Evidence based treatment
Topical treatment for facial burns

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Abstract

**Background:** Burn injuries are an important health problem. They occur frequently in the head and neck region - the area central to a person’s identity, that provides our most expressive means of communication. Topical interventions are currently the cornerstone of treatment of partial-thickness burns to the face.

**Objectives:** To assess the effects of topical interventions on wound healing in people with facial burns of any depth.

**Search methods:** We searched the Cochrane Wounds Group Specialised Register (searched 12 November 2012); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 10); Ovid MEDLINE (1950 to November Week 1 2012); Ovid MEDLINE - In-process & Other Non-Indexed Citations (searched November 12, 2012); Ovid EMBASE (1980 to 2012 Week 45); and EBSCO CINAHL (1982 to 9 November 2012) for relevant trials. We did not apply date or language restrictions.

**Selection criteria:** Randomised controlled trials (RCTs) that evaluated the effects of topical treatment for facial burns were eligible for inclusion in this review.

**Data collection and analysis:** Two review authors independently assessed and included the references identified by the search strategy. Included trials were assessed using a risk of bias form, and data were extracted using a standardised data extraction sheet. For dichotomous and continuous outcomes, we calculated risk ratios and mean differences, respectively, both with 95% confidence intervals (CI).

**Main results:** We included five RCTs, comprising a total of 119 participants. Two studies compared two different antimicrobial agents and three compared a biological or bioengineered skin substitute with an antimicrobial agent. All studies had small sample sizes and were at high risk of bias. Heterogeneity of interventions and outcomes prevented pooling of data. In three studies time to complete wound healing was significantly shorter for those using a skin substitute than for those using an antibacterial agent, but the quality of the evidence was low. Pain was significantly reduced with the use of skin substitutes in both studies that reported this outcome in all groups, range mean differences -2.00 (95% CI -3.82 to -0.18) to -4.00 (95% CI -5.05 to -2.95) on a 10-point scale.

**Authors’ conclusions:** There is insufficient high quality research and evidence to enable conclusions to be drawn about the effects of topical interventions on wound healing in people with facial burns.
Background

Burn injuries are an important health problem, resulting in 45,000 admissions annually in the United States of America (USA), of which more than 25,000 admissions to hospitals with specialised burn centres [1]. In the United Kingdom, approximately 13,000 people a year are admitted to hospital for treatment of burns [2], while in the Netherlands the annual figure is about 1800 people [3], 550 to 600 of whom are treated in one of the three Dutch burn centres. Mortality rates from burn injuries have substantially decreased because of major improvements in burn care made in the 20th century. This has resulted in a shift in attention towards the functional outcome after a burn injury rather than mortality [4]. The head and neck region is estimated to be the site of burn injury in between 27% [5] and 60% [6,7] of burn cases. The face is central to our identity and also provides our most expressive means of communication. Appearance, communication and other basic senses and abilities such as hearing, smelling and breathing may be affected as a direct result of a facial burn, or its sequelae [8]. Impaired function and distorted appearance may both induce psychological problems, problems with social reintegration and affect quality of life [9].

Description of the condition

A burn injury to the skin occurs when some, or all, the different layers of skin are destroyed by physical energy delivered via a hot liquid, flame, contact with a hot surface, ultraviolet/infrared radiation, radioactivity, electricity or chemicals [10]. Severity of burn wounds is characterised by their size and depth as well as their location and associated injuries. The size of a burn is measured by the percentage of Total Body Surface Area affected (% TBSA), which is the percentage of the surface area of the skin burned, while the depth of a burn is determined by the layers of skin destroyed. So far, no consensus has been reached on the exact classifications of burns, especially not in relation to the classification of depth [11]. In general, skin burns are classified as either superficial partial-thickness burns, deep partial-thickness burns or full-thickness burns. In superficial partial-thickness burns only the epidermal layer and the superficial part of the dermis is destroyed. Healing generally occurs within two weeks, with very little, or no, scarring, due to the migration of epithelial cells to the surface of the skin. In deep partial-thickness burns, the epidermis and most of the dermis is destroyed, with damage to deeper structures within the skin such as blood vessels, nerves and hair follicles. If re-epithelialisation does not occur within two to three weeks, then hypertrophic scarring may occur [12,13]. Finally, full-thickness burns involve all the layers of skin and may involve structures underneath, such as muscle and bone, leaving little chance of healing from the epithelial elements at the bottom of the wound. In the case of a very small burn, healing might occur by contraction and growth of epithelial cell from the wound edges. Full-thickness burns will nearly always result in hypertrophic (raised) scarring. Hypertrophic scarring can be assessed with different tools, but there is still no consensus concerning its definition [14].

Topical treatment for facial burns
Full-thickness facial burns are rare, since the face’s high vascularity rapidly dissipates heat. Facial burns are often caused by flash burns, which usually cause partial-thickness burns. Nonetheless, full-thickness facial burns do occur, especially in flame and contact burns, and in the event of prolonged exposure to a heating source, for example if the person was unconscious or paralysed at the time of accident. In addition, in some places (e.g. nose and ears) facial skin is very thin, and, therefore, more vulnerable to deep burns. When nose and ears are deeply burned, the anatomical structures can change or disappear.

Immediately after the thermal injury the surfaces of burn wounds are sterile, but they are rapidly colonised by a variety of micro-organisms. These micro-organisms originate from the patient’s own skin, respiratory and gastro-intestinal flora, and also from contact with contaminated surfaces in the external environment, hands of healthcare workers and even air. Burn wounds provide a favourable niche for microbial colonisation and proliferation because of their protein-rich environment and avascular necrotic tissue. This avascularity of eschar (necrotic tissue) results in impaired migration of host immune cells and restricts delivery of systemically administered antimicrobial agents to the area. The most common burn wound pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Microbial colonisation of burn wounds has been associated with delayed wound healing, increased need for surgical interventions and prolonged length of stay at burn centres.

Once 30% of the total body surface area has been burned there may be systemic (whole body) responses in addition to local responses. This occurs because of the release of inflammatory mediators at the site of injury. Besides generating excessive oedema in burns, these systemic reactions can further compromise the healing of a burn wound, and so it is important to consider adequate local treatment, as well as systemic management of a burn, as this may influence the final outcome of the injury.

Another possible outcome of a burn injury is hypertrophic scarring, which occurs when the balance between collagen synthesis and breakdown is disrupted. The post-burn hypertrophic scar may present itself either as a pink to red in colour and slightly thickened, or as a red to purple inelastic mass of skin tissue. If a hypertrophic scar surrounds openings such as the eyes or mouth, functional impairment of the face can occur. The eyes for instance, may not close, due to the inelasticity and contraction of the hypertrophic skin, and the mouth may not open maximally. Furthermore, these scars can result in discomfort, because of itching, and sometimes cause neuropathic (nerve) pain. The degree of hypertrophic scarring differs among individuals and depends on a variety of factors, one of which is time to wound healing, with hypertrophic scar formation being seen more often when wound healing takes more than 21 days. In general, a deeper burn wound results in the formation of more hypertrophic tissue. Other factors that affect hypertrophic scarring are race, age, genetic factors, type of injury, anatomic region and mechanical tension on the wound.
Description of the intervention

The focus of this review is topical treatment for facial burns. Topical treatment comprises any remedy, agent, substance, device or skin substitute that is placed on the face as a therapy for burn wounds. This definition excludes invasive surgical intervention, which is another important treatment in burn care. Excluding this intervention is necessary in order to narrow the scope of this review and increase the comparability of outcomes. Numerous dressings and topical ointments are used to treat facial burns. Hansen et al. (2004) conducted a survey on the standards of topical wound care for facial burns among burn centres in the USA[^25]. Most burn centres used topical bacitracin for partial-thickness facial burns and silver sulphadiazine (SSD) or bacitracin for full-thickness facial burns, with variations in treatment modalities. A survey of European burn centres reported that most centres agreed that some kind of antibacterial topical agent should be used, particularly for deep facial burns, but there were large variations in practice[^26]. Before applying topical or surgical treatment, a burn wound surface might need additional preparation in the form of debridement (removal of dead tissue). The debridement of burns is divided in two main approaches, namely:

- superficial debridement: cleaning the wound surface using a brush, gauze or chemical, and removing the superficial loose wound surface;
- surgical debridement: the excision of the burn wound, with removal of all non-vital tissue.

In this review only superficial debridement will be considered.

How the intervention might work

Interventions used in topical treatment of facial burns can be divided into four main categories: wound preparation agents and antiseptics; wound dressings; antimicrobial agents; and other treatments, including alternative remedies. An elaboration of each category is described below.

**Wound preparation agents and antiseptics:** Antiseptics are topical agents designed to reduce or eliminate micro-organisms in a wound. They can be used to cleanse facial burn surfaces after injury, or to prepare wounds for surgical debridement, or the application of a further topical agent[^27]. Examples of antiseptics include chlorhexidine digluconate and povidone iodine. Other wound-preparation agents include enzymatic debriding agents. These agents prepare the wound by chemical debridement, but their use is controversial for facial burns[^28].

**Wound dressings:** Wound dressings, including biological dressings and bioengineered skin substitutes, are used to create an optimal environment for epidermal wound healing. For a long time, a moist environment was regarded as optimal[^29], however, more recently Jonkman (1989) has suggested that epidermal wound healing is best accelerated in an environment “between moist and dry”, i.e. a more jelly-like wound exudate environment[^30]. Nowadays,
several wound dressings have these moist or gel-forming qualities. Occlusive dressings, such as hydrocolloids and hydrogel dressings, form a moist or jelly-like environment by incorporating wound fluids into the dressing. Semi-occlusive dressings (e.g. polyurethane film, foam or a hydrofibre) permit evaporation of excess water and prevent maceration, while maintaining a moist environment. Silicon-coated nylon dressings function primarily as non-adherent dressing layers, and, therefore, reduce potential damage during dressing changes. Simple wound dressings, such as synthetic non-adherent or paraffin gauze dressings, sometimes incorporate medication such as chlorhexidine.

Biological dressings (e.g. cadaver allografts (skin from corpses) and porcine (pig) skin xenografts) can be used to treat partial-thickness burns. These provide temporary wound coverage until full healing can be achieved, or until autografting (skin graft(s) using the patient’s own skin) can take place. Their use is limited due to their lack of availability, acceptability, and the possibility of disease transfer. Another biological dressing, amnion (derived from the membranous sac that surrounds the developing embryo), has recently been proposed as a wound dressing for burn treatment. In addition, bioengineered skin substitutes can be used as “smart dressings” in topical therapy; these not only provide immediate wound cover, but are also available in large quantities, with a negligible possibility of disease transfer. Unfortunately, most skin substitutes are expensive and considerable expertise is required to select the appropriate material for the situation.

Antimicrobial agents: Topical antimicrobial agents are used with the aim of controlling and limiting infection, and they are central to topical burn therapy. The ideal topical prophylactic antimicrobial agent would have a broad spectrum of activity with a long duration of action, low toxicity and the ability to penetrate eschar (necrotic tissue) without being absorbed by the body. Ideal topical antimicrobials do not hamper epithelial outgrowth and deliver a high concentration of active ingredients to devitalised, devascularised and potentially necrotic wounds, helping to provide a favourable wound healing environment. Use of topical antimicrobials may help to minimise wound deepening, and the need for extensive debridement and subsequent grafting. This is fundamentally important for facial wounds, where overzealous debridement may affect function and appearance.

The antimicrobial agents used in burn care include silver preparations. Silver sulphadiazine (SSD), in particular, is widely used and acts on burn eschar to limit the extent of non-viable tissue in situations where surgery is either not possible, or would not be the immediate first option - as in facial burns. Cerium nitrate is another antimicrobial agent which penetrates burned tissue and has a broad spectrum of activity against Gram-positive and Gram-negative bacteria, and fungal species, especially in combination with SSD. Cerium nitrate also has a hardening effect on burn eschar, which is thought to prevent bacterial ingress and helps maintain a moist wound. Furthermore, cerium is supposed to bind and denature the lipid-protein complex released from burned skin responsible for the profound immunosuppression
associated with major cutaneous burns \cite{35,36}. Despite their popularity and widespread use, silver-based modalities are not without complications, including frequently observed delayed wound healing, which might be due to the retardation of sloughing in partial-thickness burns. In addition, increased hypertrophic scarring has been described with SSD; while skin irritation, black staining of the skin and the possibility of systemic absorption of silver have also been reported \cite{32,37}. Furthermore, a Cochrane systematic review concluded that “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” \cite{38}. Other antimicrobial agents include natrium fusidate and nitrofuran. It has been reported that some antimicrobial medications might delay proper healing mechanisms of the wound \cite{39,40}, and that improper use can contribute to the emergence of resistant microbes \cite{20}. In this review, simple wound dressings will be included in this antimicrobial category when they contain an antimicrobial medication.

Other treatments, including alternative remedies: Several additional forms of topical therapy are available, including alternative remedies such as honey and Aloe vera. Honey is said to prevent bacterial growth, form a physical barrier, act as an enzymatic debrider and promote epithelialisation and angiogenesis (formation of new blood vessels). Aloe vera could accelerate the wound healing process and rate of re-epithelialisation in partial-thickness burns \cite{41,42}. Other alternative remedies, such as covering with banana or cabbage leaves, or potato skins, are sometimes used in places where treatment resources are limited. Any other topical treatment for facial burns which does not fall into one of the main groups above will be included in this category of alternative remedies.

Why it is important to do this review

Treatment of facial burns is more demanding than treatment of burns on other parts of the body, not only because of the location of vital sensory and communication organs but also because the face is highly vascular. This high vascularity increases the self-healing potential of facial burns and, therefore, justifies a conservative approach to treatment, though this may require intensive daily care. There is uncertainty about which treatment is the most effective for facial burns, and, consequently, there are large variations in practice \cite{26,28}. Since treatment contributes to outcome - which is especially important for facial burns in terms of both physical and psychological functioning - it is important to consider the most effective treatment.

Existing guidelines to support clinical decision making in burn care are predominantly practice-based or are concerned with the general treatment of burns. For example, an evidence-based guideline was published on treatment of burns and scalds in primary care \cite{43}. In addition, several systematic reviews have been published in the field of wound care; in 2008 a review on dressings for superficial and partial-thickness burns was published \cite{44}, and in the same year
the use of honey as a topical treatment for wounds was systematically reviewed\textsuperscript{[145]}, however neither review specifically considered facial burns. Another systemic review by Vermeulen et al. (2007) reviewed the use of topical silver for treating infected wounds\textsuperscript{[21]}, and Storm-Versloot et al. (2010) recently reviewed the effects of topical silver for prevention of wound infection\textsuperscript{[38]}. In conclusion, current published reviews do not address the effectiveness of topical treatment for facial burns.

**Objectives**

To evaluate the effects of topical interventions on wound healing in people with facial burns of any depth.

**Methods**

**Criteria for considering studies for this review**

*Types of studies:* We considered all randomised controlled trials (RCTs) that evaluated the effects of topical treatments for facial burns. We decided to consider controlled clinical trials (CCTs) only in the absence of RCTs.

*Types of participants:* We considered studies that included people of any age with a facial burn wound of any degree in any care setting. Any type of burn injury was eligible (flame, scald, chemical etc).

*Types of interventions:* Studies were considered for inclusion if topical therapy was applied and compared with any comparator intervention. We defined topical therapy as any remedy, agent, substance, device or skin substitute (biological or bioengineered) that was applied to the surface of the facial wound in the acute phase with the aim of treating the burn. We defined the acute phase as the period of wound healing that occurs up to wound closure (epithelialisation). We divided the topical interventions considered for inclusion into the following four categories:

- wound preparation agents and antiseptics;
- wound dressings, e.g. occlusive and semi occlusive dressings, biological and bio-engineered dressings;
- antimicrobial agents;
- other treatments, including alternative remedies.

The previously stated definition of topical therapy excluded surgical debridement as an index intervention in this review. Comparator interventions could include any other intervention, no intervention or a placebo intervention.
Types of outcome measures: Study outcomes did not form part of the selection process. We divided outcomes into primary and secondary outcomes; these are listed below.

Primary outcomes:
- Time to complete wound healing.
- Change in wound surface area over time, or the proportion of the burn wound surface area that had healed within a specified time period.
- Wound infection (as defined by the trial authors).

We accepted any definition of change in wound surface area over time, or proportion of wound surface area healed in a specified time period. In addition, we accepted any definition of wound infection. All primary outcomes were assessed as short-term endpoints (i.e. three months).

Secondary outcomes:
- Proportion of facial burns requiring (reconstructive) surgery.
- Scar quality: observed and self-reported (any definition of scar quality was accepted).
- Pain.
- Patient satisfaction.
- Adverse effects: classified as: diagnosed by a clinician, diagnosed by laboratory results or patient-reported symptoms.
- Quality of life.
- Length of hospital stay (LOS).

Because we anticipated that primary studies would report and analyse secondary outcomes at different time points, we prespecified time points as either short-term or long-term. The short-term endpoints (i.e. up to three months post burn) included the outcomes: pain, patient satisfaction, adverse effects and length of hospital stay; the long-term endpoints (i.e. after 3 months and up to 12 months post burn) included the outcomes: proportion of facial burns requiring (reconstructive) surgery, scar quality and quality of life.

Search methods for identification of studies

Electronic searches: We searched the following electronic databases for reports of randomised controlled trials:
- Cochrane Wounds Group Specialized Register (Searched 12 November 2012);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 10);
- Ovid MEDLINE (1950 to November Week 1 2012);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, searched November 12 2012);
- Ovid EMBASE (1980 to 2012 Week 45);
- EBSCO CINAHL (1982 to 9 November 2012).
The search strategies for CENTRAL, Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in the published version of this review. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)\(^{[46]}\). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN)\(^{[47]}\). No date or language restrictions were applied.

In addition, we searched the International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch) (Search 19 November 2012).

**Searching other resources:** We checked reference lists within all studies and major review articles retrieved in an effort to identify any additional relevant studies. We sent emails to all authors of included studies requesting information on unpublished data and ongoing studies.

**Data collection and analysis**

*Selection of studies:* Without restrictions on language of publication or publication status, two review authors (CH and JH) independently assessed the titles and abstracts of studies identified from the search in terms of their relevance and design. We obtained full versions of articles if they matched the inclusion criteria from this initial assessment. The review authors independently assessed full text articles and determined a final selection of trials eligible for this review. Another review author (MvB) evaluated any discrepancies and advised in case of disagreement.

*Data extraction and management:* Two review authors (CH and JH), working independently, extracted and summarised details of trials using a data extraction sheet. They extracted data on the following items:

- Characteristics of the trial: method of randomisation, setting, location of care, country, source of funding.
- Participants: number, age, gender, type of burn, percentage Total Body Surface Area (TBSA) burned, burn depth, concurrent illnesses.
- Intervention topical agents: type of dressing, dose used, frequency of dressing changes, time elapsed before treatment, concurrent interventions.
- Comparator intervention: see above.
- Outcomes: types of outcomes measured, timing of outcomes.
- Results.

The authors resolved any discrepancies by discussion with a third review author (MvB), and contacted the trial authors when information was missing from published reports or clarification was needed. Data from trials published in duplicate were included only once, but were maximally data extracted.
Assessment of risk of bias in included studies: Two review authors (CH and JH) made systematic and independent assessments of the risk of bias of each trial, using the Cochrane Risk of Bias criteria\textsuperscript{48}. The criteria relate to the following issues:

- sequence generation;
- allocation concealment;
- blinding of participants, care providers and outcome assessors;
- incomplete outcome data: assessment of drop-out rate and intention-to-treat analysis;
- selective outcome reporting;
- other sources of bias: baseline similarity, co-interventions, compliance, similar timing of outcome assessment.

Risk of bias increases with each criterion that is judged to be negative. A detailed description of criteria for a judgement of ‘low risk of bias’, ‘high risk of bias’ or ‘unclear risk of bias’ can be found in the published version of this review. Any discrepancies in judgement between the two review authors was resolved by discussion with a third review author (MvB). Final assessment of risk of bias was presented in a risk of bias summary figure, which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give to the results of each study.

Measures of treatment effect: Data analysis was performed according to the guidelines of the Cochrane Collaboration\textsuperscript{49}. One review author (CH) entered quantitative data into RevMan, this was checked by another review author (JH), and analysed using the Cochrane Collaboration’s associated software (RevMan). For each outcome, summary estimates of treatment effect (with 95% confidence intervals (CI)) were calculated for every comparison. Dichotomous outcomes were presented as risk ratios (RR) (also called relative risks) (see Cochrane Reviewers Handbook 9.2.2\textsuperscript{49}) with 95% CI, and continuous outcomes were presented as mean differences (MD) with 95% CI. We intended to use standardised mean differences (SMD) on occasions when studies assessed the same outcome (e.g. quality of life) but measured the outcome in different ways. Time to wound healing would be analysed as a survival (time-to-event) outcome if possible, using an appropriate analytical method (i.e. hazard ratio, Cochrane Reviewers handbook 9.2.6\textsuperscript{49}).

Unit of analysis issues: We addressed the level at which randomisation occurred in our analysis. In general, the unit of randomisation and measurement was expected to be the patient. Any deviations were described and addressed in the analysis.

Dealing with missing data: We contacted the original investigators to request missing data whenever possible.
Assessment of heterogeneity: We planned to explore both clinical and statistical heterogeneity. Clinical heterogeneity was assessed using information on type of dressing, dose used and frequency of dressing changes. We planned to test statistical heterogeneity using the chi squared test and estimate the amount of heterogeneity using $I^2$ (with 95% CI)\textsuperscript{[49,50]}, which examines the percentage of total variation across studies due to heterogeneity rather than to chance.

Assessment of reporting biases: We planned to measure publication bias by the Begg funnel plot\textsuperscript{[51]} and the Egger test\textsuperscript{[52]}, if the included studies were homogeneous and sufficient in number.

Data synthesis: We planned to perform a meta-analysis for each primary outcome if clinical and statistical homogeneity indicated this would be appropriate\textsuperscript{[50]}, and calculate summary estimates of treatment effect for every comparison. We planned to conduct a narrative overview, structured by the type of comparison, when statistical meta-analyses was inappropriate.

Subgroup analysis and investigation of heterogeneity: We planned to investigate heterogeneity through subgroup and sensitivity analysis\textsuperscript{[49]}, when there was a sufficient number of studies in the meta-analysis (i.e. more than 10). We planned to conduct subgroup analysis for:

- Partial-thickness burns compared with full-thickness burns, as the effects of topical interventions were expected to differ between patient groups with different burn depths.
- Adequate concealment of allocation (low risk of bias versus unclear, or high risk of bias).

Sensitivity analysis: If there were a sufficient number of studies in the meta-analysis, we planned to perform a sensitivity analysis showing how conclusions might be affected if studies at high risk of bias were excluded from the analyses. We planned to explore the effect of excluding studies with unclear and inadequate sequence generation and unclear and inadequate allocation concealment within the sensitivity analysis.

Results

Description of studies

Results of the search: The search identified, after initial de-duplication, 416 articles. Two review authors (CH and JH) independently assessed the titles and abstracts of these articles and judged 20 citations to be potentially eligible for the review. Two citations appeared to be duplicates,
decreasing the number of unique articles to 18. Full texts of the eligible articles were obtained and assessed by the same two review authors. They completed data extraction forms and the risk of bias table, and screened the references in the articles for additional eligible studies. No additional studies were identified with this “snowballing” method. The full text of two articles [53,54] was published only in Chinese and were assessed by Chinese speakers who decided that they were not RCTs. An additional search in the International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch) resulted in one additional, potentially eligible trial [55].

**Included studies:** Assessment of the 18 potentially eligible articles (20 citations) resulted in the inclusion of five studies (six citations) [56-61]. The characteristics of these studies are described in Table 1 and are summarised below. The characteristics of four studies [62-65] are described in Table 2 and will be assessed in the next update of this review. The details of the trial retrieved from the International Clinical Trials Registry Platform Search Portal [55] has been added to the Table 2 also, while we keep in contact with the trialists regarding the progress of the trial.

**Health care settings**

All five RCTs took place in burn centres; three in the USA [57-60]; one in Singapore [56] and one in Germany [61].

**Participants**

A total of 119 participants (55 intervention, 64 control) were recruited to the five included studies (range of sample size 10 to 39), although it is possible that this number might be lower due to a possible overlap of participants between two studies [57-59], which potentially would decrease the total to 98. Age and percentage TBSA burned of the included participants are summarised below. The mean age and standard deviation (SD) or standard error (SE) were reported in three studies [57-60], and one study reported median age only (34.3 years), and range (24 to 67 years) of the whole study population [61]. In Desai et al. (1991), the mean age was 11.4 years (SE 1.2 years) in the intervention group and 9.5 years (SE 1.6 years) in the control group [60]. In Demling et al. (1999) and Demling et al. (2002), the mean age varied from 29 years (SD 7 years) to 44 years (SD 10 years) [57-59]. Percentage TBSA burned was reported in four studies [56-60] and varied from 1.56% (SE 0.18) in the control group in Ang et al. (2000) [56], to 50% (SE 6) in the control group in Desai et al. (1991) [60]. Horch et al. (2005) did not provide information about the percentage TBSA burned [61].

**Interventions**

One study compared two different antimicrobial agents: Moist Exposed Burn Ointment (MEBO) and silver sulphadiazine (SSD) [56]. Another study compared routine care plus an antimicrobial agent (i.e. 1% gentamicin cream) administered via iontophoresis (use of an
electric current to move a drug through the skin to a deep site) with routine care alone. The routine care comprised of the application of mafenide acetate (another antimicrobial substance) every six hours.

The remaining three studies compared skin substitutes with antimicrobial agents. In Demling et al. (1999) and Demling et al. (2002), the intervention group received bio-engineered skin substitutes (TransCyte®) and the control group received standard care with topical antibiotics. TransCyte® is a bilayered, biologically-active, temporary skin substitute with an outer flexible knitted-nylon layer permeable to water vapour but impermeable to bacteria that decreases environmental insults. The inner layer is impregnated with human fibronectin and collagen Type I. In Demling et al. (1999), the standard care consisted of application of bacitracin two to three times a day in mid-dermal burns, while this procedure was preceded by the application of SSD in the first one to two days in deeper burns. Demling et al (2002) did not provide additional information about the topical antibiotic used in standard care.

In Horch et al. (2005), the biological skin substitute used was an allograft (glycerolised cadaver skin), and the topical antimicrobial ointment was SSD. In both groups the application of treatment followed superficial debridement. No studies investigated wound preparation agents and antiseptics or other treatment, including alternative remedies.

Outcomes

Four studies included time to complete wound healing as an outcome of interest, but differed in their definition of this outcome, measuring it as number of days to complete wound healing, number of days to complete re-epithelialisation, time in days to more than 90% re-epithelialisation, and time in days to more than 95% re-epithelialisation. In addition, Ang et al. (2000) reported the number of participants healed at 10 days. Wound infection was a pre-specified outcome in three studies, and another study reported this outcome although it had not be pre-specified in the methods section. Demling et al. (2002) determined wound infection with quantitative swab cultures, using a cut-off value of 105 organisms/g. Demling et al. (1999) and Desai et al. (1991) determined wound infection with qualitative outcome measures, which included increased exudate and surrounding cellulitis, and the appearance of chondritis. The Horch et al. (2005) trial did not describe how infection was measured.

Secondary outcomes reported in the five studies included the need for (reconstructive) surgery, hypertrophic scarring, pain, length of hospital stay and adverse effects. Ang et al. (2000) and Desai et al. (1991) examined the need for (reconstructive) surgery with a follow-up of six months post-burn. Hypertrophic scarring was an outcome in one study, but a measurement instrument was not described. Pain was reported as an outcome of interest only in the Demling studies. Both studies used a 10-point scale to assess pain (0 for no pain and 10 for worst pain). Two studies reported the length of hospital stay, and additional adverse effects were reported in Horch et al. (2005) and Desai et al. (1991).
Sponsorship

One study explicitly stated that none of the authors had commercial associations or financial interests that might pose a conflict of interest\(^{[56]}\), while Horch et al. (2005)\(^{[61]}\) and Desai et al. (1991)\(^{[60]}\) provided no information about sponsorship. In Demling et al. (1999)\(^{[57]}\) and Demling et al. (2002)\(^{[58,59]}\) the intervention was an explicitly mentioned brand, but it was not stated whether this application was sponsored or purchased.

Excluded studies: Nine studies (10 citations) were excluded because they were not RCTs\(^{[53,54,66-70]}\), or because the focus of the study was not on facial burns\(^{[71,72]}\).

Risk of bias in included studies

Two review authors (CH and JH) independently assessed risk of bias in the five included studies and initially disagreed on 14 judgements. Thirteen disagreements were resolved by discussion, and one disagreement was presented to a third review author (MvB) for final judgement. This one disagreement was related to the avoidance or similarity of co-interventions in Demling et al.1999\(^{[57]}\). Most of the other disagreements were related to blinding of the outcome assessor, which sometimes differed between short-term and long-term follow-up. Details of the risk of bias judgements for the five studies are presented in a summary figure (Figure 1) and are described below.

Figure 1: Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
Allocation (selection bias): For risk of bias assessment the term “allocation” included sequence generation and allocation concealment, which both had to be considered.

Sequence generation
Of the five included studies, only Ang et al. (2000) described the method of sequence generation adequately \cite{56}. Ang et al. (2000) described the method as: “Randomly alternating permuted sub-blocks of size 4 and 6, with equal numbers per treatment within each sub-block, were used to obtain an overall block size of 10” \cite{56}. The other four studies stated only that participants were randomised, but did not describe the method of sequence generation \cite{57-61}.

Allocation concealment
Of the five included studies, only Ang et al. (2000) described the method of allocation concealment employed adequately, stating that allocation was determined by means of telephone calls to a research unit during office hours or by sealed envelopes after office hours \cite{56}. The other four studies did not describe the method of allocation concealment \cite{57-61}.

Blinding (performance bias and detection bias): Review authors had to judge the blinding of participants, care providers and outcome assessors. None of the five studies reported blinding of participants or care providers, and so, because the nature of treatments made it impossible to blind them, the reviewers made a judgement of “no” rather than one of “unclear”. Blinding of outcome assessors was reported in one study \cite{56}; two studies clearly did not undertake blinded outcome assessment \cite{57-59}, and in two studies it was unclear whether the outcome assessor was blinded \cite{60,61}.

Incomplete outcome data (attrition bias): The item “incomplete outcome data” consisted of two topics: drop-out rate and intention-to-treat analysis (ITT). The drop-out rate was described and acceptable (i.e. did not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias) in three studies \cite{56,58,59,61}, while two studies did not report it or make it evident in the outcome assessment \cite{57,60}. ITT-analysis was performed in one study \cite{58,59}; another study did not report ITT-analysis specifically, but it appeared likely when the study was assessed \cite{61}. One study stated that ITT-analysis was performed, but assessment of the study showed clearly that it had not \cite{56}. The final two studies were unclear on this point \cite{57,60}.

Selective reporting (reporting bias): Four studies were classified as free of suggestion of selective outcome reporting \cite{56-59,61}, but one was not \cite{60}. In Demling et al. (1999), the pre-specified outcome of length of hospital stay was not reported for major burns, because other non-facial burns interfered with this outcome and prolonged hospital stay \cite{57}. Desai et
(1991) listed wound healing as an outcome of interest but did not report it in the results section \(^{[60]}\).

**Other potential sources of bias:** Review authors considered four other potential sources of bias (i.e. baseline characteristics, co-interventions, compliance and timing of outcome assessment). The baseline characteristics between intervention and control group were similar in three studies \(^{[57-59,60]}\). In Ang et al. (2000), the description of baseline characteristics was limited to only one important prognostic indicator (i.e. % TBSA burned), which was insufficient to make a judgement of low risk of bias for baseline similarity \(^{[56]}\). In Desai et al (1991) the percentage TBSA burned in both groups was not similar and no information was provided about etiology \(^{[60]}\). Co-interventions were avoided, or similar, in one study \(^{[57]}\); cleaning procedures were different in one study \(^{[56]}\); no information was provided about co-interventions in two studies \(^{[60,61]}\), and one study stated “subsequent care in the intervention group when needed”, but did not report whether this care was applied \(^{[58,59]}\). Compliance with the intervention was acceptable in all five studies \(^{[56-61]}\). The timing of the outcome assessment was similar in all groups in all five studies \(^{[56-61]}\).

**Effects of interventions**

Heterogeneity of studies with regard to interventions and outcomes prevented assessment of reporting biases and limited data synthesis to a narrative overview, structured by the type of comparison. Because meta-analysis was inappropriate, no subgroup and sensitivity analyses were performed. The effects of interventions are presented in Table 1 and summarised below.

**Comparison: antimicrobial agents compared with other antimicrobial agents**

Two studies compared antimicrobial agents with another antimicrobial agent in 54 people \(^{[56,60]}\).

**Primary outcomes**

*Time to complete wound healing:* One study reported time to complete wound healing \(^{[56]}\). A study by Ang et al. (2000) compared Moist Exposed Burn Ointment (MEBO) with silver sulphadiazine (SSD) in 39 people with partial thickness facial burns \(^{[56]}\). Although time to complete wound healing was an outcome of interest in this study, the authors reported only the range of this outcome for the intervention group (2-35 days) and stated that MEBO resulted in healing rates similar to those seen with SSD dressings. After adjusting for initial percentage Body Surface Area (BSA) burned of the face wound, the hazard ratio for healing was 0.84 (95% CI 0.38 to 1.85) (no statistically significant difference).

*Proportion completely healed in specified time period:* Ang et al. (2000) also reported the proportion of participants who were completely healed at 10 days (14 out of 17 participants in the MEBO group and 17 out of 22 participants in the SSD group); risk ratio (RR) 1.07 (95% CI 0.78 to 1.46) (no statistically significant difference) \(^{[56]}\).
Wound infection: Desai et al. (1991) compared routine care (application of mafenide acetate cream dressings every six hours) plus an antimicrobial agent (gentamicin) administered via iontophoresis with routine care alone in 15 participants with ear burns. Three participants in the intervention group and four participants in the control group developed infection and chondritis (inflammation of cartilage), RR 0.86 (95% CI 0.29 to 2.58) (no statistically significant difference).

Secondary outcomes
Need for further surgery: The need for further surgery was reported by Ang et al. (2000). At six months post-burn no participant in either the MEBO group (n = 17) or the SSD group (n = 20) received surgery. Desai et al. (1991) reported that the mean number of surgical procedures in the intervention group was 1.2 (SE 0.1) and 1.0 (SE 0) in the control group. This difference was statistically significant (P < 0.05) in favour of the control group.

Adverse effects of treatment: The adverse effects of treatment were reported in one study. Desai et al. (1991) documented the appearance of gentamicin-resistant organisms in 29% of the participants in the group receiving gentamicin via iontophoresis, and in 0% of the participants in the control group, resulting in a RR of 5.63 (95% CI 0.31 to 100.52) (no statistically significant difference).

Length of stay (LOS): In Desai et al. (1991), the mean LOS was significantly shorter in the intervention group, 26 days (SD 2.6 days), compared with 38 days (SD 8.5 days) in the control group (mean difference -12.00, 95% CI -18.20 to -5.80), but there was no significant difference in LOS after adjusting for burn size.

Scar quality, pain, patient satisfaction and quality of life were not reported in these trials.

Comparison: wound dressings (skin substitutes) compared with antimicrobials
Three studies compared a skin substitute (a bio-engineered skin substitute or allograft) with an antimicrobial (either bacitracin or SSD or an unspecified antibacterial ointment) in 65 people.

Primary outcomes
Time to complete wound healing: Three studies reported time to complete wound healing but as they did not use the appropriate statistical method for their analyses these data were not plotted graphically. Time to healing is a form of time to event data, more correctly analysed using survival methods which can account for censoring (i.e., just for the time that people were observed so it takes account of when they dropped out), it is inappropriate to report and analyse time to wound healing as if it were a continuous variable unless everyone healed and there was no loss to follow up. Demling et al. (1999) divided 21 participants into two groups for minor and major burns. Wounds in the minor burns skin substitute group had a mean healing time of eight days (SD 1 day), which was
significantly less than the mean healing time of 12 days (SD 3 days) in the bacitracin group (P < 0.05). Similar results were reported for major burns where the skin substitute group had a mean healing time of eight days (SD 2 days), which was significantly less than the mean healing time of 14 days (SD 4 days) in the bacitracin group (P < 0.05) [57]. In Demling et al. (2002), wounds in the skin substitute group had a mean healing time of nine days (SD 4 days; n = 16), which was significantly less than the mean healing time of 15 days (SD 4 days; n = 18) in the antibacterial ointment group (P < 0.05) [58,59]. Horch et al. (2005) reported the median time to re-epithelialisation, which was significantly less in the allograft group (10.5 days; n = 5) compared to the SSD group (12.4 days; n = 5) (P < 0.05) [61].

Wound infection: Three studies reported wound infection as an outcome. In Demling et al. (1999) and Demling et al. (2002) none of the participants in the intervention or the control groups showed signs of infection [57-59]. In Horch et al. (2005) none of the participants in the intervention group showed local infections, while there was no information about wound infection in the control group [61].

Secondary outcomes

Scar quality: Scar quality was a reported outcome in Horch et al. (2005). Scar quality was defined as the incidence of hypertrophic scar formation six months post-burn. At that point none of the participants in the intervention group (n = 5) and two participants in the control group (n = 5) had hypertrophic scar formation, resulting in a non-significant risk ratio (RR) of 0.20 (95% CI 0.01 to 3.35) [61]. Horch et al. (2005) did not report a measurement tool or provide a definition used to classify scars as hypertrophic [61].

Pain: Pain was an outcome of interest in both studies by Demling [57-59], which used a 10-point scale to measure it (0 for no pain and 10 for worst pain). Pain measurements were made during, and between, facial care. Demling et al. (1999) divided the participants into two groups for minor and major burns [57]. In the minor burn group, the mean pain score during facial care in the intervention group was 2 (SD 1) and 5 (SD 1) in the control group (mean difference -3.00, 95% CI -4.24 to -1.76); while the mean pain between facial care in the intervention group was 1 (SD 0.5) and 3 (SD 2) in the control group (mean difference -2.00, 95% CI -3.81 to -0.19). In the major burns group, the mean pain during facial care in the intervention group was 2 (SD 1) and 5 (SD 1) in the control group (mean difference -3.00, 95% CI -4.19 to -1.81); while the mean pain between facial care in the intervention group was 2 (SD 1) and 4 (SD 2) in the control group (mean difference -2.00, 95% CI -3.82 to -0.18). All the above mean differences were statistically significant (P < 0.05) [57].

In Demling et al. (2002), the mean pain during facial care in the intervention group was 3 (SD 1) and 7 (SD 2) in the control group (mean difference -4.00, 95% CI -5.05 to -2.95); while the mean pain between facial care in the intervention group was 2 (SD 1) and 4 (SD 2) in the control group (mean difference -2.00, 95% CI -3.05 to -0.95) [58,59]. Both mean differences were statistically significant (p < 0.05).
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Inclusion criteria and main baseline characteristics</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang et al. (2000)</td>
<td>Partial-thickness burns up to 40% BSA burned and suffering facial burns % TBSA burned (Mean; SE; range): I: 2.16; 0.38; 0.13-6.0; C: 1.56; 0.18; 0.5-3.5.</td>
<td>I (n = 17): Moist Exposed Burn Ointment (MEBO), 1 mm thick layer applied 6 times/day. C (n = 22): SSD applied 2 times/day.</td>
<td>Primary outcomes Number of days taken for face-wound to heal: I: 2-35 days (range); C: not reported. Proportion completely healed in 10 days: I: 14/17; C: 17/22. Secondary outcome Need for reconstructive surgery 6 months PB: I 0/17; C: 0/20.</td>
</tr>
<tr>
<td>Demling et al. (1999)</td>
<td>Partial-thickness (mid dermal) burns of at least 50% of the facial surface. Mean age (SD years): Minor burns: I: 31(8); C: 29(7). Major burns: I: 44(10); C: 40(8). % TBSA burned (Mean, SD)): Minor burns: I: 1(3); C: 7(2). Major burns: I: 32(9); C: 30(8).</td>
<td>I (n = 10): Biological skin substitute coated with fibroinectin (TransCyte). C (n = 11): Topical antibiotics (bacitracin)</td>
<td>Primary outcomes Mean number of days to &gt; 99% re-epithelisation (SD): Minor burns: I: 8(1); C: 12(3); P &lt; 0.05 Major burns: I: 8(2); C: 14(4); P &lt; 0.05. Signs of local wound infection: Minor burns: I: 0; C: 0; Major burns: I: 0; C: 0. Secondary outcomes Pain during facial care (Mean, SD): Minor burns: I: 2(1); C: 5(1) Major burns: I: 7(1); C: 5(1). Pain between facial care (Mean, SD): Minor burns: I: 1(0.5); C: 3(2); Major burns: I: 2(1); C: 4(2). Mean length of stay (SD): Minor burns: I: 1(0.5); C: 3(1); Major burns: Not reported.</td>
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<tr>
<td>Demling et al. (2002)</td>
<td>Major burns including partial-thickness facial burns at least middermal in depth. Mean age (SD): I: 39(9); C: 40(8). % TBSA burned (Mean, SD): I: 24(8); C: 21(9).</td>
<td>I (n = 16): Bioactive skin substitute (a bilayered, biologically active, temporary skin substitute (TransCyte)). C (n = 18): Antibacterial ointment, no further details available</td>
<td>Primary outcomes Mean number of days to &gt; 95% re-epithelisation (SD): I: 9(4); C: 15(4); P &lt; 0.05. Signs of infection diagnosed with swab cultures exceeding 105 organisms/g: I: 0; C: 0. Secondary outcomes Pain during facial care (Mean, SD): I: 2(1); C: 7(2). Pain between facial care (Mean, SD): I: 2(1); C: 4(7).</td>
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<tr>
<td>Desai et al. (1991)</td>
<td>Ear burns admitted within 72 hours of burn injury. Mean age (SE): I: 1.4(1.2); C: 9.5(1.6). % TBSA burned (Mean, SE): I: 35(7); C: 50(6).</td>
<td>I (n = 7): Gentamicin iontophoresis + routine care (mafenide acetate). C (n = 8): Routine care only (6-hourly application of mafenide acetate).</td>
<td>Primary outcome Cases of wound infection diagnosed with the occurrence of chondritis: I: 3; C: 4. Secondary outcomes Mean number (SE) of surgical procedures required: I: 1.2(0.1); C: 1.0(0); P &lt; 0.05. Adverse effect of treatment: occurrence of gentamicin-resistant micro-organisms: I: 29%; C: 0%. Mean length of stay (SE): I: 26(1); C: 38(3).</td>
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<tr>
<td>Horch et al. (2005)</td>
<td>Superficial and deep partial-thickness facial burns. Median age (range): I + C: 34.3(24-67).</td>
<td>I (n = 5): Glycerolised alginate cadaver (corpses) skin. C (n = 5): Open treatment with SSD ointment</td>
<td>Primary outcomes Median number of days to complete re-epithelisation: I: 10.5; C: 12.4; P &lt; 0.05. Signs of underlying infection: I 0; C: not reported Secondary outcomes Hypertrophic scar formation: I 0; C: 2. Adverse effect of treatment: localized partial integration of the biological dressing: I 1; C: 0.</td>
</tr>
</tbody>
</table>

Abbreviations: I = intervention group; C = control group; TBSA = Total Body Surface Area; SE = Standard Error; PB = post-burn; SD = Standard Deviation; P = P value.
Table 2. Characteristics of studies awaiting classification and ongoing studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hindy (2009)</td>
<td>Superficial dermal burns to the face</td>
<td>I1: Sodium carboxymethyl-cellulose silver (Aquacel Ag®).</td>
<td>Time necessary for healing.</td>
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<td>I2: Moist Exposed Burn Ointment (MEBO®).</td>
<td>Pain.</td>
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<td>I3: Saline soaked dressing</td>
<td>Quality of healing.</td>
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<td>Patient satisfaction.</td>
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<td>C: placebo hydrogel.</td>
<td>Time to complete wound healing.</td>
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<td>Adverse effects.</td>
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<td>I2: Moist Exposed Burn Ointment (MEBO®).</td>
<td>Rate of infection</td>
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<td>Time to total healing.</td>
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<td>Frequency of dressing changes.</td>
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<td>Pain.</td>
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<td>Cost benefit.</td>
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<td>Patient discomfort.</td>
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<td>Incidence of hypertrophic scarring.</td>
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<tr>
<td>Oen et al. (2012)</td>
<td>Adults admitted to one of the 3 Dutch Burn Centres with burn injuries involving the face.</td>
<td>I1: cerium nitrate SSD (flammacerium).</td>
<td>Number of participants requiring surgical excision of their facial burns.</td>
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<tr>
<td></td>
<td></td>
<td>I2: silver sulphadiazine (SSD) (flammazine).</td>
<td>Quality of life and self-esteem.</td>
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<td>Quality of scar.</td>
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<td>Scar elasticity, vascularisation and pigmentation.</td>
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<td>Hypertrophic surface area.</td>
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<tr>
<td>Lehne (2012)</td>
<td>Adults admitted to the burn unit with a minimum of 1% partial-thickness burns each side of the face.</td>
<td>I: Collagenase</td>
<td>Difference in wound bed establishment.</td>
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<td></td>
<td></td>
<td>C: Bacitracin</td>
<td>Pain.</td>
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<td>Anxiety.</td>
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<td>Itch levels.</td>
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<td>Wound healing.</td>
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</tbody>
</table>

Abbreviations: I = intervention group; C = control group.
**Adverse effects of treatment:** Adverse effects of treatment was reported in one study \[61\]. In Horch et al. (2005), one participant in the intervention group suffered a localised integration of the biological dressing, which was removed by two repeated dermabrasion manoeuvres. After these manoeuvres, no more visible allograft remnants remained \[61\].

**Length of stay (LOS):** Length of stay (LOS) was reported by Demling et al. (1999), for the minor burns group only where the mean LOS was significantly less in the intervention group at 1 day (SD 0.5 days), compared with 3 days (SD 1 day) for the control group (mean difference -2.00, 95% CI -2.98 to -1.02) \[57\].

Need for (reconstructive) surgery, patient satisfaction and quality of life were not reported in these trials.

## Discussion

### Summary of main results

We included five randomised controlled trials in this review that evaluated the effect of a variety of topical interventions for facial burns. Three studies compared skin substitutes with different antimicrobial agents whilst two studies compared two different antimicrobial agents. None of the studies investigated wound preparation agents, antiseptics or other treatments, including alternative remedies. The variety of topical interventions evaluated and differences in outcome measures between studies made pooling of data inappropriate, therefore, the results have been presented in a narrative overview by comparison. This summary of main results is divided in two primary outcomes (i.e. wound healing and wound infection) and all secondary outcomes have been combined.

### Wound healing

Wound healing was variously measured and reported as: time to complete wound healing, average proportion of wound completely healed within a specified time period, change in wounds and percentage of wound healed during follow up. Time to complete wound healing was reported in four studies, but only Ang et al. (2000) used survival methods (the appropriate approach to statistical analysis of time to event data) \[56\]. This study compared two antimicrobial agents (MEBO and silver sulphadiazine) in 39 participants and found a similar risk of healing with both interventions (hazard ratio 0.84, 95% CI 0.38 to 1.85) \[56\]. The other three studies compared a wound dressing (i.e. skin substitute (Transcyte® and allograft)) with an antimicrobial agent. The difference in mean time to complete wound healing in days was significantly reduced with the skin substitutes in two of the studies \[57-59\]. The third study reported a statistically significant reduction in median days to complete wound healing, which also favoured the skin substitutes (i.e. intervention group 10.5 days, control group 12.4 days) \[61\]. Thus, the results of all three studies of skin substitutes compared with antimicrobial
agents favoured the skin substitutes. A cautious conclusion might be that the time to complete wound healing is shorter with the application of skin substitutes compared with topical antimicrobials. A reason for our caution is that none of the three studies used the appropriate statistical method - survival analysis - for these analyses and if not all participants were completely healed or if there were withdrawals during the study this estimate will be biased. The proportion of the wound that was completely healed in a specified time period was reported in Ang et al. (2000), where the results did not show a statistically significant difference. Consequently we can only confidently conclude that there is no high quality evidence of a difference in facial burn wound healing between the antimicrobials studied and either alternative antimicrobials or skin substitutes.

Wound infection
Four studies addressed wound infection as a negative outcome. Demling et al. (1999) and Demling et al. (2002) reported no occurrence of wound infection in any group; Horch et al. (2005) reported no occurrence of wound infection in the intervention group, but did not provide information about the control group; Desai et al. (1991) reported three cases of chondritis in the intervention group and four cases in the control group. These data were insufficient to support any definite conclusions.

Secondary outcomes
Except for patient satisfaction and quality of life, all other secondary outcomes (need for (reconstructive) surgery, scar quality, pain, adverse effects of treatment and length of stay) were addressed by at least one study. One study addressed the number of surgical procedures required, which significantly favoured the control group. One study addressed the need for reconstructive surgery; none of the participants needed any in the follow-up period. The follow-up period in this study was six months post-burn, which might be too short for a full assessment of the need for reconstructive surgery. Reconstructive surgery can be divided into urgent, essential and desirable procedures. The urgent and essential procedures might be performed within a six-month follow-up period, but the desirable procedure is usually postponed until scars have fully matured. This maturation can take a year or longer. Therefore, differences in the need for reconstructive surgery between intervention and control group might appear in a later phase.

An adverse effect of treatment that consisted of a localised integration of the biological dressing (removed by two dermabrasion manoeuvres) was reported in Horch et al. (2005). Another adverse effect of treatment was reported in Desai et al. (1991) where gentamicin-resistant micro-organisms appeared in the intervention group. The only study that assessed scar quality did not find a significant treatment effect. Both studies that assessed pain found significantly better results for the groups receiving skin substitutes. The results showed a greater mean difference in pain levels during facial care sessions, which scored 3 to
4 points on the pain scale compared to pain experienced between facial care sessions, which scored 2 points. This finding might not be surprising because the intervention group had hardly any wound dressing sessions: after the application of a skin substitute, facial care was usually restricted to the first day, although the control group received facial care two or three times a day. The two studies that addressed length of stay did report a statistically significant difference \(^{[57,60]}\), but only in the minor burns sub-group \((n = 10)^{[57]}\), or before adjusting for burn size \(^{[60]}\). After adjusting for burn size in Desai et al. (1991) no difference could be determined between the intervention and control groups for length of hospital stay \(^{[60]}\). All secondary outcomes should be interpreted with caution due to wide 95% confidence intervals and lack of sufficient data.

**Overall completeness and applicability of evidence**

The objective of this review was to assess the effectiveness of topical interventions on wound healing in people with facial burns of any depth. All topical interventions were eligible for inclusion, but only seven different interventions were identified. Furthermore, four of the included studies investigated only partial-thickness burns, and one did not specify the depth(s) of the facial burns of its participants \(^{[60]}\). None of the included studies addressed the outcomes of patient satisfaction or quality of life. Therefore, overall completeness has clearly not been achieved. The included studies were heterogeneous, so we could not assess publication bias with a Begg funnel plot or an Egger test. In addition, applicability of evidence might be restricted to specialised burn centres in developed countries, because of the relatively high costs of skin substitutes.

**Quality of the evidence**

The evidence combined in this review was of insufficient quality to allow definite conclusions to be drawn. In particular, the methodological quality of the included studies was relatively low: all five studies had small sample sizes, ranging from 10 to 39, which increase the spread of confidence intervals and decrease validity of results. While pooling data from small trials could increase statistical power and give a more precise overall estimate of effect size, the studies in this review did not compare similar interventions and had different outcome measures, which prevented pooling. Most of the included studies had other shortcomings regarding sequence generation, allocation concealment, blinding and intention-to-treat (ITT) analysis. Only one study described sequence generation and allocation concealment adequately \(^{[56]}\); the other four studies only stated that participants were randomised. Blinding of participants and care providers is not easy in studies that compare topical interventions, but outcome assessors could have been blinded. Despite this possibility, only one study reported blinding of outcome assessors for all outcomes \(^{[56]}\). Intention-to-treat analysis was reported and confirmed in only one study \(^{[58,59]}\). Another study did not report ITT-analysis, but it appeared likely when the study was assessed \(^{[61]}\). The other three studies did not perform ITT-analysis \(^{[56]}\), or did not report this.
clearly [57,60], possibly introducing bias. As a result of all these deficiencies, evidence from the included studies should be interpreted with caution.

Potential biases in the review process
Potential bias in the review process might have arisen as a result of the minimal response to our queries from authors of the eligible studies. The review authors tried to contact study authors by email in an attempt to retrieve all possible data to assess the studies thoroughly. Despite issuing a reminder, we received only one reply from Branski et al. (2008) with answers to our questions [66]. As a result of those answers, we excluded this study as sequence generation and allocation concealment were inadequate and therefore judged not to be a randomised controlled trial. Four other studies scored unclear on these items, but as additional information was not provided, they were included. Another potential bias might have occurred due to a possible patient overlap between Demling et al. (1999) [57] and Demling et al. (2002) [58,59]. Both studies were performed in the same hospital, and did not provide inclusion periods. Therefore, we were unable to confirm whether there was a patient overlap, or determine how one might alter our conclusions.

Agreements and disagreements with other studies or reviews
In general, the results of this review are in accordance with the results of the included studies, but some conclusions in the studies are slightly premature. None of the studies provided firm evidence, so conclusions should be cautious. This review agrees with the statement in Horch et al. (2005) that “it would be worthwhile to perform more clinical studies with a larger number of patients to further evaluate the effect and function of allogenic skin for facial burns” [61], and shows this statement is applicable for skin substitutes in general. Furthermore, the small number of included studies in this review is in accordance with a Cochrane review on a similar topic with a broader search [44]. In that review, burns of all types - except hand burns - were eligible, resulting in 26 included studies. In this review only facial burns were eligible, resulting in five included studies. Another review investigated the methodological quality of randomised controlled trials in burn care [74]. Danilla et al. (2009) included 257 eligible studies (from OVID Medline 1950 to January 2008) and concluded that “the reporting standards of RCTs are highly variable and less than optimal in most cases” [74]. Furthermore, their results showed an increase in RCTs over time without a significant improvement in methodological quality. These findings are in line with our results, as four out of the five included RCTs were performed in the last decade, but included no studies of high methodological quality. In summary, the number of studies in burn care is growing, but the body of evidence is still hampered due to an insufficient number of studies that follow appropriate evidence-based standards.
Authors’ conclusions

Implications for practice
There is insufficient high quality research and evidence to enable conclusions to be drawn about the effects of topical interventions on wound healing in people with facial burns.

Implications for research
In order to improve the quality of the evidence, future studies should be designed in conjunction with a trials expert and a statistician and include a sample size calculation. An appropriate sequence generation and allocation concealment should be used in order to reduce risk of bias, and blinding should be attempted. Although it is difficult to blind participants and care providers, it is possible to blind outcome assessors. A sample size calculation should be used in order to increase statistical power and give a more precise overall estimate of effect size. Furthermore, future trialists might add patient satisfaction and quality of life to their outcomes of interest, as these outcomes are especially important for patients. In addition, future trialists might give some extra thought to the outcome wound healing, as this outcome can be reported in numerous ways and it is not always analysed correctly (i.e. survival analyses). Ideally, all trialists should use the same measurement for wound healing, and as a result, allow comparisons to be made. We suggest a clinical important measurement, for instance time to 95% wound healing, that could be considered as the percentage of wound healing necessary for discharge to outpatient management. This subjective wound assessment, performed by an experienced observer, is found to be a reliable and valid tool. Topical interventions are numerous, so future research should focus on those interventions most likely to benefit patients.

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Declarations of interest

Magriet van Baar, Irma Oen, Esther Middelkoop and Marianne Nieuwenhuis were involved in a trial\(^\text{[65]}\) which has been added to Table 2 and may be eligible for inclusion in future updates of this review. No other conflicts of interest are declared.

Sources of support

*Internal source:* The Association of Dutch Burn Centres, Netherlands  
*External source:* NIHR/Department of Health (England), (Cochrane Wounds Group), UK
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Chapter 3


Topical treatment for facial burns