Intervention (type of silver dressing or topical silver, dose of silver, frequency of dressing changes, co-interventions).
- Comparative intervention (type of dressing or topical application, dose of silver (where applicable), number of dressing changes, co-interventions).
- Primary outcomes: rate of wound infection; wound healing.

- Secondary outcomes: number and proportion of adverse events; rate of use of systemic antibiotics; pain; patient satisfaction; quality of life (QoL); length of hospital stay (LOS), and cost of treatment.

Assessment of risk of bias in included studies

Two review authors (CV and MS) independently assessed the risk of bias of each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (**Higgins 2008**). Any disagreement was referred to a third review author (DU) for adjudication.

The following criteria were applied, and graded, as follows:

1. Sequence generation: was the allocation sequence randomly generated? Yes/No/Unclear

2. Allocation concealment: was allocation adequately concealed? Yes/No/Unclear

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

- Was the participant blinded to the intervention? Yes/No/Unclear
- Was the care provider blinded to the intervention? Yes/No/Unclear
- Was the outcome assessor blinded to the intervention? Yes/No/Unclear

4. Incomplete outcome data: were incomplete outcome data adequately addressed?

- Was the drop-out rate described and acceptable (i.e. < 20%) Yes/No/Unclear
- Were all randomised participants analysed in the group to which they were allocated? (i.e. using intention-to-treat (ITT) analysis) Yes/No/Unclear

Other sources of potential bias:

- Were the groups similar at baseline for the most important prognostic indicators? Yes/No/Unclear
- Was the trial sponsored by a manufacturer who had a potential interest in the results? Yes/No/Unclear
- Were co-interventions avoided or given to all groups? Yes/No/Unclear

Appendix 4 outlines the criteria on which the judgements were based in detail. We completed the risk of bias table for each eligible study and present an assessment of risk of bias using a 'risk of bias summary figure'. This display of internal validity indicates the weight readers may give the results of each study.

Data synthesis

Quantitative data were entered into RevMan 5 by one review author (CV) and were checked by a second (MS).

Summary estimates of treatment effect (with 95% confidence intervals (CI)) were calculated for each outcome and every comparison. For continuous outcomes, the mean difference (MD) is presented. For dichotomous outcomes, the risk difference (RD) is presented; this is an absolute effect measure that expresses the difference between the experimental and control event rates, and allows calculation of the number needed to treat (NNT). We refrained from a sensitivity analysis because of the lack of replication of comparisons.

Subgroup analysis and investigation of heterogeneity

We conducted prespecified subgroup analyses for different wound types: burns, acute (e.g. surgical), chronic (e.g. ulcers) and mixed wound types.

Where studies evaluated similar interventions in a similar population we assessed statistical heterogeneity using the Chi^2 test and estimated the amount of heterogeneity using I^2. Where pooling seemed appropriate in view of clinical and methodological similarities between studies, we planned to use a fixed-effect model where I^2 was below 25%. We did not intend to pool studies where inter-study heterogeneity was high (I^2 greater than 75%), and we intended to use a random-effects model when I^2 was between 25% and 75% (**Higgins 2003**). We constructed a funnel plot to test for publication bias (**Egger 1997**).

Results

Description of studies

Results of the search

The search identified 313 titles of potential relevance. Discrepancy in judgement regarding suitability occurred in approximately 10% of all abstracts, but was resolved after adjudication by a third review author. After the first screening, 59 citations were considered potentially relevant. Full text articles were obtained and screened by two review authors independently against the inclusion criteria (Figure 1). One ongoing trial (two citations) was identified (**Serena 2008**) (Characteristics of ongoing studies), and four trials are awaiting assessment (**Chen 2006**; **Hirsch 2008**; **Li 2006**; **Wang 2008**) (Characteristics of studies awaiting classification).

Figure 1.

Open Figure

Flowchart

Trials were excluded if no infection or healing parameters were reported; or if silver-containing agents were not used in one of the treatment arms; if the trials were not RCTs; or if trials were published in abstract form only and no additional information could be retrieved from the trial authors to allow a decision regarding eligibility for inclusion to be made.

Included studies

Twenty-six trials (33 citations) met the inclusion criteria (Characteristics of included studies). All 26 were published between 1980 and 2008. Study sizes ranged from 14 to 465 participants, and a total of 2066 participants were enrolled. The majority of trials (i.e. 21 of the 26 (81%)) included fewer than 80 participants.

Burns were the most frequently studied wound type (20 out of 26 (77%)), and there was substantial variation between trials in the percentage of total body surface area (TBSA) and depth of burn studied (14 trials studied partial-thickness or superficial burns, six studied full-thickness burns). One trial included a range of types of wound (i.e. venous leg ulcers, partial-thickness burns and donor sites) (Hutchinson 1993). The remaining trials included minor soft tissue injuries (Dire 1995), open surgical or traumatic wounds (Jurczak 2007), venous leg ulcers (Wunderlich 1991), and diabetic foot ulcers (Jacobs 2008; Jude 2007).

Around half of the trials (14 out of 26 (54%)) compared 1% silver sulphadiazine (SSD) cream with another topical agent or dressing without silver (Afilalo 1992; Carneiro 2002; Dire 1995; Gerding 1988; Gerding 1990; Hansbrough 1995; Homann 2007; Hutchinson 1993; Jacobs 2008; Mashhood 2006; Noordenbos 1999; Soroff 1994; Subrahmanyam 1998; Wyatt 1990). Six trials (23%) compared 1% SSD with other silver-containing topical agents or dressings such as Acticoat®, Aquacel® Ag, Hydron® AgSD, Sildimac®, SSD-cerium nitrate, and SSD with chlorhexidine digluconate cream (Caruso 2006; De Gracia 2001; Fang 1987; Inman 1984; Miller 1990; Muangman 2006). One trial compared a silver-coated gauze dressing (Acticoat®) with another topical agent or dressing without silver (Innes 2001), and one trial compared a silver-coated gauze dressing (Acticoat®) with 0.5% silver nitrate solution (Tredget 1998). One trial compared an activated charcoal dressing containing silver (Actisorb Plus®) with other topical agents (Wunderlich 1991). Two trials compared a hydrofibre dressing, containing ionic silver (Aquacel®), with other topical agents (Jude 2007; Jurczak 2007). One trial compared a 0.5% silver nitrate solution with two other agents (Livingston 1990).

While most of the trials had two treatment arms, two trials had three treatment arms (Hutchinson 1993; Livingston 1990), and one trial had four treatment arms (Dire 1995).

All but two trials reported infection rates (Mashhood 2006; Soroff 1994), but the definitions of infection varied. Four trials (15%) defined infection as the presence of more than 10^5 organisms per gram of tissue (Inman 1984; Livingston 1990; Miller 1990; Tredget 1998); 15 trials (58%) accepted positive wound swabs or clinical signs of infection as evidence of infection. Seven trials (27%) provided no definition of infection (Afilalo 1992; Caruso 2006; Gerding 1990; Hansbrough 1995; Noordenbos 1999; Soroff 1994; Wyatt 1990). Twenty-one trials (81%) reported healing rates predominantly in terms of days to complete healing, or time to complete re-epithelialisation.

Pain was the secondary outcome measure most frequently reported. Three trials reported a sample size calculation (Caruso 2006; Jude 2007; Jurczak 2007). It was not clear whether informed consent was obtained in 11 trials, and in 13 trials the ethics review board approval was not reported.

Excluded studies

The Characteristics of excluded studies table provides details of the 18 trials (20 citations) that did not meet the inclusion criteria. Six trials were not RCTs (**De Boer 1981**; **Hadjiiski 1999**; **Munster 1980**; **Silver 2007**; **Stair 1986**; **Verdú 2004**), five trials were only published in abstract form with no further information forthcoming from the study authors (**Lanzara 2008**; **Molnar 2004**; **Planinsek 2007**; **Riesinger 2006**; **Yue Seng 2005**), in four trials wounds were already infected (**Huang 2007**; **Jorgensen 2006**; **Münter 2006**; **Subrahmanyam 1991**). The three remaining trials were excluded because they did not compare dressings (**Ganai 2002**); no data was reported on the effect of silver (**Guilbaud 1993**); and the silver compound was not the comparator under investigation rather it was the type of bag covering the hand (**Terrill 1991**).

Risk of bias in included studies

A summary of the assessment of risk of bias based on the criteria outlined in **Higgins 2008** is given in Figure 2 and Figure 3. Additionally, a brief descriptive analysis of the studies is provided below. In general, the overall methodological quality of the included trials was relatively poor, although a few trials were at low risk of bias.

Figure 2.

Open Figure

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 3.

Open Figure

Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Allocation

Treatment allocation was reported as random in all included studies, but the method of generating the randomisation sequence was not always clear. Only three trials reported their method of allocation sufficiently clearly to determine that allocation was concealed (**Gerding 1988**; **Gerding 1990**; **Jurczak 2007**).

In sixteen trials the unit of allocation was the individual patient (**Afilalo 1992**; **Carneiro 2002**; **Caruso 2006**; **De Gracia 2001**; **Dire 1995**; **Hutchinson 1993**; **Inman 1984**; **Jacobs 2008**; **Jude 2007**; **Jurczak 2007**; **Livingston 1990**; **Mashhood 2006**; **Muangman 2006**; **Subrahmanyam 1998**; **Wunderlich 1991**; **Wyatt 1990**), and in the remaining ten trials the unit of allocation

was the wound (Fang 1987; Gerding 1988; Gerding 1990; Hansbrough 1995; Homann 2007; Innes 2001; Miller 1990; Noordenbos 1999; Soroff 1994; Tredget 1998).

Blinding

One trial reported double-blinding with regard to the treatment given (Dire 1995), and two trials reported blinding of outcome assessors (Homann 2007; Wyatt 1990). All other trials did not report blinding sufficiently.

Incomplete outcome data

Drop-out rate described and acceptable?

Follow-up was less than 80% in three trials (Afilalo 1992; Hansbrough 1995; Hutchinson 1993), and unclear in two trials (Fang 1987; Inman 1984). In the remaining 21 trials there were either no dropouts, or the proportion of dropouts was less than 20%.

ITT analysis

We defined intention-to-treat (ITT) analysis as occurring when all randomised participants were reported or analysed in the group to which they were allocated for the most important time point of outcome measurement, irrespective of non-compliance and co-interventions. Thirteen trials conducted an ITT analysis, but thirteen either did not (Afilalo 1992; Caruso 2006; De Gracia 2001; Dire 1995; Gerding 1988; Gerding 1990; Homann 2007; Inman 1984; Soroff 1994; Wyatt 1990), or it was unclear whether this principle was applied (Fang 1987; Hutchinson 1993; Miller 1990).

Other potential sources of bias

Financial support

Twelve trial groups reported that they had received financial support from one or more companies. One trial reported that it did not received financial support (Noordenbos 1999), while the remaining 13 trials did not report this aspect at all.

Baseline comparability

In 22 trials the treatment groups appeared to be broadly comparable at baseline for wound size, aetiology and duration. Baseline comparability was unclear in one trial (Mashhood 2006), and in the remaining three trials the treatment groups were not comparable at baseline (Inman 1984; Jude 2007; Soroff 1994). In Inman 1984 scald burns were more frequent in the SSD group than in the SSD/chlorhexidine digluconate cream group; no adjustments in the analysis were made to compensate for this imbalance. In the trials Jude 2007 and Soroff 1994 the wound size at baseline seemed different between both groups, although their authors had stated no differences.

Co-interventions

The intervention of interest appeared to be the only systematic difference in the management of treatment groups within 23 of the included trials. In three trials it was unclear whether there was any imbalance in co-interventions delivered (Caruso 2006; Hutchinson 1993; Muangman 2006).

Analysis of time to healing as a continuous variable

It is not appropriate to analyse time-to-event data - such as time to 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 experienced the event (e.g. healing). 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. A hazard ratio is interpreted in a similar way to a risk ratio, as it describes how many times more (or less) likely a participant is to experience the event at a particular point in time if they receive the experimental rather than the control intervention. Inappropriate analysis of outcome data can introduce bias in the interpretation of the results.

Effects of interventions

Diverse interventions were evaluated in the 26 included trials, and, as a result, pooling was possible for only two trials. We have presented the results according to wound type, i.e. acute wounds (first burns and then other wounds), chronic wounds, and mixed wounds. Within each wound type we investigated the following comparisons:

1. topical silver-containing agents compared with topical agents or dressings without silver (SSD versus no silver);
2. dressings containing silver compared with any dressings without silver (silver versus no silver);
3. comparisons between alternative topical preparations of silver, e.g. SSD cream (SSD versus silver);
4. comparisons between alternative silver-containing dressings including dose comparisons (silver versus silver).

For each outcome and comparison the results are presented below. Trial details are summarised in the Characteristics of included studies.

We were only able to assess the possibility of publication bias for one comparison, SSD/silver versus no silver, where we performed a funnel plot for the outcome of infection rate (Figure 4). The funnel plot included 10 trials with 11 comparisons demonstrating symmetry, indicating no publication bias.

Figure 4.

Open Figure

Funnel plot of comparison: 12 SSD/SILVER vs NO SILVER, outcome: 12.1 Number of patients developed wound infection.

1. Acute wounds: burns

1.1 Topical silver-containing agents compared with topical agents without silver (silver sulphadiazine (SSD) versus no silver)

Eleven trials compared a topical application containing silver (1% silver sulphadiazine cream, SSD) with another topical agent or dressing not containing silver. Only two trials compared similar interventions and were pooled (**Gerding 1988**; **Gerding 1990**), while the remainder were considered separately.

1.1.1 SSD cream compared with biosynthetic dressing (Biobrane®) (two trials)

Gerding 1988 enrolled 43 patients with 50 acute partial-thickness burns, and **Gerding 1990** enrolled 52 patients with 56 acute partial-thickness thermal wounds in two trials comparing 1% SSD cream with a biosynthetic dressing.

Primary outcome: infection rate

Gerding 1988 defined wound infection on clinical grounds in conjunction with semi-quantitative surface swab cultures. In this trial a mixture of paired and unpaired data were presented; seven patients were used as matched controls by randomising the paired wounds to treatment with opposite modalities. **Gerding 1990** defined wound infection on clinical grounds, but did not give a detailed description. In **Gerding 1988** 4/23 wounds in the SSD group, and 4/27 in the biosynthetic dressing group were judged to be infected. While in **Gerding 1990**, 2/26 wounds in the SSD group and 3/30 in the biosynthetic dressing group were judged to be infected. Pooling these two trials (I^2 = 0%) using a fixed-effect model showed no statistically significant difference between groups (RD 0.00; 95% CI -0.12 to 0.12) (Analysis 1.1).

Primary outcome: wound healing rate

Both Gerding trials reported the standard error of the mean; the standard deviation (SD) was calculated for our analysis. In both trials, healing was defined as complete re-epithelialisation. **Gerding 1988** reported the mean time to complete healing as 21.3 days (SD 11.03) in the SSD group, and 13.7 days (SD 6.75) in the biosynthetic dressing group, while **Gerding 1990** reported the mean time to complete healing as 15.0 days (SD 6.12) in the SSD group and 10.6 days (SD 4.38) in the biosynthetic dressing group. Both trials reported a statistically significant difference in favour of the biosynthetic dressing, however, these original trials analysed time to healing (a time-to-event outcome) as a continuous variable, which is inappropriate and potentially misleading (since it cannot take account of people who did not heal). We did not have access to the original data and therefore could not re-analyse it.

Secondary outcome: pain

Both trials measured pain on a scale from one (none) to five (severe). The pain score was statistically significantly lower in the biosynthetic dressing groups (pooled, fixed-effect, MD 1.41; 95% CI 0.99 to 1.83). Both trials reported standard error of the mean, we calculated the SD for the purposes of analysis (Analysis 1.2).

Secondary outcome: costs

Gerding 1988 reported no statistically significant differences in the mean material costs, based on the total cost of topical cream, dressing materials and medications used in each case. Nursing costs were $238 in the SSD group and $71 in the biosynthetic dressing group (P value < 0.001). No SDs were reported; therefore no mean difference could be calculated. Gerding 1990 reported that mean costs, based on hospital charges, were significantly lower in the biosynthetic dressing group (MD 70; 95% CI 15.5 to 124.5) (Analysis 1.3).

1.1.2 SSD cream compared with biosynthetic dressing with human fibroblast skin substitute (Transcyte on Biobrane mesh) (one trial)

Noordenbos 1999 enrolled 14 patients, each with two partial-thickness burns of similar size, and compared SSD cream on one burn with a biosynthetic dressing combined with human fibroblasts on the other.

Primary outcome: infection rate

The trial report defined wound infection as cellulitis. Six of the 14 burns in the SSD group, and none in the biosynthetic dressing group developed cellulitis. The number of burns that developed cellulitis was significantly lower in the biosynthetic dressing group (RD 0.43; 95% CI 0.16 to 0.70). (Analysis 2.1). The number needed to treat (NNT) with biosynthetic dressings was two, in order to prevent one additional patient developing cellulitis.

Primary outcome: wound healing rate

The report defined healing as 90% re-epithelialisation. The mean time to 90% healing in the SSD group was 18.14 days, compared to 11.14 days in the biosynthetic dressing group. The mean time to healing was significantly shorter in the biosynthetic dressing group. Time to healing is a time-to-event outcome, however, the trialists did not analyse it as such and, therefore, this effect estimate may be inaccurate.

1.1.3 SSD cream with chlorhexidine-impregnated gauze (Bactigras®) compared with hydrocolloid dressing (Duoderm® Hydroactive) (one trial)

Afilalo 1992 enrolled 48 patients with partial-thickness burns and compared a layer of SSD cream covered by chlorhexidine-impregnated gauze (Bactigras) with a hydrocolloid dressing (Duoderm Hydroactive).

Primary outcome: infection rate

Wound infection was not defined in this trial, but was based on the unblinded, subjective opinion of the investigator or the plastic surgeon, and, therefore, was subject to bias. One

participant out of 24 in the SSD with chlorhexidine-impregnated gauze group developed an infection, and 2/24 in the hydrocolloid dressing group. There was no statistically significant difference in the number of patients that developed a wound infection (RD: -0.04, 95% CI -0.18 to 0.09) (Analysis 3.1).

Primary outcome: wound healing rate

The trialists defined healing as complete re-epithelialisation. The mean time to complete healing was 11.2 days in the SSD with chlorhexidine-impregnated gauze group, and 10.7 days in the hydrocolloid group. There was no statistically significant difference in the mean time to complete healing. Again, this time-to-event outcome had been inappropriately analysed as a continuous variable rather than by survival analysis, and, therefore, was inaccurate.

Secondary outcome: pain

The pain scores at baseline and the second visit (24 hours after the initial visit) were assessed. Pain was measured on a scale from 1 to 10. There was no statistically significant difference in the groups for the median pain score at baseline or at the second visit.

Secondary outcome: patient satisfaction

Overall satisfaction was reported as excellent or satisfactory for all patients, and there was no statistically significant difference between the groups.

1.1.4 SSD cream compared with hydrocolloid dressing (DuoDerm® Hydroactive) (one trial)

Wyatt 1990 enrolled 50 patients with minor, second-degree burn injuries in order to compare the effects of SSD cream with hydrocolloid dressings.

Primary outcome: infection rate

Wound infection was defined on clinical grounds, but how exactly was unclear. None of the patients developed a wound infection (RD 0.00; 95% CI -0.09 to 0.09) (Analysis 4.1).

Primary outcome: wound healing rate

Healing was defined as complete healing. The mean time to complete healing was 15.59 days in the SSD group, and 10.23 days in the hydrocolloid dressing group. The mean time to complete healing was significantly shorter in the hydrocolloid group. Again, this time-to-event outcome was inappropriately analysed as a continuous variable, and is, therefore, inaccurate.

Secondary outcome: pain

Pain was measured on a scale from one (no pain) to 10 (maximum pain). The mean pain score was 2.28 in the SSD group, and 1.09 in the hydrocolloid dressing group. The mean reported pain score was significantly lower in the hydrocolloid group (MD 1.19; 95% CI 0.56 to 1.82) (Analysis 4.2).

1.1.5 SSD cream compared with honey (two trials)

Mashhood 2006 enrolled 50 patients with superficial and partial-thickness burns. Subrahmanyam 1998 enrolled 50 patients with superficial thermal burns. Both compared the effects of SSD cream with pure, unprocessed, undiluted honey. Mashhood 2006 described it as 'traditional medicine honey' and Subrahmanyam 1998 stated only that the honey was obtained from hives.

Primary outcome: infection rate

While Mashhood 2006 defined wound infection on clinical grounds, and via swabs for bacterial density and culture, infection rate was not reported. For Subrahmanyam 1998 wound infection was defined clinically (presence of pus or slough), and by means of bacterial cultures. There was no statistically significant difference between the two groups in this trial with respect to clinical evidence of wound infection in the short term (day 7), but in the longer term (day 21), the honey group demonstrated significantly fewer infections (RD 0.20; 95% CI 0.03 to 0.37) (Analysis 5.1). The NNT with honey was five, in order to prevent one wound infection.

Primary outcome: wound healing rate

In the Mashhood 2006 trial healing was defined as 100% epithelialisation. The number of wounds completely healed was reported after two, four and six weeks' treatment. At the two and four weeks' treatment time-points, the honey group did significantly better. The number of wounds completely healed after two weeks was 5/25 in the SSD group and 13/25 in the honey treated group (RD -0.32; 95% CI -0.57 to -0.07) (Analysis 5.2). The number of wounds completely healed after four weeks was 15/25 in the SSD group and 25/25 in the honey treated group (RD -0.40; 95% CI -0.60 to -0.20). The NNT with honey was three, in order to promote the healing of one extra wound. All wounds were completely healed after six weeks.

In the Subrahmanyam 1998 trial healing was defined as "patients with clinical and histological evidence of epithelialisation". The number of patients with clinical evidence of wound healing was reported on days 21 and 30, with histological evidence of wound healing reported for days 7 and 21. There was no statistically significant difference between the two groups for the clinical evidence on day 30. For the other time points, the honey group performed significantly better than the SSD group. The number of patients with clinical evidence of wound healing on day 21 was 21/25 in the SSD group and 25/25 in the honey group (RD -0.16; 95% CI -0.31 to -0.01) (Analysis 5.3). The NNT with honey was six, in order to promote the healing of one extra wound.

Secondary outcome: pain

Mashhood 2006 reported pain on the basis of the number of participants who were free of pain after one, two, three and four weeks of treatment. While there was no statistically significant difference between the two groups at the start and end of the trial (i.e. weeks 1 and 4), there was a statistically significant difference between groups in the middle (i.e. weeks 2 and 3), with more patients free of pain in the honey group (RD -0.36; 95% CI -0.61 to -0.11) (Analysis 5.4). We calculated the Mann-Whitney U test: z = -2.823, P value = 0.005.

Secondary outcome: costs

Mashhood 2006 reported the cost of dressing material for one percent of body surface area burnt. The cost of dressing material for each percent of body surface area burnt was PKR 0.10/2 g for SSD, and PKR 0.75/5 ml for honey. No SDs were reported, so no mean difference could be calculated.

1.1.6 SSD cream compared with liposome hydrogel containing polyvinyl-pyrrolidone iodine (PVP-I) (one trial)

Homann 2007 enrolled 47 patients with 94 partial-thickness burns (degree IIa).

Primary outcome: infection rate

Wound infection was defined using clinical criteria such as inflammation. When wound infection was suspected, wound swabs were taken for microbiological investigation. None of the patients developed a wound infection (RD 0.00; 95% CI -0.04 to 0.04) (Analysis 6.1).

Primary outcome: wound healing rate

Healing was defined as 95% to 100% re-epithelialisation. There was no statistically significant difference in the mean time to complete healing (11.3 days for the SSD group, 9.9 days for the liposome hydrogel containing polyvinyl-pyrrolidone iodine (PVP-I) group). Again, this time-to-event outcome was inappropriately analysed as a continuous variable rather than by means of survival analysis.

Secondary outcome: adverse events

There was no statistically significant difference between the groups with respect to wound necrosis and wound itching (RD 0.02; 95% CI -0.05 to 0.10) (Analysis 6.2).

Secondary outcome: pain

Pain was measured, but the method the trialists used was not reported. There was no statistically significant difference in the number of patients reporting wound pain (RD -0.02; 95% CI -0.16 to 0.12) (Analysis 6.3).

1.1.7 SSD cream compared with collagenase ointment applied with polymyxin B sulfate/bacitrin (Santyl®) (two trials)

Soroff 1994 enrolled 15 patients with 30 partial-thickness burns. Hansbrough 1995 enrolled 79 patients with 158 partial-thickness burns.

Primary outcome: infection rate

Soroff 1994 did not report infection rate. Hansbrough 1995 did not define wound infection, but the number of patients with cellulitis were reported. There was no statistically significant difference in the number of patients who developed cellulitis between the groups (11/79 in the SSD group; 12/79 in the collagenase ointment applied with polymyxin B sulfate/bacitrin (Santyl®) group), (RD -0.01; 95% CI -0.12 to 0.10) (Analysis 7.1).

Primary outcome: wound healing rate

Soroff 1994 defined healing as complete re-epithelialisation and time to a clean wound bed (determined by the disappearance of injured dermis), while Hansbrough 1995 defined healing as complete re-epithelialisation and time to a clean wound bed (determined by the absence of retained dermis). In both trials, healing was significantly better in the Santyl® group. In Soroff 1994 the median time to complete epithelialisation was 15 days in the SSD group and 10 days in the Santyl® group (P value 0.00007). In the Hansbrough 1995 trial, the mean time to epithelial closure was 22.1 days in the SSD group, and 19.0 days in the Santyl® group (no SD was reported) (P value < 0.001). Again, this time-to-event outcome was inappropriately analysed as a continuous variable.

Secondary outcome: pain and adverse events

Hansbrough 1995 reported pain as an adverse event and described it as burning or stinging. The number of patients reporting pain was significantly lower in the SSD group (RD -0.19; 95% CI -0.31 to -0.07) (Analysis 7.2). The NNT with SSD was five, in order to prevent one patient from experiencing pain. Soroff 1994 reported three patients who described a burning sensation at the wound site in the Santyl® group.

1.1.8 SSD cream/chlorhexidine (Silverex) compared with diphenyldantoin (Phenytoin) (one trial)

Carneiro 2002 enrolled 64 patients with second degree burns.

Primary outcome:infection rate

Bacterial cultures were obtained on days 5 and 10. Negative cultures were defined as the absence of pathogens. The number of positive bacterial cultures on both days was significantly lower in the diphenyldantoin group. At day 10 15/32 cultures were positive in the SSD/chlorhexidine group compared with 3/32 in the diphenyldantoin group (RD 0.38; 95% CI 0.17 to 0.58) (Analysis 8.1).The NNT with diphenyldantoin was three, in order to prevent one additional positive culture.

Primary outcome: wound healing rate

Wound healing was defined as complete healing. There was no statistically significant difference between the groups in the rate of complete healing; 24/32 wounds in the SSD/chlorhexidine group were completely healed, and 29/32 in the diphenyldantoin group (RD -0.16; 95% CI -0.34 to 0.02) (Analysis 8.2).

Secondary outcome: pain

Pain was measured in categories: moderate to severe pain or discomfort; mild; or no pain or discomfort. Statistically significantly more patients reported moderate to severe pain or discomfort in the SSD/chlorhexidine group (17/32), than in the diphenyldantoin group (7/32) (RD 0.31; 95% CI 0.09 to 0.54) (Analysis 8.3).

Secondary outcome: length of hospital stay

The mean length of hospital stay was 16.3 days in the SSD/chlorhexidine group and 14.2 days in the diphenyldantoin group (not statistically significant). No SDs were reported; therefore no mean difference could be calculated.

Summary for burns: SSD versus no silver

Eleven trials compared SSD with a range of non-silver comparators in participants with superficial or partial-thickness burns. Only four of the eleven trials reported adequate sequence generation (Afilalo 1992; Gerding 1988; Gerding 1990; Homann 2007), and only two described allocation concealment (Gerding 1988; Gerding 1990), therefore these trials were generally of at least moderate, (or unknown), risk of bias and the findings should be interpreted with this in mind.

- Infection rate was reported in nine trials. Six trials found no statistically significant differences (Afilalo 1992; Gerding 1988; Gerding 1990; Hansbrough 1995; Homann 2007; Wyatt 1990), and three trials found a statistically significant increase in infection with SSD compared with the non-silver comparators (Carneiro 2002; Noordenbos 1999; Subrahmanyam 1998).
- Time to complete healing was reported in eight trials, though in each trial this had been inappropriately analysed as a continuous variable ("mean time") rather than as a time-to-event outcome. Six trials showed a statistically significant difference in favour of non-silver dressings (Gerding 1988; Gerding 1990; Hansbrough 1995; Noordenbos 1999; Soroff 1994; Wyatt 1990), and two trials showed no differences (Afilalo 1992; Homann 2007), however, these data would be inaccurate if not all the participants were followed to complete healing.
- The proportions of wounds healed and unhealed at specific time points were reported in three trials. Two trials showed a statistically significant difference in favour of non-silver dressings (Mashhood 2006; Subrahmanyam 1998), and one trial showed no difference (Carneiro 2002).
- Pain was reported in eight trials. While one trial showed a statistically significant difference in favour of SSD (Hansbrough 1995), five trials showed a statistically significant difference is favour of non-silver dressings (Carneiro 2002; Gerding 1988; Gerding 1990; Mashhood 2006; Wyatt 1990), and two trials showed no difference (Afilalo 1992; Homann 2007).

1.2 Dressings containing silver compared with any dressings without silver (silver versus no silver)

1.2.1 Nanocrystalline silver coated dressing (Acticoat®) compared with hydrophilic polyurethane dressing (Allevyn®) (one trial)

Innes 2001 enrolled 17 patients, with 18 paired adjacent burn sites, who required a split-thickness skin graft.

Primary outcome: infection rate

Wound infection was defined clinically by criteria such as erythema, induration, purulent discharge, and malodour. Every third day, swabs were taken and were rated as 1 (light growth), 2 (medium growth), or 3 (heavy bacterial growth). There was no statistically significant difference in the number of patients who developed an infection, or in the number of positive cultures at any time point. None of the patients developed a wound infection (RD 0.00; 95% CI -0.11 to 0.11) (Analysis 9.1).

Primary outcome: wound healing rate

Healing was defined as 90% or more re-epithelialisation. Healing was significantly faster in the hydrophilic polyurethane dressing group (Allevyn®) (14.5 days for the nanocrystalline silver coated dressing (Acticoat®) group, and 9.1 days for the Allevyn® group). Again, this time-to-event outcome was inappropriately analysed as a continuous variable. The number of wounds healed by day of discharge showed a statistical significance in favour of Allevyn® (RD -0.69; 95% CI -0.92 to -0.45) (Analysis 9.2). The NNT with Allevyn® was six, in order to promote one additional wound to heal.

Secondary outcome: cost

The mean cost per cm^2 was USD 0.088 in the Acticoat® group and USD 0.059 in the Allevyn® group. No SDs were reported, so no mean difference could be calculated.

1.2.2 Silver nitrate (0.5%) compared with Ringer's lactate (one trial)

Livingston 1990 enrolled 52 patients with burns who required skin grafting. The trial had three treatment groups; silver nitrate (0.5%) (19 participants), Ringer's lactate (15 participants), and neomycin with bacitracin (18 participants).

Primary outcome: infection rate

Wound infection was defined as present when there were more than 10^5 organisms per gram of tissue. The silver nitrate group showed significantly fewer infections (2/19 infections in the silver nitrate group; 8/15 in the Ringer's lactate group) (RD -0.43; 95% CI -0.72 to -0.14) (Analysis 10.1). The NNT with silver nitrate was two, in order to prevent one wound infection. Mean time to development of wound infection was significantly shorter in the Ringer's lactate group (13.7 days in the silver nitrate group, versus 5.5 days in the Ringer's lactate group). Again, the outcome was inappropriately analysed as a continuous variable.

Secondary outcome: length of hospital stay

Length of hospital stay was only reported for subgroups, and was reported as being significantly shorter for patients in the silver nitrate group with wounds covering 20% to 40% TBSA.

1.2.3 Silver nitrate (0.5%) compared with neomycin with bacitracin (one trial)

In the same trial (**Livingston 1990**), the comparison arm of silver nitrate (0.5%) (19 participants) was compared with the neomycin with bacitracin arm (18 participants).

Primary outcome: infection rate

Wound infection was defined as present when there were more than 10^5 organisms per gram of tissue. There was no statistically significant difference in the number of patients who developed an infection (2/19 in the silver nitrate group and 6/18 in the neomycin with bacitracin group) (RD -0.23; 95% CI -0.49 to 0.03) (Analysis 11.1). Mean time to development of wound infection was significantly shorter in the neomycin with bacitracin group (13.7 days in the silver nitrate group versus 5.5 days in the neomycin with bacitracin group). Again, this time-to-event outcome was inappropriately analysed as a continuous variable.

Secondary outcome: length of hospital stay

Length of hospital stay was only reported for subgroups, and there were no statistically significant differences between them.

Summary for burns: silver versus no silver

Both trials investigated burns requiring skin grafting. Only one of the trials reported adequate sequence generation (**Livingston 1990**), and neither trial reported adequate allocation concealment.

- Infection rate was reported in both trials with a total of three dressing comparisons. Two comparisons showed no differences (**Innes 2001**; **Livingston 1990**), and one comparison showed a statistically significant difference in favour of silver nitrate (**Livingston 1990**).
- Time to complete healing was reported in one trial (**Innes 2001**), which showed a statistically significant difference in favour of non-silver dressings however it had been wrongly analysed as a continuous variable (with mean healing time calculated) whereas time to healing is a time-to-event outcome which should be subject to analysis by survival methods.
- The number of wounds healed was reported in one trial (**Innes 2001**), which showed a statistically significant difference in favour of non-silver dressings.

An overview of the number of patients who developed a wound infection for all trials comparing SSD/silver versus no silver is given in Analysis 12.1. A funnel plot (Figure 4) revealed no evidence of publication bias for wound infection.

1.3 Comparisons between alternative topical preparations of silver, e.g. SSD cream (SSD versus silver)

1.3.1 SSD cream compared with nanocrystalline silver-coated dressing (Acticoat®) (one trial)

Muangman 2006 enrolled 50 patients, with partial-thickness burns.

Primary outcome: infection rate

Wound infection was defined as the presence of erythema, induration, purulent discharge and malodour. There was no statistically significant difference in the number of patients who developed an infection (4/25 in the SSD group; 3/25 in the nanocrystalline silver-coated dressing (Acticoat®) group) (RD 0.04; 95% CI -0.15 to 0.23) (Analysis 13.1).

Secondary outcome: pain

Pain was measured on a visual analogue pain scale from 1 (no pain) to 10 (extreme pain). Background pain, between dressings, was significantly lower in the Acticoat® group (5 in the SSD group, 4 in the Acticoat® group) (MD 1.00; 95% CI 0.64 to 1.36) (Analysis 13.2).

Secondary outcome: length of hospital stay

The mean length of hospital stay was 21 days in both groups (MD 0.00; 95% CI -6.43 to 6.43) (Analysis 13.3).

1.3.2 SSD cream compared with hydrofibre dressing containing ionic silver (Aquacel® Ag) (one trial)

Caruso 2006 enrolled 82 patients, with superficial, mid-dermal or mixed partial-thickness burns.

Primary outcome: infection rate

Wound infection was not defined. There was no statistically significant difference in the number of patients who developed an infection (6/40 in the SSD group; 8/42 in the hydrofibre dressing containing ionic silver (Aquacel® Ag) group) (RD -0.04; 95% CI -0.20 to 0.12) (Analysis 14.1).

Primary outcome: wound healing rate

Healing was defined as either 100% re-epithelialisation, including open areas; less than 1 cm fully re-epithelialised area; or re-epithelialisation less than 100% but to the extent that surgical interventions were not required. There were no differences in healing within 21 days (24/40 in the SSD group; 31/42 in the Aquacel® Ag group) (RD -0.14; 95% CI -0.34 to 0.06) (Analysis 14.2). For the time to complete re-epithelialisation only median values were given: 17 days in the SSD group and 16 days in the Aquacel® Ag group (P value 0.517). No MD could be calculated. The time to complete re-epithelialisation was analyzed using life table methods. Kaplan Meier survival curves for each treatment group were plotted.

Secondary outcome: adverse events

Adverse events were defined as any untoward medical occurrence that was new or worsened during the trial. There were no statistically significant differences between SSD and Aquacel® Ag for adverse events (RD -0.03; 95% CI -0.24 to 0.19) (Analysis 14.3).

Secondary outcome: use of systemic antibiotics

There was no statistically significant difference between groups in the number of patients that used antibiotics (RD -0.04; 95% CI -0.20 to 0.12) (Analysis 14.4).

Secondary outcome: pain

Pain was measured on a visual analogue scale from 1 (no pain) to 10 (extreme pain). The mean pain score per week was 4.77 in the SSD group and 3.63 in the Aquacel® Ag group (P value 0.003). No SDs were reported, so no mean difference could be calculated. Pain was also measured on an observational scale. Patients were able to grade the extent to which the dressings reduced pain from "extremely well" to "not very well at all". Patients reported statistically significantly less pain associated with the Aquacel® Ag dressing (P value 0.002).

Secondary outcome: costs

Different components of costs were measured and combined later to be able to calculate cost effectiveness. For most components no SDs were reported, so no mean difference could be calculated. All costs were expressed as US dollars. There was no statistically significant difference in the mean total costs of clinical care ($1181 for the SSD group and $1040 for the Aquacel® Ag group) (MD $141; 95% CI -216 to 498) (Analysis 14.5). The average cost effectiveness, calculated from the total cost of clinical care, divided by the proportion of patients with full epithelialisation, was $1968 (95% CI $1483 to $2690) in the SSD group and $1409 (95% CI $1050 to $1858) in the Aquacel® Ag group.

1.3.3 SSD cream compared with synthetic dressing containing silver (Hydron-AgSD) (one trial)

Fang 1987 enrolled 27 patients with 54 second degree burns, with areas of similar size and injury matched.

Primary outcome: infection rate

Wound infection was determined by taking swabs for bacterial colonisation and reporting on the number of positive cultures. The time-point(s) at which the swabs were taken was not reported. The number of positive culture swabs was significantly higher in the SSD group (46/98 swabs in the SSD group; 32/98 in the synthetic dressing containing silver (Hydron-AgSD) group) (RD 0.14; 95% CI 0.01 to 0.28) (Analysis 15.1). The NNT with Hydron-AgSD was seven, in order to prevent one positive culture.

Primary outcome: wound healing rate

No definition of healing was reported. Fang 1987 stated that wounds healed equally in both groups, no data were reported to support this statement.

1.3.4 SSD cream (Flamazine®) compared with 1% SSD plus 0.2% chlorhexidine digluconate cream (Silvazine®) (one trial)

Inman 1984 enrolled 121 patients with fresh, full-thickness burns.

Primary outcome: infection rate

Wound infection was defined by clinical criteria such as softening of eschar, erythema, or colour change accompanied with a quantitative culture with 10^5 or more organisms per gram of burn tissue. There was no statistically significant difference between the groups in the number of patients that developed an infection (12/67 in the SSD group; 10/54 in the SSD with chlorhexidine digluconate cream group) (RD -0.01; 95% CI -0.14 to 0.13) (Analysis 16.1).

Secondary outcome: use of systemic antibiotics

There was no statistically significant difference between groups in the use of antibiotics during the in-hospital period (RD 0.10; 95% CI -0.03 to 0.24) (Analysis 16.2).

Secondary outcome: pain

Pain was not defined. There was no statistically significant difference between groups in the number of patients who experienced extreme pain at the time when cream was being applied (RD -0.02; 95% CI -0.07 to 0.03) (Analysis 16.3).

1.3.5 SSD cream compared with SSD cream containing cerium nitrate (SSD-CN) (one trial)

De Gracia 2001 enrolled 60 patients with moderate and severe burns.

Primary outcome: infection rate

In the De Gracia 2001 trial, wound sepsis was defined as wound deterioration with severe inflammation. Wound biopsies were taken and bacterial growth on culture media was reported. De Gracia 2001 found no statistically significant difference between the groups for any infection outcome. The number of patients developing sepsis after ten days was 3/30 in the SSD group and 0/30 in the SSD-cerium nitrate (SSD-CN) group (RD 0.10; 95% CI -0.02 to 0.22) (Analysis 17.1).

Primary outcome: wound healing rate

The De Gracia 2001 trial defined healing as complete re-epithelialisation, or wounds being ready for skin grafting. Re-epithelialisation was categorised into four groups: 'quick' (0 to 14 days), 'moderate' (15 to 21 days), 'slow' (22 to 35 days), and 'very slow' (more than 35 days). We calculated the Chi^2 statistic as 5.233, and the P value as 0.155. There were no statistically significant differences between the groups.

The mean number of days until complete re-epithelialisation was significantly shorter in the SSD-CN nitrate group (25.1 days in the SSD group; 17.2 days in the SSD-CN group). The mean time to readiness to accept a skin graft was significantly shorter in the SSD-CN group (24.6 days in the SSD group (17 participants); 13.6 days in the SSD-CN group (nine participants).

Once again, these were time-to-event outcomes that had been inappropriately analysed as continuous data.

Secondary outcome: adverse events

In the **De Gracia 2001** trial skin rashes were observed in both groups, but did not differ significantly between the groups. A subjective stinging effect was significantly higher in the SSD-CN group (RD -0.37; 95% CI -0.58 to -0.15) (Analysis 17.2). The NNT with SSD was three, in order to prevent one participant experiencing a stinging effect.

Secondary outcome: use of systemic antibiotics

There was no statistically significant difference between groups in the number of patients who received oral antibiotics for at least seven days (RD -0.03; 95% CI -0.20 to 0.13) (Analysis 17.3).

Secondary outcome: length of hospital stay

There was no statistically significant difference between groups in the mean length of hospital stay (MD 7.4; 95% CI -1.69 to 16.49) (Analysis 17.4).

1.3.6 SSD cream compared with Dimac containing SSD (Sildimac®) (one trial)

Miller 1990 enrolled 59 patients with two separate, comparable, sustained full-thickness burns.

Primary outcome: infection rate

Wound infection was defined as present when there were more than10^5 organisms per gram of tissue. Wound biopsies were obtained before treatment, and every seven days thereafter until the last day of treatment. Positive cultures were defined as any growth of any organism. Wound infection was based on clinical judgement. There was no statistically significant difference between the groups in the number of patients who developed an infection at any time point. Clinical wound infection occurred in 2/51 patients in the SSD group and 1/51 patients in the Dimac SSD group (RD 0.02; 95% CI -0.05 to 0.09) (Analysis 18.1).

Secondary outcome: adverse events

There was no statistically significant difference between groups in the number of patients reporting local adverse effects (such as burning and stinging) (RD 0.03; 95% CI -0.10 to 0.16) (Analysis 18.2). Six patients reported adverse effects at both the SSD site and the Dimac SSD site.

Summary for burns: SSD versus silver

Two trials investigated partial-thickness burns and four trials full-thickness or severe burns. Only two out of six trial reports described adequate sequence generation (**Caruso 2006**; **Miller 1990**), and none described adequate allocation concealment.

- Infection rates were reported in six trials. No statistically significant differences were found in five trials (Caruso 2006; De Gracia 2001; Inman 1984; Miller 1990; Muangman 2006), though one trial showed a statistically significant difference for the number of positive-culture swabs in favour of the synthetic silver dressings (Fang 1987).
- Time to complete healing was reported in two trials. One trial used appropriate analysis methods and showed no statistically significant differences (Caruso 2006), and the second trial analysed a time-to-event outcome (time to complete healing) inappropriately as a continuous variable (De Gracia 2001) and showed a statistical significance in favour of the SSD-cerium nitrate group.
- The number of wounds healed was reported in three trials. None of the trials showed statistically significant differences (Caruso 2006; De Gracia 2001; Fang 1987).
- Pain was reported in three trials. One trial showed no statistically significant differences (Inman 1984), while two trials showed a statistically significant difference in favour of the silver-containing dressings Acticoat® and Aquacel® Ag (Caruso 2006; Muangman 2006).

1.4 Comparisons between alternative silver-containing dressings including dose comparisons (silver versus silver)

1.4.1 Nanocrystalline silver-coated dressing (Acticoat®) compared with fine-mesh gauze with silver nitrate (0.5%) (one trial)

Tredget 1998 enrolled 30 patients with 60 deep partial- and full-thickness burns.

Primary outcome: infection rate

Wound infection was defined as present when there were more than 10^5 organisms per gram of tissue present. Bacteraemia was defined as the presence of the same bacterium isolated from the blood and the burn wound at concentrations of more than 10^5 organisms per gram of tissue. Significantly fewer patients developed a wound infection in the nanocrystalline silver-coated (Acticoat®) group (5/17 in the Acticoat® group; 16/17 in the fine-mesh gauze with silver nitrate group) (RD -0.65; 95% CI -0.89 to -0.40) (Analysis 19.1). The NNT with nanocrystalline silver was two, in order to prevent one infection. There was no statistically significant difference between groups in the number of patients who developed bacteraemia (1/17 in the Acticoat® group and 5/17 fine-mesh gauze with silver nitrate group) (RD -0.24; 95% CI -0.48 to 0.01) (Analysis 19.2).

Primary outcome: wound healing rate

Healing was defined as complete re-epithelialisation; the authors reported there was no difference between the treatments, but no data were reported to support this statement.

Secondary outcome: pain

Pain was measured on a visual analogue scale from 1 (not painful) to 5 (very painful). Only the mean pain score on dressing removal was significantly lower in the Acticoat® group, but not the mean overall pain score (MD -0.28; 95% CI -0.93 to 0.37) (Analysis 19.3).

2. Acute wounds: other wounds

2.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)

Dire 1995 enrolled 465 patients with minor, uncomplicated, soft-tissue wounds requiring sutures into a study that compared three antimicrobial regimens with paraffin-impregnated gauze. Data from 39 enrolled participants were excluded for protocol violations, so only 426 participants were included in the analysis (i.e. not analysed by intention-to-treat). The trial had four treatment groups in which the following numbers of participants completed the trial; SSD cream (99 participants), bacitracin zinc ointment (109 participants), neomycin sulphate (110 participants), and petrolatum (108 participants). We compared each of these antimicrobial alternatives with SSD cream.

Wound infection was defined as any subjective or objective sign or symptom of infection, e.g. fever, erythema, oedema, induration, tenderness, heat, exudate, adenopathy, and lymphangitis. Wounds were classified into one of five categories based upon clinical assessment, ranging from no signs of infection (384 participants), simple stitch abscess (25 participants), surrounding cellulitis (14 participants), accompanying lymphangitis (three participants), and systemic symptoms (no participants).

2.1.1 SSD cream compared with bacitracin zinc ointment

Primary outcome: infection rate

There was no statistically significant difference between groups in the number of patients who developed wound infections (12/99 in the SSD group; 6/109 in the bacitracin zinc group) (RD 0.07; 95% CI -0.01 to 0.14) (Analysis 20.1).

2.1.2 SSD cream compared with neomycin sulphate

Primary outcome: infection rate

Significantly fewer patients developed wound infections in the neomycin sulphate group (12/99 in the SSD group; 5/110 in the neomycin sulphate group) (RD 0.08; 95% CI 0.00 to 0.15) (Analysis 21.1). The NNT with neomycin sulphate was 13, in order to prevent one infection.

2.1.3 SSD cream compared with petrolatum

Primary outcome: infection rate

There was no statistically significant difference between groups in the number of patients who developed wound infections (12/99 in the SSD group; 19/108 in the petrolatum group) (RD -0.05; 95% CI -0.15 to 0.04) (Analysis 22.1).

2.2 Dressings containing silver compared with dressings without silver (silver versus no silver)

2.2.1 Hydrofibre dressing containing ionic silver (Aquacel® Ag) compared with povidone iodine gauze (one trial)

Jurczak 2007 enrolled 67 patients with open surgical wounds or open traumatic wounds all healing by secondary intention to a randomised controlled trial comparing silver-containing hydrofibre (hydrofibre-Ag) with povidone iodine gauze.

Primary outcome: infection rate

Wound infection was defined on clinical criteria such as warmth, redness, increased tenderness, swelling, increased exudate or purulent discharge, and malodour. There was no statistically significant difference in the number of patients who developed a wound infection during the trial period (4/35 in the Aquacel® Ag group; 4/32 in the povidone iodine group) (RD -0.01; 95% CI -0.17 to 0.14) (Analysis 23.1).

Primary outcome: wound healing rate

Healing was defined as epithelialisation, but also reduction in wound area in mm^2, and reduction in wound depth in mm were reported. The mean time to complete healing was 14.1 days in the Aquacel® Ag group and 13.9 days in the povidone iodine group (log-rank test: not statistically significant). There was no statistically significant difference in the number of patients with complete wound healing at two weeks (8/35 in the Aquacel® Ag group; 3/32 in the povidone iodine group) (RD 0.13; 95% CI -0.04 to 0.31) (Analysis 23.2). The authors stated that the adjusted mean reduction in wound area was 551 mm^2 in the Aquacel® Ag group and 401 mm^2 in the povidone iodine group. The adjusted mean reduction in wound depth was 9 mm in the Aquacel® Ag group and 10 mm in the povidone iodine group. How, and why, the adjustment was made was not reported. The authors stated that both reductions were statistically significant when compared with baseline, but, when compared with each other, no statistically significant difference was found. No SDs were reported; therefore the mean difference could not be calculated.

Secondary outcome: adverse events

Adverse events were defined as any event that occurred during the trial period, e.g. allergy, skin burn, haemorrhage. There was no statistically significant difference between the groups (RD -0.09; 95% CI -0.21 to 0.02) (Analysis 23.3).

Secondary outcome: pain

Pain was measured on a visual analogue scale from 1 (no pain) to 10 (worst pain imaginable). Although no statistically significant differences were found for the pain score at dressing removal and application, the decrease in mean pain score from baseline when the dressings were in place was -0.7 for Aquacel® Ag versus 0 for povidone iodine gauze, though no SD was given. The overall ability to manage pain could be scored as excellent, good, fair or poor. The pain management was evaluated at the final visit (i.e. when the wound was completely healed or at week 2). Overall 70.6% of participants rated pain management as excellent in the Aquacel® Ag group compared with 22.6% in the povidone iodine gauze group. There was a statistically significant difference in the ability to manage pain in favour of the Aquacel® Ag group; P value < 0.001.

Summary for acute *wounds:* SSD/silver versus no silver

One of the two trials reported adequate sequence generation and adequate allocation concealment (Jurczak 2007).

- Infection rate was reported in both trials with a total of four different dressing comparisons. Three comparisons (Dire 1995; Dire 1995; Jurczak 2007) were not statistically significantly different, and one comparison (Dire 1995) showed a statistically significant difference in favour of neomycin sulphate.
- Time to complete healing was reported in one trial (Jurczak 2007), and was not statistically significant.
- The number of wounds healed was reported in one trial (Jurczak 2007), and was not statistically significant.
- Pain was reported in one trial (Jurczak 2007), and showed a statistically significant difference in favour of hydrofibre dressing containing ionic silver.

3. Chronic wounds

3.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)

3.1.1 SSD cream compared with Bensal HP with QRB7 (one trial)

Jacobs 2008 enrolled 40 patients with Wagner grade 1 or 2 diabetic foot ulcers in a trial comparing SSD with Bensal HP with QRB7, which is a mixture of 6% benzoic acid, 3% salicylic acid and 3% extract of Q rubra (an extract of oak (*Quercus rubra)* bark).

Primary outcome: infection rate

Wound infection was defined on the basis of clinical signs (foul odour, exudate, or erythema) and bacterial cultures. None of the treated wounds demonstrated growth of pathogenic bacteria at six weeks.

Primary outcome: wound healing rate

Healing was defined as the percentage reduction in total wound size (derived by adding the individual wound areas for each participant in each group) at two, four and six weeks. Complete healing was not defined. The "collective" wound diameter of the Bensal HP-treated patients had decreased by 72.5%, whereas the collective diameter of the SSD group had reduced by 54.7% (Student t test: P value 0.059).

There was no statistically significant difference in the number of patients with complete wound healing within six weeks (6/20 in the SSD group; 8/20 in the Bensal HP group) (RD -0.10; 95% CI -0.39 to 0.19) (Analysis 24.1).

Secondary outcome: adverse events

None of the patients experienced adverse effects.

3.2 Dressings containing silver compared with non-silver dressings (silver versus no silver)

3.2.1 Activated-charcoal dressing containing silver (Actisorb Plus®) compared with conventional phase-adapted therapy using diverse topical modalities (one trial)

Wunderlich 1991 enrolled 40 patients with venous leg ulcers of whom 38 were followed to study completion.

Primary outcome: infection rate

Every two weeks swabs were taken and were rated as 0 (no bacterial growth), 1 (light bacterial growth), 2 (medium bacterial growth), or 3 (heavy bacterial growth). The authors reported no differences in infection rates, but no actual data were reported.

Primary outcome: wound healing rate

Healing was defined as granulation (on an ordinal scale from 0 to 3), epithelialisation (on an ordinal scale from 0 to 3), and also as the reduction of the mean ulcer area in cm^2. There was no statistically significant difference in the number of patients healed after six weeks of treatment (6/19 patients in the charcoal-silver group; 2/19 patients in the conventional phase-adapted therapy using diverse topical modalities group) (RD 0.21; 95% CI -0.04 to 0.46) (Analysis 25.1).

3.2.2 Hydrofibre dressing containing ionic silver (Aquacel® Ag) compared with calcium alginate dressing (Algosteril®) (one trial)

Jude 2007 enrolled 434 patients with diabetic foot ulcers (Wagner grade 1 and 2). Although, at baseline, the calcium alginate dressing group (Algosteril®) seemed to have larger ulcers, and more patients in the hydrofibre dressing containing ionic silver (Aquacel® Ag) group were receiving antibiotics, the authors stated that the groups were comparable.

Primary outcome: infection rate

Wound infection was defined on the basis of clinical signs and/or bacterial cultures. There was no statistically significant difference in the number of patients who developed wound infection (11/67 in the Aquacel® Ag group; 8/67 in the Algosteril® group) (RD 0.04; 95% CI -0.07 to 0.16) (Analysis 26.1).

Primary outcome: wound healing rate

Healing was defined as complete re-epithelialisation, and as the reduction of the mean ulcer area in percentage and ulcer depth. Healing speed was defined as a weekly reduction in absolute and percentage ulcer area. Only the mean time to complete healing was significantly lower in the Aquacel® Ag group (52.6 days +/- 1.8 days (SD) Aquacel® Ag group; 57.7 days +/- 1.7 days (SD) Algosteril® group) (MD -5.1; 95% CI -5.69 to -4.51) (Analysis 26.2). Time in days to 100% healing was estimated by Kaplan-Meier survival analysis.

The number of patients with complete wound healing within eight weeks was 21/67 in the Aquacel® Ag group and 15/67 in the Algosteril® group (RD 0.09; 95% CI -0.06 to 0.24) (Analysis 26.3). The mean percentage ulcer area reduction by eight weeks was 58.1% in the Aquacel® Ag group and 60.5% in the Algosteril® group (MD -2.4; 95% CI -18.72 to 13.92) (Analysis 26.4). The reduction in mean ulcer depth at eight weeks was 0.25 cm in the Aquacel® Ag group and 0.13 cm in the Algosteril® group (MD 0.12; 95% CI -0.05 to 0.29) (Analysis 26.5).

Secondary outcome: adverse events

Adverse events were not clearly defined. One of the events mentioned was infection. There was no statistically significant difference in the number of patients who experienced adverse effects (25/67 in the Aquacel® Ag group; 26/67 in the Algosteril® group) (RD -0.01; 95% CI -0.18 to 0.15) (Analysis 26.6).

Summary for chronic wounds: SSD/silver versus no silver

Two of the three trials reported adequate sequence generation (**Jacobs 2008**; **Jude 2007**), and none adequate allocation concealment.

- Infection rate was reported in three trials (**Jacobs 2008**; **Jude 2007**; **Wunderlich 1991**), and showed no statistically significant differences.
- Time to complete healing was reported in one trial (**Jude 2007**), and was significantly faster with the silver hydrofibre (Aquacel® Ag) dressing. Time to healing was appropriately analysed using survival analysis.
- The number of wounds healed was reported in all three trials, and showed no statistically significant difference.

4. Mixed wounds

4.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)

Hutchinson 1993 enrolled 292 patients with venous leg ulcers, partial-thickness burns or partial-thickness donor sites. The trial had three treatment groups; SSD cream/hydrocolloid (58 participants), hydrocolloid alone (108 participants), and non-occlusive paraffin impregnated gauze (126 participants). The results are presented comparing SSD cream to each of the comparators.

Wound infection was defined using clinical criteria such as erythema, oedema, pain and purulent discharge.

4.1.1 SSD cream/hydrocolloid compared with hydrocolloid alone (one trial)

Primary outcome: infection rate

There was no statistically significant difference in the number of patients who developed a wound infection (0/58 in the SSD/hydrocolloid group, and 2/108 in the hydrocolloid group) (RD -0.02; 95% CI -0.06 to 0.02) (Analysis 27.1).

4.1.2 SSD cream/hydrocolloid compared with non-occlusive paraffin impregnated gauze

Primary outcome: infection rate

Significantly fewer patients in the SSD/hydrocolloid group developed a wound infection when compared with the non-occlusive paraffin impregnated gauze group (0/58 in the SSD/hydrocolloid group; 7/126 in the non-occlusive paraffin impregnated gauze group) (RD -0.06; 95% CI -0.10 to -0.01) (Analysis 28.1). The NNT with SSD/hydrocolloid was 18, in order to prevent one infection.

Summary for mixed wounds: SSD versus no silver

This trial did not report adequate sequence generation, nor adequate allocation concealment, therefore effect estimates may be biased.

- Infection rate was reported in this trial with a total of two different dressing comparisons. One comparison showed a statistically significant difference in favour of SSD/hydrocolloid, and the other showed no differences.

Summary for all wounds: SSD/silver versus no silver

Infection rate

Infection rates were reported in 17 trials with a total of 21 different dressing comparisons. One comparison showed a statistically significant difference in favour of silver nitrate dressings (Livingston 1990), 15 comparisons showed no differences, and five comparisons

using SSD showed a statistically significant difference in favour of non-silver dressings (Carneiro 2002; Dire 1995; Hutchinson 1993; Noordenbos 1999; Subrahmanyam 1998).

Wound healing rate

Time to complete wound healing was reported in eleven trials. One trial showed a statistically significant difference in favour of hydrofibre dressing with ionic silver (Jude 2007), three trials showed no differences (Afilalo 1992; Homann 2007; Jurczak 2007), and seven trials showed a statistically significant difference in favour of non-silver dressings (Gerding 1988; Gerding 1990; Hansbrough 1995; Innes 2001; Noordenbos 1999; Soroff 1994; Wyatt 1990). In most cases, time to complete wound healing was inappropriately regarded as a continuous outcome and the analysis of these outcomes was, therefore, flawed, leading to potentially misleading results.

Eight trials reported the number of wounds completely healed. Five trials showed no differences (Carneiro 2002; Jacobs 2008; Jude 2007; Jurczak 2007; Wunderlich 1991), and three trials showed a statistically significant difference in favour of non-silver dressings(Innes 2001; Mashhood 2006; Subrahmanyam 1998).

Adverse events

Adverse events were reported in four trials. None of them showed statistically significant differences (Homann 2007; Jacobs 2008; Jude 2007; Jurczak 2007).

Pain

Pain was reported in nine trials, but was expressed in different ways, e.g. the need for analgesia, or on a visual analogue scale (VAS). Overall, the reported pain scores were low in the majority of these trials, and the absolute differences in pain scores between the studied interventions were minimal. Two trials showed a statistically significant difference in favour of silver-containing dressings (Hansbrough 1995; Jurczak 2007), two trials found no differences (Afilalo 1992; Homann 2007), and five trials showed a statistically significant difference in favour of non-silver dressings (Carneiro 2002; Gerding 1988; Gerding 1990; Mashhood 2006; Wyatt 1990).

Patient satisfaction

Patient satisfaction was reported in one trial (Afilalo 1992), and showed no statistically significant differences.

Length of hospital stay

Length of hospital stay was reported in two trials, with a total of three dressing comparisons. Only one patient group treated with silver nitrate for burns covering 20% to 40% of the total body surface area experienced significantly shorter hospital stay compared with participants who received Ringer's lactate (Livingston 1990). No statistically significant differences were present for any of the other groups (Livingston 1990), or trial (Carneiro 2002).

Costs

Costs were reported in four trials. One trial (Innes 2001), found that the mean costs per cm^2 of dressing - based on price lists supplied by the manufacturers - were lower in the non-silver dressings group, compared with the silver-containing dressing group. One trial reported costs of dressings per percent of body surface burnt (Mashhood 2006), but differences were not reported. Both of the remaining two trials showed a statistically significant difference in favour of non-silver dressings (Gerding 1988; Gerding 1990).

Discussion

This review highlights the lack of conclusive evidence on the effects of silver-containing dressings or agents to prevent wound infection and to promote wound healing. In particular, there was no evidence to support the use of silver sulphadiazine (SSD) for prevention of wound infection in patients with partial-thickness burns. None of the trials indicated a beneficial effect for SSD for other outcomes when compared with other silver-containing or non-silver dressings. Furthermore, there was evidence that SSD may delay wound healing, may be more expensive, and may be more painful when applied to burns. The few trials on full-thickness burns and acute, chronic, or mixed wounds showed insufficient evidence for a beneficial effect of silver-containing dressings to decrease infection rates and to aid wound healing.

Only one trial showed significantly better results in terms of infection rates when another agent was added to the silver-containing dressing: infection rates were significantly lower than with SSD cream alone when a synthetic dressing was added to silver sulphadiazine cream (Hydron-SSD) (Fang 1987). The nanocrystalline form of silver present in the Hydron-SSD dressing, which releases silver ions faster, might explain the better results in burns. Furthermore, most trials used 1% SSD cream, but its effect might be dose-related (Fuller 1994). On the other hand, higher doses could also result in higher toxicity and more adverse effects (Lansdown 2002).

Recently published literature had already suggested the lack of evidence of effectiveness for silver-containing dressings and topical agents in burns. Hussain 2006 published a Best Evidence Topic report on burns, including evidence from RCTs and CCTs. The authors concluded that there was little evidence for using silver-containing dressings to prevent wound infection, and that such products tend to delay wound healing. Furthermore, silver may have serious cytotoxic activity on various host cells (Atiyeh 2007). In minor thermal burns (less than 15% TBSA) SSD cream was found to delay healing time and increase pain when compared with other treatments (Wasiak 2006). Wasiak 2008 also evaluated different dressings for burn wounds and found evidence for a delayed healing time for SSD. Similarly, Bergin 2006 found no RCTs that evaluated the effects of silver-containing dressings for the treatment of diabetic foot ulcers, and Vermeulen 2007 found three RCTs and concluded that there was insufficient evidence of effectiveness for silver-containing dressings as a treatment for infected wounds.

The following limitations of this review should be noted

Firstly, the methodological quality of the 26 included trials was relatively low, and a large proportion of the evidence presented here is accrued from trials which demonstrate a high or uncertain risk of bias. Most of the studies had small sample sizes and were, therefore, at risk of not detecting any existing differences, and of incurring chance baseline imbalances for important prognostic factors. Only one-third of the trials reported adequate sequence generation, and even fewer reported allocation concealment. Blinding of participants and care providers was not really possible, but outcome assessors could have been blinded, or healing confirmed by blinded assessment of photographs. This was almost never achieved or reported. Similarly the drop-out rate or reasons for drop-out were not always described.

The duration of follow-up of the included studies ranged from a few days to more than three months, whilst in only five studies was follow-up continued until complete wound re-epithelialisation was achieved (Homann 2007; Mashhood 2006; Noordenbos 1999; Soroff 1994; Wyatt 1990). In some trials the length of follow-up was unclear, or too short, and almost half of the trials were supported financially by a single manufacturer. If this caused publication bias - which was shown to be present in studies on negative pressure wound therapy (Peinemann 2008) - the real effect is likely to be even less favourable.

Secondly, one strength of a systematic review is the ability to pool data from several - often small - trials to achieve greater statistical power and a more precise overall effect size estimate. In this review few data could be pooled because the trials did not compare similar interventions, and there was considerable heterogeneity in the wounds being compared. Therefore, the lack of conclusive evidence for the effects of silver-containing dressings remains.

Thirdly, some trials used repeated measurements, for example, healing rate or swabs taken (e.g. at three, six, or nine days for one endpoint). This may illustrate the eagerness of the investigators (or the sponsors) to identify any sign of a treatment difference, at the cost of an increased chance of false positive results, while the shorter intervals are not relevant to patients. Furthermore, outcome parameters were measured in different ways and on different scales. Many secondary outcomes were based on subjective concepts such as "ease of use", "comfortable to wear". These subjective findings can hardly help in clinical practice and should be measured with standardised objective measurements whenever possible. Also, some trials measured "time per dressing", or "costs per cm^2". These measures alone are meaningless and should be reported in combination with other aspects of costs.

Fourthly, the majority of studies that reported outcomes such as time to healing or time to skin grafting, incorrectly reported and analysed these outcomes as continuous - rather than time-to-event - variables. The problem with this approach is that the time to the event is only known for those people who actually experienced it (in this case healing, or grafting), and no information is obtained from those who were observed, but did not experience the event. This approach may introduce bias. Time-to-event data, such as time to wound healing, should be analysed using survival analysis in which the treatment effect is expressed as a hazard ratio.

Finally, eight trials did not attempt to define infection. Some trials defined infection only on clinical grounds and others merely on the presence of bacterial cultures. It is clearly difficult

to interpret the results of studies that do not define their main outcomes. We reported the definition of infection and healing as used by the study authors and were unable to conduct any pooling due to heterogeneity.

Apart from the definition used, Sibbald 2005 stated that chronic wounds always contain bacteria and a diagnosis of infection should be based on clinical signs and not solely on bacterial cultures.

Authors' conclusions

Implications for practice

There is currently insufficient evidence that silver-containing dressings prevent wound infection or promote wound healing; the available evidence is low both in volume and quality. There is some evidence from small, poor-quality trials, that silver sulphadiazine does not reduce wound infection and slows down wound healing in people with partial-thickness burns.

Implications for research

More studies, and particularly studies with a low risk of bias, are needed to confirm any effect of silver-containing dressings in full-thickness burns and other wound groups. Future research must develop clear, valid, and reliable measures of wound infection. The use of common, quantifiable, and clinically-relevant endpoints (time to complete wound healing, number and time to wound infection, pain, adverse events, costs, and, preferably, a validated scale for patient satisfaction) should always be used. Whilst it is very difficult to blind patients and medical professionals with regard to the intervention, it is possible to blind outcome assessors, or to use computer programmes to measure wound size. Future research must adopt a survival approach for the analysis of time-to-event data, such as time to healing.

Finally, a sufficiently long follow-up period of at least six months is essential if treatment effects in chronic wounds are to be detected. Interventions under evaluation should be thoroughly, and clearly, described. For this purpose use of the revised CONSORT statement is recommended in order to report these trials adequately.

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Data and analyses

Download statistical data

Comparison 1. Silver sulfadiazine (SSD) cream (1%) vs biosynthetic dressing (Biobrane®)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients that developed wound infection	2	106	Risk Difference (M-H, Fixed, 95% CI)	-.00 [-0.12, 0.12]
2 Mean pain scores	2	106	Mean Difference (IV, Fixed, 95% CI)	1.41 [0.99, 1.83]
3 Costs based on hospital charges (US dollars)	1	56	Mean Difference (IV, Fixed, 95% CI)	70.0 [15.54, 124.46]

Comparison 2. SSD cream (1%) vs biosynthetic dressing with skin substitute (Transcyte® on Biobrane® mesh)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients that developed wound infection	1	28	Risk Difference (M-H, Fixed, 95% CI)	0.43 [0.16, 0.70]

Comparison 3. SSD cream (1%) with chlorhexidine-impregnated gauze (Bactigras®) vs hydrocolloid (Duoderm® Hydroactive)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients that developed wound infection	1	48	Risk Difference (M-H, Fixed, 95% CI)	-0.04 [-0.18, 0.09]

Comparison 4. SSD cream (1%) vs hydrocolloid (Duoderm® Hydroactive)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients that developed wound infection	1	42	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.09, 0.09]
2 Mean pain scores	1	42	Mean Difference (IV, Fixed, 95% CI)	1.19 [0.56, 1.82]

Comparison 5. SSD cream (1%) vs honey

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with clinical evidence of wound infection	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 7	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Day 21	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Number of wounds completely healed	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
2.1 week 2	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 week 4	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 week 6	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of patients with clinical evidence of wound healing (day 21)	1	50	Risk Difference (M-H, Fixed, 95% CI)	-0.16 [-0.31, -0.01]
4 Number of patients reporting free of pain	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
4.1 week 1	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 week 2	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 week 3	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 week 4	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. SSD cream (1%) vs liposome hydrogel with polyvinyl-pyrrolidone iodine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients that developed wound infection	1	86	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.04, 0.04]
2 Number of patients with adverse effects	1	86	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.05, 0.10]
3 Number of patients reporting wound pain	1	86	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.16, 0.12]