Early excision and grafting for burns

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Abstract

Background: Burn injuries are an important health problem. The functional and cosmetic outcome of a burn depends on the size, depth and treatment of the burn. It is generally understood that superficial burns heal well with topical treatment alone, while deep partial-thickness and full-thickness burns often require surgical treatment. However, there is debate about the optimal timing of surgery.

Objectives: To assess the effects of early excision and grafting on scar quality in people with burns of all depths.

Search methods: We searched the Cochrane Wounds Group Specialised Register (searched 3 October 2013); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 10); the NHS Economic Evaluation Database (The Cochrane Library 2013, Issue 10); Ovid MEDLINE (1948 to September Week 4 2013); Ovid MEDLINE (In-process & Other Non-Indexed Citations October 1, 2013); Ovid EMBASE (1974 to 2013 Week 39); and EBSCO CINAHL (1982 to 27 September 2013) for relevant trials. We did not apply date or language restrictions.

Selection criteria: Randomised controlled trials (RCTs), both published and unpublished, that evaluated the effects of early excision and grafting in people with burns were eligible for inclusion in this review.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.

Main results: We included ten RCTs, comprising a total of 416 participants. All studies had relatively small sample sizes (13 to 85) and had some methodological limitations. Heterogeneity of interventions and outcomes prevented pooling of data for most results. Three studies addressed scar quality as an outcome but there was insufficient data to support any definite conclusions. Additional results indicated that early excision and grafting reduced the number of positive wound swabs and length of hospital stay. On the other hand, four studies addressed the proportion of participants requiring surgery; 48% (34 out of 71) of the participants that received conservative treatment had wounds that healed without surgery. In addition, four studies showed that conservative treatment reduced blood loss as a result of the operation.

Authors’ conclusions: There is insufficient high quality research and evidence to enable definite conclusions to be drawn about the effects of early excision and grafting on scar quality in people with burns.


Background

Burn injuries are an important health problem. Worldwide it is estimated that each year over 195,000 people die from fire-related burn injuries and millions more suffer from burn-related disabilities and disfigurement [1]. In the United States of America (USA), annually 40,000 people are admitted for burns, including 30,000 admissions to hospitals with specialised burn centres [2]. In the United Kingdom, approximately 13,000 people per year are admitted to hospital for treatment of burns [3], while in the Netherlands the annual figure is about 1800 people [4], 550 to 600 of whom are treated in one of the three Dutch burn centres [5].

Major improvements in burn care in the twentieth century mean that mortality rates from burn injuries have substantially decreased. This has resulted in a shift in attention from mortality towards morbidity, for example, the functional outcome after a burn injury [6]. It is generally understood that superficial burns heal well with few or no functional or aesthetic problems. However, the best treatment for deep partial or full-thickness burns remains controversial [7]. In the United States, there seems to be consensus on early excision and grafting [8], while in Europe, usually, a more conservative approach is applied. In conservative treatment, surgery is postponed until clinical assessment indicates that surgery is inevitable. Eventually both United States and Europe excise and graft deep partial-thickness burns, but optimal timing of this intervention is unclear. Timing is important because early excision could reduce length of hospital stay but increases the risk of overzealous excision, while delayed excision reduces the risk of overzealous excision but increases the risk of wound infection and length of hospital stay. Overzealous excision could also increase risk of scarring. Scars usually appear when wound healing takes more than two weeks or after surgical treatment. Therefore, it might be beneficial to postpone surgery until it becomes evident whether a wound will heal within two weeks.

Description of the condition

A burn injury of the skin occurs when some or all the different layers of the skin are destroyed by physical energy such as hot liquid, flame, contact burns or ultraviolet/infrared radiation, radioactivity, electricity or chemicals [9]. In addition to the localisation of a burn and associated injuries, severity of burn wounds is characterised by size and depth. The size of a burn is assessed by the Total Body Surface Area percentage (TBSA%), which is the percentage of the skin surface area burned. The depth of a burn is determined by which layers of the skin are destroyed, only the epidermis or both the epidermis and the dermis. So far, no consensus has been reached on the exact classifications of burns, especially not in relation to the classification of depth [10]. In general, skin burns are classified by depth 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 due to the migration of epithelial cells from the stratum
basale to the surface, with very little or no scarring. 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, glands and hair follicles. The damage of glands and hair follicles hampers the migration of epithelial cells from the stratum basale surrounding these accessory structures. Healing generally takes more than two to three weeks and occurs due to the migration of epithelial cells from the wound edges and the sparse epithelial elements present in the bottom of the wound. Finally, full-thickness burns involve all layers of the skin and may involve structures underneath, such as muscle and bone, leaving little chance of healing from the epithelial elements in the bottom of the wound. In case of a very small full-thickness burn, healing might occur by contraction and epithelial cell growth from the wound edges \[8\]. Full-thickness burns will always result in scarring and often result in hypertrophic scarring. In addition, hypertrophic scarring may also occur when re-epithelialisation does not occur within two to three weeks \[11,12\].

Burn wound surfaces are sterile immediately following thermal injury, but they are rapidly colonised by a variety of micro-organisms \[13,14\]. Those micro-organisms not only originate from the patient’s own skin, respiratory and gastro-intestinal flora, but also from contact with contaminated external environmental surfaces, hands of healthcare workers and even air \[13-15\]. Burn wounds provide a favourable niche for microbial colonisation and proliferation because of their protein-rich environment and avascular necrotic tissue \[13,16\]. This avascularity of eschar (necrotic tissue) results in impaired migration of host immune cells and restricts delivery of systemically administered antimicrobial agents to that area. The most common burn wound pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa* \[17\]. Colonisation of burn wounds has been associated with delayed wound healing, increased need for surgical interventions and prolonged length of stay at burn centres \[18\].

In addition to local responses, severe burn injuries can also induce systemic responses like cardiovascular, respiratory, metabolic and immunological changes. The release of inflammatory mediators at the site of injury has a systemic effect once a burn reaches 30% of the total body surface area \[19\]. These systemic reactions, besides generating excessive oedema in burns as a result of increased capillary permeability, can further compromise wound healing. 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.

Hypertrophic scarring occurs if the balance between collagen synthesis and breakdown is disrupted \[8\]. The post-burn hypertrophic scar might present itself as a pink to red, slightly thickened or as a red to purple inelastic mass of skin tissue. Functional impairment can occur, especially if a hypertrophic scar crosses a joint or surrounds openings like eyes. For instance, a contracture of the elbow may result in a limited range of motion and even cause restrictions in daily life activities. Another example are eyes that may not close due to the inelasticity and contraction of the hypertrophic skin. Furthermore, scars can result in discomfort because of itching and sometimes cause neuropathic pain after burn injury \[20\]. 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 if wound healing takes more than 21 days. In general, a deeper burn wound results in the formation of more hypertrophic tissue. Other factors involved with 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 early excision and grafting for burns. In this section we will elaborate on the different surgical excision and grafting techniques used in burns as well as issues of timing.

The surgical excisions performed in burns can roughly be divided in escharotomy and surgical debridement. Escharotomy is a surgical procedure used to treat full-thickness, circumferential burns. In those burns, the combination of a leathery-like, inelastic burned skin and the swelling of underlying tissue can obstruct circulation and cause cell death in healthy body parts due to ischaemia (e.g. a circumferential full-thickness burn around the forearm can cause necrosis of the hand with even amputation as a result). In order to prevent cell death and amputation, incisions (escharotomies) are made through the eschar until blood flow to the body part at risk is restored. Furthermore, escharotomies to the chest are used to restore respiration and are indicated when burned skin prevents expansion of the chest necessary for respiration. Surgical debridement on the other hand, is the excision with removal of all non-vital tissue of the burn wound and can be divided in two main approaches, namely: fascial and tangential excision. Fascial excision, or avulsion, is only practised in full-thickness burns and consists of tearing away the burned skin and underlying subcutaneous tissue. This technique will cause body deformities but reduces blood loss compared to tangential excision. Tangential excision is the most commonly used technique in burn surgery and often combined with grafting. With this technique all non-viable tissue is removed layer by layer, preserving as much viable tissue as possible. Nowadays, this procedure can be even more precise with the development of hydro surgery which is especially used in critical functional and aesthetic areas.

Grafting is the transplantation of skin onto an excised burn wound in order to provide temporary or permanent wound closure. The timing of grafting can be immediate (i.e. in the same procedure as the initial excision) or delayed (i.e. in a subsequent procedure) and the skin transplant can originate from the same individual (autologous), another individual of the same species (allogeneic or homologous) or from a different species (xenogeneic or heterologous). There are two different kind of grafts, namely: full-thickness graft (FTG) and split skin graft (SSG). A FTG consists of the epidermis and all of the dermis, and is used more in reconstructive surgery than primary surgery. A SSG consists of the epidermis and some of the dermis, and is often used in primary surgery. A SSG can be applied as a meshed, unmeshed or Meek-Wall graft. An untreated SSG is
unmeshed, but when small incisions are made in the SSG, it can be expanded up to six times its original size and is called a meshed graft. Another technique to increase the surface of a graft even more is the Meek-Wall technique. With this technique the SSG is divided into little squares, or skin islands, and transplanted on an excised burn wound.

Timing of excision can be divided into early and delayed or late excision, but definitions of these concepts are under debate. Choi et al. (2008) state that “all excision procedures done before the natural separation of the eschar are considered an early excision, and all done afterward are considered delayed excision”, while Kirn et al. (1998) defined early excision as operative excision within seven days post-burn. Herndon et al. (2007) advocate early excision and grafting in major burns without explicitly defining ‘early’, and in the review by Ong et al. (2006) ‘early’ ranges from < 24 hours to < 144 hours post-burn. In conclusion, there is no consensus on a cut-off point between early and delayed excision.

**How the intervention might work**

Early excision and immediate or delayed grafting for burns provides an early wound closure or coverage which might have beneficial effects on infection, survival and scarring. In particular, a reduced infection rate seems probable because early wound closure limits the time a wound is exposed to possible invading pathogens colonising the wound. Colonised burn wounds have been associated with delayed wound healing, increased need for surgical interventions and prolonged length of stay at burn centres. The effects on survival might be a result of early excision of eschar. Removal of eschar is thought to decrease the release of inflammatory mediators which could cause systemic effects. Systemic effects, like systemic inflammatory response syndrome (SIRS), sepsis and multi-organ failure, compromise wound healing and can cause death. Effects of early excision and grafting on scarring could be beneficial or harmful, depending on the depth of the burn wound. In full-thickness and deep partial-thickness burns there will be scarring regardless of intervention, but early excision and grafting could provide early wound closure and could reduce the severity of scarring. Superficial partial-thickness burns, on the other hand, could heal without scarring when conservative treatment is applied, while surgical treatment will always leave scars. Often the depth of a burn is not either superficial partial-thickness or deep partial-thickness but a mix of those depths. In these cases, early excision and grafting could be overzealously executed and cause scarring in areas that would have been able to reepithelialise without surgical intervention. Conservative treatment could give the superficial partial-thickness areas time to reepithelialise with little or no scarring, but postponing excision of the deep partial-thickness areas too long will cause more extensive scars.
Why it is important to do this review
Surgical procedures are an important intervention in burns, but there is no consensus on the best timing of surgical intervention. One review states that “early excision of burns reduces mortality in patients without inhalational injury, increases blood transfusion requirements and reduces the length of hospital stay in patients” [29], but this review is non-systematic and not up-to-date. Several systematic reviews have been published in the field of wound care, but most of them focus on wound dressings [31] and other topical treatments [18,32] instead of surgical procedures. Despite these reviews, 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, concerning the treatment of burns and scalds in primary care [33]. Systematic reviews are necessary to increase the body of underlying evidence for these guidelines. In conclusion, published reviews do not address the effectiveness of early excision and grafting in burns.

Objectives
To assess the effects of early excision and grafting on scar quality in people with burns of all depths.

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 early excision and grafting in people with burns. We decided to consider quasi-randomised controlled trials only in the absence of RCTs.

Types of participants: We considered studies that included people of any age with burns 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 early excision and grafting was applied and compared with any comparator intervention. Whilst there was no clear consensus on the definition of ‘early’ we defined early excision as excision within a week post-burn. We considered any kind of graft. Comparator interventions could include any other intervention (e.g. different excision technique or grafts, ointments), no intervention or a placebo intervention on condition that timing of excision was different compared to the intervention. The timing or type of grafting did not form part of the selection process.
Types of outcome measures: Study outcome did not form part of the selection process. We divided outcomes into primary and secondary outcomes; these are listed below.

Primary outcomes; three outcome measures were considered primary outcomes. These primary outcomes consisted of one positive and two negative outcomes. The positive primary outcome was the following:

- scar quality: observed and self reported (any definition of scar quality was accepted).

The negative primary outcomes were the following:

- wound infection (any definition);
- mortality.

Secondary outcomes; eight outcome measures were considered secondary outcomes. These outcomes were the following:

- proportion of burns requiring reconstructive surgery;
- pain;
- time to complete wound healing;
- length of hospital stay;
- adverse effects;
- patient satisfaction;
- quality of life;
- costs of treatment.

Search methods for identification of studies

Electronic searches: We searched the following electronic databases for reports of randomised controlled trials:

- Cochrane Wounds Group Specialised Register (searched 3 October 2013);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 10);
- the NHS Economic Evaluation Database (The Cochrane Library 2013, Issue 10);
- Ovid MEDLINE (1948 to September Week 4 2013);
- Ovid MEDLINE (In-process & Other Non-Indexed Citations October 1, 2013);
- Ovid EMBASE (1974 to 2013 Week 39);

The search strategies for CENTRAL can be found in the published protocol of this review.[34] This search strategy was modified as appropriate for other databases. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE; sensitivity- and precision-maximising version (2008 revision); Ovid format. This filter is published in the Cochrane Handbook for Systematic Reviews of Interventions (‘Cochrane Handbook’).[35] The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).[36] No date or language restrictions were applied. In addition we searched the International Clinical Trials

**Searching other resources:** We checked citation lists within all reports of included studies and major review articles 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 same two 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 baseline information: number, age, gender, type of burn, percentage total body surface area (TBSA) burned, burn depth, inhalation injury, concurrent illness;
- intervention: time elapsed before treatment, percentage TBSA grafted, types of excision, types of grafting, 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. The criteria relate to the following issues:

- sequence generation;
- allocation concealment;
- blinding of participants and care providers;
• blinding of outcome assessors;
• incomplete outcome data: assessment 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 and trial sponsorship.

Risk of bias increases with each criterion that is judged to be negative. A detailed description of criteria for a judgement of ‘low risk’, ‘high risk’ or ‘unclear risk’ of bias can be found in the published protocol of this review [34]. 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. A plus (+), minus (-) or question mark (?) were used to indicate low, high or unclear risk of bias, respectively. 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 [38]. 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) [39]. 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 Handbook 9.2.2 [38]) 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 Handbook 9.2.6 [38]).

**Unit of analysis issues:** We addressed the level at which randomisation occurred in our analysis. In general, the unit of randomisation and measurement was likely to be the person. 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 early excision, timing of early excision and body part burned. We planned to test statistical heterogeneity using the Chi² test and estimate the amount of heterogeneity using the I² statistic with 95% CI [38,40], 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 \cite{41} and the Egger test \cite{42}, 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 \cite{40}, 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. We focused on direct comparisons between surgical interventions. No totals were calculated if trial heterogeneity was considerable ($I^2$ statistic greater than 75%). If pooling was appropriate ($I^2$ statistic less than 75%) we used both a fixed-effect and a random-effects model. The fixed-effect model ignores heterogeneity and gives an estimate of the intervention effect, assuming a single intervention effect. A random-effects model incorporates heterogeneity amongst studies \cite{38,43}.

Subgroup analysis and investigation of heterogeneity: We planned to investigate heterogeneity through subgroup and sensitivity analyses \cite{38}, when there was a sufficient number of studies in the meta-analysis (i.e. more than 10). We planned to conduct subgroup analysis for the following groups:

- % TBSA burned (<20% TBSA versus 20% or more TBSA);
- age (<5 years versus 5 to 60 years versus 60 years and older);
- adequate concealment of allocation (low risk of bias versus unclear or high risk of bias).

Sensitivity analysis: If there was a sufficient number of studies in the meta-analyses, 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 exclude studies with unclear sequence generation and unclear allocation concealment.

Results

Description of studies

Results of the search: The search identified, after initial de-duplication, 512 articles. Two review authors (CH and JH) independently assessed the titles and abstracts of these articles and judged 26 citations to be potentially eligible for the review. Six citations appeared to be duplicates, decreasing the number of unique articles to 20. 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. An additional search in the International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/) did not result in additional, potentially eligible trials.

**Included studies:** Assessment of the 20 potentially eligible articles (26 citations) resulted in the inclusion of 10 studies (14 citations)\(^\text{[44-57]}\). The characteristics of these studies are described in **Table 1** and are summarised below.

**Health care settings**

Eight RCTs took place in burn centres; six in the USA\(^\text{[44-46,54,55,57]}\); one in England\(^\text{[47]}\) and one in Egypt\(^\text{[53]}\). One RCT took place in a Division of Plastic and Reconstructive Surgery in Lithuania\(^\text{[48-52]}\) and one in a General Surgery Department in India\(^\text{[56]}\). Four of the RCTs conducted in the USA were performed by the same research group\(^\text{[44,46,54,57]}\).

**Participants**

A total of 416 participants (224 wounds in intervention group, 226 wounds in control group) were recruited to the 10 included studies (range of sample size 13 to 85). It is possible that this number might be lower due to a possible overlap of participants between three studies\(^\text{[46,54,57]}\), which potentially would decrease the total to 366. Nine studies randomised the participants, whereas one study randomised 20 hands of 16 participants\(^\text{[56]}\). Two studies randomised the participants and, when applicable, analysed both hands in the allocated group\(^\text{[48-53]}\). Age and percentage TBSA burned of the included participants are summarised below. The mean age and standard error (SE) of the participants in the only paediatric study\(^\text{[44]}\) was 1.8 years (SE 0.4 years) in the intervention group and 1.9 years (SE 0.5 years) in the control group. The other nine studies included only adults\(^\text{[48-52,54]}\), participants between 17 and 55 years\(^\text{[46]}\), children and adults\(^\text{[45,47,55,56]}\), or were unclear whether children were excluded\(^\text{[53,57]}\). The mean age and standard deviation (SD) of the participants in those nine studies varied from 15.4 years (SD 14.6 years) to 46.7 years (SD 2.8 years). Mean percentage TBSA burned was reported in all 10 included studies and varied from 5.5% (SD 1.1%) in the intervention group in Engrav et al.\(1983\)\(^\text{[45]}\) to 66.7% (SEM 6.1%) in the intervention group in Rutan et al.\(1986\)\(^\text{[54]}\).

**Interventions**

All studies compared early excision and grafting within a week post-burn with a kind of conservative treatment. Two studies only stated that conservative treatment consisted of delayed excision and grafting\(^\text{[44]}\) or grafting alone\(^\text{[47]}\). In four studies, conservative treatment consisted of daily application of silversulfadiazine\(^\text{[45,54,55,57]}\) and two studies performed delayed excision and grafting if no re-epithelialisation occurred after application of silversulfadiazine in 14 days\(^\text{[48-52]}\) or 21-24 days post-burn\(^\text{[46]}\). One study performed delayed excision and grafting when spontaneous separation of eschar occurred after vigorous irrigation by saline and
application of antimicrobial ointments in the form of betadine or nitrofurazone\cite{53}. In one study, conservative treatment consisted of application of honey dressings on alternate days\cite{56}.

Primary outcomes
Three studies included scar quality as an outcome of interest, but differed in their measurement. In Engrav et al.\cite{1983}, scar quality was presented as the proportion of scars that had blisters, abnormal contour, surface irregularity, hypertrophy or loss of motion\cite{45}, whereas Maslauskas et al.\cite{2005} used the Vancouver Scar Scale and a patient-rated cosmetic appearance of the scar on a four point scale (lower scores represent better scar quality for both scales)\cite{48-52}. The third study\cite{56} used cosmetic wound appearance three months post discharge as scar quality measurement. Wound infection was reported in five studies and determined as clinically significant wound infection or sepsis\cite{44}, number of days septic (4 out of 7 pre-specified criteria)\cite{46}, positive wound swabs or blood cultures\cite{47} or positive wound swabs from wounds in which infection was suspected clinically\cite{48-52,56}. Four studies reported mortality\cite{46,47,56,57}.

Secondary outcomes
Secondary outcomes reported in the ten studies included the proportion of burns requiring reconstructive surgery, time to complete wound healing, length of hospital stay, adverse effects and costs of treatment. One study reported the proportion of burns requiring reconstructive surgery\cite{45} and one study included wound healing as an outcome of interest, measuring it as time in days until 5\% and 2\% of whole skin loss was left\cite{47}. Six studies\cite{44-46,53,56,57} reported length of hospital stay and one study reported costs of treatment\cite{45}. Adverse effects were reported in six studies, four studies reported the proportion of burns requiring surgery\cite{44,45,55,56}, one study reported proportion of wounds with partial graft loss and need for re-grafting\cite{53} and one study reported percentage graft take five days post-operative\cite{56}. Furthermore, one study reported complications of surgery\cite{45} and two studies reported blood loss\cite{44,46}. None of the studies reported pain, patient satisfaction or quality of life as outcome measure.

Excluded studies: Ten studies (12 citations) were excluded for different reasons; four studies because they were not RCTs\cite{58-63}, three studies because excision and grafting was not performed within a week post-burn\cite{64-66}, one study because excision and grafting was not an intervention\cite{67} and two studies because there was no difference in timing of excision\cite{68,69}.
Risk of bias in included studies

Two review authors (CH and JH) independently assessed risk of bias in the ten included studies and initially disagreed on 14 judgements. All disagreements were resolved by discussion. Details of the risk of bias judgements for the ten 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. A plus (+), minus (-) or question mark (?) represents a judgement of low, high or unclear risk of bias, respectively.

Allocation (selection bias):
For risk of bias assessment the term “allocation” included sequence generation and allocation concealment, which both had to be considered and are summarised below.

Sequence generation
Of the ten included studies, three studies \cite{45,46,53} described the method of sequence generation adequately, that is by pulling cards \cite{45}, using random number charts \cite{46} or random allocation software \cite{53}. Additionally, one study \cite{56} described the method of sequence generation in personal communication, that is by chit method. The other six studies stated only that participants were randomised, but did not describe the method of sequence generation \cite{44,47,52,54,55,57}.

Allocation concealment
Of the ten included studies, two studies \cite{45,53} described the method of allocation concealment
adequately, that is by pulling cards\textsuperscript{[45]} or using random allocation software [53]. Additionally, one study\textsuperscript{[56]} described the method of allocation concealment in personal communication, that is by chit method. The other seven studies did not describe the method of allocation concealment\textsuperscript{[44,46-52,54,55,57]}.

\textit{Blinding (performance bias and detection bias):} Review authors had to judge the blinding of participants, care providers and outcome assessors. None of the ten studies reported blinding of participants or care providers, but the nature of treatments made it impossible to blind them. Nevertheless, reviewers made a judgement of low risk of bias because the outcomes were not likely to be influenced by the lack of blinding of participants and care providers. None of the ten studies reported blinding of outcome assessors. Nevertheless, reviewers made a judgement of low risk of bias for five studies\textsuperscript{[44,46,54,55,57]} because the outcomes were not likely to be influenced by the lack of blinding of outcome assessors. In contrast, the reviewers made a judgement of unclear risk of bias for three studies\textsuperscript{[47-53]} because some of the outcomes in these studies could have been influenced by the lack of blinding of outcome assessors. After personal communication with Engrav et al.(1983)\textsuperscript{[45]} and Subrahmanyam et al.(1999)\textsuperscript{[56]}, the reviewers made a judgement of high risk of bias and low risk of bias, respectively. Engrav et al.(1983) performed no blinding which could have influenced outcome assessment\textsuperscript{[45]}, whereas Subrahmanyam et al.(1999) described blinding as: “The assessor was the doctor mentioned in the acknowledgements and not aware of the alootment”\textsuperscript{[56]}.

\textit{Incomplete outcome data (attrition bias):} The item “incomplete outcome data” consisted of two topics: drop-out rate and intention-to-treat (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 seven studies\textsuperscript{[44,47-54,56,57]}, whereas one study\textsuperscript{[46]} was judged “unclear” because there were discrepancies between the numbers in the tables and the numbers in the text. Drop-out rates in two studies\textsuperscript{[45,55]} were not acceptable and therefore judged to have high risk of bias. In Engrav et al.(1983), the drop-out rate exceeded 30\% for long-term follow-up in the control group without description of reasons for drop-out\textsuperscript{[45]}. In Salisbury et al.(1982), 28 participants started the study but only 16 completed the study without describing the reasons for drop-out\textsuperscript{[55]}. None of the ten studies reported ITT-analysis explicitly, but it appeared likely for eight studies\textsuperscript{[44,45,47-54,56,57]}, whereas one study\textsuperscript{[46]} was judged “unclear” because there were discrepancies between the numbers in the tables and the numbers in the text. Salisbury et al. (1982) clearly did not undertake ITT-analysis, as the control group was divided in a group that needed delayed excision and grafting and a group that healed with conservative treatment\textsuperscript{[55]}. These groups were analysed separately while this was not pre-specified in the methods section, therefore, the reviewers made a judgement of high risk of bias.
Selective reporting (reporting bias): All ten studies were classified as free of suggestion of selective outcome reporting, including one study\[46\] that did not report length of hospital stay and operating room procedures for a subgroup with inhalation injury. Because the high mortality in that subgroup prevented meaningful analyses for these outcomes in survivors, the reviewers made the judgement of low risk of bias.

Other potential sources of bias: Review authors considered four other potential sources of bias, that is, baseline characteristics, co-interventions, compliance and timing of outcome assessment. The baseline characteristics between intervention and control group were similar in seven studies\[44,45,47-53,55,56\]. In Herndon et al. (1989), the distribution of gender and etiology at baseline were not similar but unlikely to have influenced outcomes\[46\]. In Rutan et al. (1986), age and percentage TBSA burned were not similar between groups and could have influenced outcomes\[54\]. The baseline characteristics in Thompson et al (1987) were not similar with regard to age, which could have influenced outcomes\[57\]. The co-interventions between intervention and control groups were similar in eight studies\[44-46,53-57\], whereas no information was provided about co-interventions in two studies\[47-52\]. Compliance was acceptable in all ten studies and timing of outcome assessment between intervention and control group was similar in eight studies\[44-52,54,55,57\]. In Omar et al. (2011), follow-up was at two weeks and two months postoperatively rather than post-burn, which was on average 11 days later in the control group\[53\]. Because the outcomes of interest were related to the operation, this difference in timing of outcome assessment was judged “low risk of bias”. In contrast, timing of outcome assessment in Subrahmanyam et al. (1999) was judged “unclear” because the mean difference in timing between both groups was 25 days\[56\]. This difference in timing could have influenced outcome assessment, especially with regard to the outcome scar quality.

The four potential sources of bias resulted in an overall judgement of “low risk of bias” for seven studies\[44-53,55\], “high risk of bias” for two studies\[54,57\]; and one study\[56\] was judged “unclear”.

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. Type of comparisons were delayed excision and grafting (comparison 1), application of antimicrobials and delayed excision and grafting if necessary (comparison 2), and honey dressings (comparison 3). The effects of interventions are presented in Table 1 and summarised below.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Induction criteria and main baseline characteristics</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desai et al. (1991)</td>
<td>Scald injuries (which were not caused by grease) of clinically indeterminant depth.</td>
<td>I (n = 12): Early excision and grafting (within 72 hours of admission). C (n = 12): Late excision and grafting (after at least two weeks of serial dressing changes and daily bathing).</td>
<td>Primary outcome: Wound infection: I: 0; C: 0. Secondary outcomes: Mean length of hospital stay (SE): I: 17 (2); C: 21 (3). Adverse effects: Proportion of burns requiring surgery: I: 12/12; C: 6/12. Adverse effects: Blood loss (Mean total body blood turnover(SE)): I: 1.2(0.3); C: 0.3(0.1).</td>
</tr>
<tr>
<td>Engqvist et al. (1983)</td>
<td>Indeterminate flame or scalds burns less than 20% TBSA burned.</td>
<td>I (n=22): Early excision and grafting (within 7 days postburn). C (n = 25): Nonoperative treatment, twice daily hydrotherapy, debridement, and application of silversulfadiazine cream.</td>
<td>Primary outcomes: Scar quality: Proportion hypertrophy: I: 3/17; C: 7/17 Proportion abnormal contour: I: 0/17; C: 2/17. Proportion surface irregularity: I: 8/17; C: 1/17. Proportion loss of motion (contracture): I: 0/17; C: 1/17. Proportion blistering: I: 2/17; C: 1/17. Secondary outcomes: Number of patients requiring reconstructive surgery: I: 1/17; C: 1/17. Mean length of hospital stay (SD): I: 16.4 (1.2); C: 25.0 (1.8); p&lt;0.05. Adverse effects: Proportion of burns requiring surgery: I: 22/22; C: 12/25. Adverse effects: Complications of surgery: I: 1/22; C: 1/12. Mean total hospital costs in dollars (including physicians charges) (SD): I: 9,063 (1,144); C: 12,702 (1,270).</td>
</tr>
<tr>
<td>Hemdon et al. (1989)</td>
<td>Burns &gt;30% TBSA second-degree and &gt;20% TBSA third-degree burns, admitted within 3 days postburn.</td>
<td>I (n = 45): Early excision (within 72 hours of admission) and immediate wound coverage with meshed autografts 4:1. C (n = 40): Conservative wound-management with silver sulfadiazine and/or sulfamylon acetate antimicrobial cream; wounds were sharply debrided 21 to 24 days postburn and gradually grafted.</td>
<td>Primary outcomes: Wound infection: Mean (SD) days septic in subgroup without inhalation injury: I: 1.8 (2.5); C: 1.7 (1.7). Subgroup with inhalation injury: not reported. Mortality: I: 18%; C: 28%. Secondary outcomes: Mean length of stay in days (SD): Subgroup without inhalation injury: I: 53 (38); C: 47 (25). Subgroup with inhalation injury: not reported. Adverse effects: Blood loss as mean (SD) total body blood turnover: calculated at 80 ml/kg body weight: Subgroup without inhalation injury: I: 2.1 (2.2); C: 0.7 (0.6). Subgroup with inhalation injury: not reported.</td>
</tr>
<tr>
<td>Study ID</td>
<td>Inclusion criteria and main baseline characteristics</td>
<td>Interventions</td>
<td>Outcomes</td>
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<td>Jackson et al. (1960)&lt;sup&gt;631&lt;/sup&gt;</td>
<td>Burn patients</td>
<td>I (n = 16): Early excision (on day of burning). C (n = 14): Delayed grafting (2-3 weeks).</td>
<td>Primary outcomes&lt;br&gt;&lt;br&gt;<em>Wound infection</em>: Not clearly reported, unable to report meaningful proportions due to mixed numbers of different studies.&lt;br&gt;&lt;br&gt;<em>Mortality (Int.)</em>: t 5 (16); C: 3 (14).&lt;br&gt;&lt;br&gt;Secondary outcome&lt;br&gt;&lt;br&gt;<em>Time to complete wound healing in days</em>: Mean days until 5% / 2% of whole skin loss (w.s.l.) left. Reported for subgroups only. Original data was reported and used for survival analyses.</td>
</tr>
<tr>
<td>Malsauskas et al. (2005)&lt;sup&gt;632&lt;/sup&gt;</td>
<td>Hand burns</td>
<td>I (n = 24 (40 hands)): Early excision/necrotophy (within 7 days postburn) and grafting. C (n = 25 (39 hands)): Conservative treatment with silver sulfadiazine until epithelialisation. Delayed necrotophy and grafting if no epithelialisation occurred during a 14 day period.</td>
<td>Primary outcomes&lt;br&gt;&lt;br&gt;<em>Scar quality:</em>&lt;br&gt;&lt;br&gt;Mean Vancouver scar scale (SD; n): t 3.62 (2.93; 38); C: 6.77 (2.96; 37), p &lt; 0.001.&lt;br&gt;&lt;br&gt;Mean cosmetic appearance on 4 point scale (SD): t 1.9 (0.78); C: 2.64 (0.84), p &lt; 0.001.&lt;br&gt;&lt;br&gt;<em>Wound infection</em>: Positive wound swap: t 11; C: 33. &lt;br&gt;&lt;br&gt;Secondary outcomes&lt;br&gt;&lt;br&gt;None</td>
</tr>
<tr>
<td>Omar et al. (2011)&lt;sup&gt;633&lt;/sup&gt;</td>
<td>Deep second and third degree hand burns.</td>
<td>I (n = 20 (25 hands)): Early excision and grafting (before 6th day postburn).</td>
<td>Primary outcomes&lt;br&gt;&lt;br&gt;None&lt;br&gt;&lt;br&gt;Secondary outcome&lt;br&gt;&lt;br&gt;<em>Wound healing</em>: Complete graft take without re-grafting: t 20 hands; C: 21 hands.&lt;br&gt;&lt;br&gt;<em>Mean length of hospital stay (SD)</em>: t 16 (2.5); C: 24 (3.4); p &lt; 0.05.</td>
</tr>
<tr>
<td>Rutan et al. (1986)&lt;sup&gt;634&lt;/sup&gt;</td>
<td>Burns &gt; 45% TBSA</td>
<td>I (n = 7): Excision and grafting (within 72 hours of injury). C (n = 6): Conservative wound-management with daily hydrotherapy and twice a day applications of silver sulfadiazine and/or mafenide acetate (antimicrobial cream).</td>
<td>Primary outcomes&lt;br&gt;&lt;br&gt;None &lt;br&gt;&lt;br&gt;Secondary outcomes&lt;br&gt;&lt;br&gt;None</td>
</tr>
<tr>
<td>Study ID</td>
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<tr>
<td>Salisbury et al. (1982)</td>
<td>Hand burns</td>
<td>I (n = 8): Early excision and grafting (within 5 days postburn).</td>
<td>Primary outcomes&lt;br&gt;None</td>
</tr>
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<td></td>
<td>Mean Age (Range): 1: 23.8 (7-40); C (healed): 19.3 (11-30); C (operated): 23.6 (7-53)</td>
<td>C (n = 12): Conservative treatment with daily hydrotherapy, eschar debridement, topical application of silver sulfadiazine cream and biological dressings (corne xenograft or cadaver allograft).</td>
<td>Secondary outcome&lt;br&gt;Adverse effects: Proportion of burns requiring surgery: I: 8/8; C: 8/12</td>
</tr>
<tr>
<td>Subrahmanyam et al (1995)</td>
<td>Burns &lt; 30% TBSA burned, haemodynamically stable and between 10 and 40 years of age.</td>
<td>I (n = 25): Early excision and grafting (before 6th day postburn)</td>
<td>Primary outcomes&lt;br&gt;Scar quality: Excellent/good/fair: I: 8/14/2; C: 12/10 (Excellent or good/fair) Wound infection: Positive bacterial swab when suspected clinically: I: 7/71; C: 42/123, p&lt;0.05. Mortality: I: 1; C: 3&lt;br&gt;Secondary outcomes&lt;br&gt;Mean length of hospital stay (likely SD): I: 21(4); C: 46 (19), p&lt;0.001. Adverse effects: Proportion of burns requiring surgery: I: 25/25; C: 11/22. Adverse effects: Mean (SD) blood replacement units: I: 35 (12); C: 21 (15). % graft take 5 days post-operative (n): I: 100% (19), 95% (5 or 6); C: 100% (2) 40%-84% (9), p&lt;0.05.</td>
</tr>
<tr>
<td>Thompson et al. (1987)</td>
<td>Burns &gt;30% TBSA burned.</td>
<td>I (n = 24): Early excision and grafting (within 72 hours of admission; which was max 5 days postburn).</td>
<td>Primary outcome&lt;br&gt;Mortality: I: 3; C: 17&lt;br&gt;Secondary outcomes&lt;br&gt;Mean length of hospital stay in days for survivors (n): I: 46 (15); C: 62 (9). Adverse effects: Blood loss: I: 124.7; C: 52.4</td>
</tr>
</tbody>
</table>

Abbreviations: I = intervention group; C = control group; TBSA = Total Body Surface Area; SE = Standard Error; SD = Standard Deviation; p = P-value; SEM = Standard Error of the Mean.
Comparison 1: early excision and grafting compared with delayed excision and grafting (2 RCTs, 54 participants)

Two studies compared early excision and grafting with late excision and grafting after serial dressing changes for at least two weeks\(^{[44]}\) or with delayed grafting two to three weeks post-burn\(^{[47]}\).

Primary outcomes

Scar quality: Scar quality was not reported in these studies.

Wound infection: In Desai et al. (1991) none of the 24 participants showed clinically significant signs of wound infection or sepsis\(^{[44]}\). Jackson et al. (1960) reported wound infections in a RCT, a pilot trial and an experimental trial together, preventing data extraction for the RCT only\(^{[47]}\).

Mortality: Jackson et al. (1960) reported non-significant higher proportions of deaths in the early excision group (5 out of 16) compared to the delayed grafting group (3 out of 14); risk ratio (RR) 1.46 (95% CI 0.42 to 5.03; P = 0.55)\(^{[47]}\).

Secondary outcomes

Time to complete wound healing: In Jackson et al. (1960), time to complete wound healing was reported as mean days until 5% and 2% of whole skin loss was left (i.e. 95% and 98% of full thickness area healed)\(^{[47]}\). Jackson et al. (1960) analysed time to complete wound 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). However, Jackson et al. (1960) reported original data allowing re-analyses with survival analyses (Kaplan-Meier). Median days until 95% of the wound was healed was 34 days (interquartile range, 23 to 61) for the early excision group (n = 16) and 41 days (interquartile range, 27 to 48; log-rank test, P = 0.77) for the delayed excision group (n = 14). Median days until 98% of the wound was healed was 57 days (interquartile range, 23 to 81) for the early excision group and 52 days (interquartile range, 27 to 67; log-rank test, P = 0.51) for the delayed excision group\(^{[47]}\).

Length of hospital stay: Desai et al. (1991) reported mean length of hospital stay with standard error; SDs were calculated for our analysis. The mean length of hospital stay was 17 days (SD 6.9) in the early excision group and 21 days (SD 10.4) in the delayed excision group (mean difference -4.00; 95% CI -11.07 to 3.07; P = 0.27)\(^{[44]}\).

Adverse effects: Desai et al. (1991) compared the proportion of participants in the intervention and control group that required surgery, which is an adverse effect in the control group. The nature of the intervention prescribed that all participants in the early excision group required surgery (12 out of 12), whereas six out of 12 participants in the delayed excision group required surgery; RR 1.92 (95% CI 1.10 to 3.35; P = 0.02)\(^{[44]}\). Furthermore, Desai et al. (1991) reported blood loss as a result of excision; the mean total body blood turnovers (TBBT) was significantly higher in the early excision group (1.2; SD 1.0) compared to the delayed excision group.
group (0.3; SD 0.2) (mean difference 0.90; 95% CI 0.28 to 1.52; P = 0.004). 

Other secondary outcomes: Proportion of burns requiring reconstructive surgery, pain, patient satisfaction, quality of life and costs of treatment were not reported in these studies.

Comparison 2: early excision and grafting compared with antimicrobial agents and delayed excision and grafting if necessary (7 RCTs, 312 participants / 346 wounds)

Seven studies compared early excision and grafting with an antimicrobial agent and delayed excision and grafting if necessary. Six studies [45,46,48-52,54,55,57] used silver sulfadiazine (SSD) and one study [53] used betadine or nitrofurazone in the control group.

Primary outcomes

Scar quality: Two studies reported scar quality as an outcome. Engrav et al. (1983) reported scar quality as the proportion of participants who had hypertrophy, abnormal scar contour, scar surface irregularity, loss of motion or blisters [45]. Hypertrophy occurred in three out of 17 participants in the early excision group and seven out of 17 in the control group that received SSD; risk ratio (RR) 0.43 (95% CI 0.13 to 1.39; P = 0.16). Abnormal scar contour occurred in none of the participants in the early excision group and two out of 17 in the control group; RR 0.20 (95% CI 0.01 to 3.88; P = 0.29). Scar surface irregularity occurred in eight out of 17 participants in the early excision group and one out of 17 in the control group; RR 8.00 (95% CI 1.12 to 57.20; P = 0.04). Loss of motion due to contractures occurred in none of the participants in the early excision group and one out of 17 in the control group; RR 0.33 (95% CI 0.01 to 7.65; P = 0.49). Blisters occurred in two out of 17 participants in the early excision group and one out of 17 in the control group; RR 2.00 (95% CI 0.20 to 20.04; P = 0.56) [45]. Maslauskas et al. (2005) reported statistically significant lower mean Vancouver Scar Scale score in the early excision group (3.65; SD 2.93) compared to the control group that received SSD (6.77; SD 2.96) (mean difference -3.12; 95% CI -4.45 to -1.79; P < 0.0001) [48-52]. Furthermore, Maslauskas et al. (2005) reported statistically significant lower mean cosmetic appearance on a 4-point scale (1 represents normal appearance and 4 represents unsatisfactory appearance) in the early excision group (1.9; SD 0.78) compared to the control group (2.64; SD 0.84) (mean difference -0.74; 95% CI -1.10 to -0.38; P = 0.0001) [48-52].

Wound infection: Two studies reported wound infection as an outcome. Herndon et al. (1989) reported mean days septic in a subgroup of survivors without inhalation injury, which was 1.8 (SD 2.5) for the 22 participants in the early excision group and 1.7 (SD 1.7) for the 10 participants in the delayed excision group (mean difference 0.10; 95% CI -1.38 to 1.58; P = 0.91) [46]. Maslauskas et al. (2005) reported statistically significant less positive wound swabs in the early excision group (11 out of 40) compared to the control group that received SSD (33 out of 39); RR 0.33 (95% CI 0.19 to 0.55; P < 0.0001) [48-52].

Mortality: Two studies reported mortality as an outcome. Herndon et al. (1989) reported
significant lower proportions of deaths in the early excision group (18 out of 44) compared to the delayed excision group (28 out of 40); RR 0.58 (95% CI 0.39 to 0.88; P = 0.01) [46]. Thompson et al. (1987) reported non-significant lower proportions of deaths in the early excision group (9 out of 24) compared to the delayed excision group (17 out of 26); RR 0.57 (95% CI 0.32 to 1.03; P = 0.06) [57]. Both studies were considered sufficiently similar to pool (in the absence of significant heterogeneity (P = 0.96; I² = 0%; Figure 2), a fixed effect model was used). Pooling both studies, 27 out of 68 participants in the early excision group and 45 out of 66 in the delayed excision group died; RR 0.58 (95% CI 0.41 to 0.81; P = 0.002; Figure 2).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early excision Events</th>
<th>Conservative Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernon 1993</td>
<td>18</td>
<td>28</td>
<td>44</td>
<td>64.3%</td>
<td>0.59 [0.39, 0.88]</td>
</tr>
<tr>
<td>Thompson 1987</td>
<td>9</td>
<td>24</td>
<td>45</td>
<td>100.0%</td>
<td>0.57 [0.32, 1.03]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>68</td>
<td>45</td>
<td>0.58 [0.41, 0.81]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%

Test for overall effect Z = 3.17 (P = 0.002)

Figure 2: Forest plot of comparison 2: Early excision and grafting vs conservative treatment with SSD and subsequent excision and grafting, outcome: Mortality.

Secondary outcomes

Proportion of burns requiring reconstructive surgery: One study [45] reported the proportion of burns requiring reconstructive surgery in approximately one year follow-up. One out of 17 participants required reconstructive surgery in both the early excision group and the control group.

Length of hospital stay: Four studies [45,46,53,57] reported length of hospital stay. Pooling was not possible due to missing data [57] and clinical heterogeneity (hand burns in participants with relatively small [45] or medium [53] mean percentage TBSA burned; or participants with major burns [46]). Engrav et al. (1983) reported significant shorter mean hospital stay in the early excision group (16.4 days; SD 1.2) compared to the delayed excision group (25.0 days; SD 1.8) (mean difference -8.60; 95% CI -9.47 to -7.73; P <0.001) [45]. Omar et al. (2011) reported significant lower mean hospital stay in the early excision group (16 days; SD 2.5) compared to the delayed excision group (24 days; SD 3.4) (mean difference -8.00; 95% CI -9.85 to -6.15; P <0.001) [53]. Herndon et al. (1989) reported the mean length of hospital stay in a subgroup of survivors without inhalation injury only, which was 53 days (SD 38) for the 22 participants in the early excision group and 47 days (SD 25) for the 10 participants in the delayed excision group (mean difference 6.00; 95% CI -16.19 to 28.19; P = 0.65) [46]. Mean length of hospital stay in Thompson et al. (1987) was reported without variance data, and only for survivors in different groups independently. Summarised mean length of hospital stay for all groups was 46 days for the 15 participants in the early excision group and 62 days for the 9 participants in the delayed excision group [57].
Adverse effects: Two studies reported proportion of burns requiring surgery as an outcome \cite{45, 55}. The nature of the intervention prescribed that all participants in the early excision group required surgery. Both Engrav et al. (1983)\cite{45} and Salisbury et al. (1982)\cite{55} studied hand burns and were considered sufficiently similar to pool (in the absence of significant heterogeneity (P = 0.23; I^2 = 29%; **Figure 3**), a fixed effect model was used). Pooling both studies, all of the 30 participants in the early excision group and 20 out of 37 in the delayed excision group required surgery; RR 1.82 (95% CI 1.34 to 2.46; P < 0.001; **Figure 3**). Three studies reported adverse effects related to the operative treatment \cite{45, 46, 57}. Engrav et al. (1983) reported complications of surgery, which occurred in both the early excision group (upper airway obstruction; 1 out of 22) and the delayed excision group (donor site infection; 1 out of 12); RR 0.55 (95% CI 0.04 to 7.96; P = 0.66)\cite{45}. Herndon et al. (1989) reported blood loss (mean total body blood turnovers (TBBT)) as a result of excision in survivors without inhalation injury, which was statistically significant more in the early excision group (2.1; SD 2.2; n = 22) compared to the delayed excision group (0.7; SD 0.6; n = 10) (mean difference 1.40; 95% CI 0.41 to 2.39; P = 0.006)\cite{46}. Thompson et al. (1987) reported blood loss (mean units of blood infused) without variance data and only for different groups independently. Summarised mean units of blood infused for all groups was 124.7 units in the early excision group and 52.4 units in the delayed excision group\cite{57}. Omar et al. (2011) reported the proportion of wounds with partial graft loss and need for re-grafting, which occurred in 5 out of 25 hands in the early excision group and 4 out of 27 hands in the delayed excision group; RR 1.35 (95% CI 0.41 to 4.47; P = 0.62)\cite{53}.

Costs of treatment: One study reported mean total hospital costs including physicians charges in United States dollars, which were statistically significant lower in the early excision group (9,063; SD 1,144) compared to the delayed excision group (12,702; SD 1,270) (mean difference -3,639; 95% CI -4,329.19 to -2,948.81; P < 0.001)\cite{45}.

Other secondary outcomes: Time to complete wound healing, pain, patient satisfaction and quality of life were not reported in these studies.

![Figure 3: Forest plot of comparison 2: Early excision and grafting vs conservative treatment with SSD and subsequent excision and grafting, outcome: Proportion of participants requiring surgery.](image-url)
Comparison 3: early excision and grafting compared with honey dressings (1 RCT, 50 participants)

One study compared early excision with honey dressings in 50 people with less than 30% TBSA burned [56].

Primary outcomes

Scar quality: Subrahmanyam et al. (1999) assessed wound appearance three months post discharge but did not describe the measurement instrument sufficiently [56]. Scars were analysed as the proportion of wounds that had “excellent or good results”, while “fair result” was the only other category stated. Excellent or good results were reported in 22 out of 24 participants in the early excision group and 12 out of 22 in the control group that received honey dressings; RR 1.68 (95% CI 1.13 to 2.51; P = 0.01). Additional data provided in personal communication conflicted the published data.

Wound infection: Wound infection in Subrahmanyam et al. (1999) was determined with positive bacterial swabs when wound infection was suspected clinically. Subrahmanyam et al. (1999) reported statistically significant less positive wound swabs in the early excision group (7 out of 71) compared to the control group that received honey dressings (42 out of 123); RR 0.29 (95% CI 0.14 to 0.61; P = 0.001) [56].

Mortality: Subrahmanyam et al. (1999) reported non-significant lower proportions of deaths in the early excision group (1 out of 25) compared to the honey treated group (3 out of 25); RR 0.33 (95% CI 0.04 to 2.99; P = 0.33) [56].

Secondary outcomes

Length of hospital stay: The mean length of hospital stay in Subrahmanyam et al. (1999) was significantly shorter in the early excision group (21 days; SD 4) compared to the honey treated group (46 days; SD 19) (mean difference -25.00; 95% CI -33.10 to -16.90; P < 0.001) [56].

Adverse effects: Subrahmanyam et al. (1999) compared the proportion of participants in the intervention and control group that required surgery [56]. The nature of the intervention prescribed that all participants in the early excision group required surgery (25 out of 25), whereas 11 out of 22 participants in the honey treated group required surgery; RR 1.96 (95% CI 1.30 to 2.96; P = 0.001). However, graft take five days post-operatively was less successful in the honey treated group. Nineteen participants in the early excision group had 100% graft take, whereas the remainder (five or six participants, unclear if deceased participant is included) had 95% graft take. Only two of the 11 excised participants in the honey treated group had 100% graft take five days post-operative, whereas the remainder nine ranged between 40% to 84% graft take. Subrahmanyam et al. (1999) reported a significantly better (P < 0.05) graft take in favour of the early excision group, however, the method of analysis was unclear and original data were not reported, therefore re-analyses was not possible [56]. Furthermore, Subrahmanyam et al. (1999) reported blood loss as mean (SD) blood replacement units. The
mean blood replacement units was significantly higher in the early excision group (35 units; SD 12) compared to the honey treated group (21 units; SD 15) (mean difference 14.00; 95% CI 6.47 to 21.53; P = 0.0003) [56].

Other secondary outcomes: Proportion of burns requiring reconstructive surgery, time to complete wound healing, pain, patient satisfaction, quality of life and costs of treatment were not reported in this study.

Discussion

Summary of main results
We included ten randomised controlled trials in this review that evaluated early excision and grafting in burns. Studies compared early excision and grafting with either:

- delayed excision and grafting (comparison 1; two studies),
- application of antimicrobial agents and delayed excision and grafting if necessary (comparison 2; seven studies), or
- application of honey dressings (comparison 3; one study).

The variety in control interventions and differences in outcome measures between studies made pooling of data inappropriate for most results, therefore, the results have been presented in a narrative overview by comparison. This summary of main results is divided in three primary outcomes (scar quality, wound infection and mortality) and all secondary outcomes have been combined.

Scar quality
Overall, there was insufficient data to support any definite conclusions that early excision and grafting improved scar quality compared to delayed excision. One study showed statistically significant better scar quality in one out of five reported scar outcomes [45] and favoured delayed excision. Two studies showed statistically significant better scar quality for three outcomes measures after early excision [48-52,56], although one of those studies [56] provided additional data in personal communication that conflicted with the published data and therefore these results should be interpreted with caution. In summary, three outcome measures favoured early excision, one outcome measure favoured delayed excision and four outcome measures showed no statistically significant differences with regard to scar quality.

Wound infection
Five studies addressed wound infection as an outcome but differed in outcome measurement. Two studies reported statistically significant less positive wound swabs in the early excision group [48-52,56], whereas two studies found no statistically significant difference in clinical signs of infection between early excision and delayed excision [44,46]. One study reported wound
infections in a RCT, a pilot trial and an experimental trial together, preventing meaningful data extraction for the RCT only. A cautious conclusion might be that although early excision reduces the number of positive wound swabs, there appears to be no clinically significant reduction in wound infection.

Mortality
Four studies addressed mortality as an outcome. Herndon et al. (1989) and Thompson et al. (1987) were considered sufficiently similar to pool and analyses showed significant lower proportions of deaths in the early excision group compared to the delayed excision group. These results should be interpreted with caution as these studies might have an overlap in participants. The other two studies reported non-significant higher or lower proportions of deaths in the early excision group. Overall, there was insufficient data to support any definite conclusions.

Secondary outcomes
Except for pain, patient satisfaction and quality of life, all other secondary outcomes (proportion of burns requiring reconstructive surgery, time to complete wound healing, length of hospital stay, adverse effects and costs of treatment) were addressed by at least one study. No statistical differences were found for the proportion of burns requiring reconstructive surgery and time to wound healing. Six studies addressed length of hospital stay, three studies significantly favoured early excision, two studies reported no significant difference and one study favoured early excision but reported mean length of hospital stay without variance data. A cautious conclusion might be that length of hospital stay is shorter with early excision and grafting compared to conservative treatment.

Seven studies addressed one or more adverse effects, that is proportion of participants requiring surgery, need for re-grafting, reduced graft take, blood loss and complications of surgery. Four studies addressed the proportion of participants requiring surgery, which can be regarded as an adverse effect in both the intervention and control group. Ideally, burn wounds in the control group heal completely with conservative treatment only, therefore delayed surgery is an adverse effect in the control group. On the other hand, this outcome indicates that a proportion of participants in the early excision group received unnecessary surgery from a wound healing perspective, which can be regarded as an adverse effect in the early excision group. The nature of the intervention prescribed that all participants in the early excision group received surgery. All four studies reported that significantly less participants in the control group required surgery compared to the early excision group. Overall, 52% (37 out of 71) of the participants in the control group required surgery. Consequently, 48% of the participants had wounds that healed without surgery. In addition, Omar et al. (2011) reported no significant difference in the proportion of wounds with partial graft loss and need for re-grafting between early and delayed excision, whereas Subrahmanyam et al.
(1999) reported a significantly better graft take five days post-operative in favour of the early excision group\textsuperscript{[56]}. However, the method of analysis in Subrahmanyam et al. (1999) was unclear and original data were not reported, therefore re-analyses was not possible. Four studies addressed blood loss as a result of excision as an adverse effect of treatment. Desai et al. (1991), Herndon et al. (1989) and Subrahmanyam et al. (1999) reported significantly more blood loss in the early excision group\textsuperscript{[44,46,56]}. The fourth study reported similar findings without variance data, therefore re-analyses was not possible\textsuperscript{[57]}. Complications of surgery were reported in Engrav et al. (1983) and consisted of one case of upper airway obstruction in the early excision group and one case of donor site infection in the delayed excision group\textsuperscript{[45]}. The final secondary outcome addressed was costs of treatment. Engrav et al. (1983) reported significantly lower mean total hospital costs in the early excision group compared to the delayed excision group\textsuperscript{[45]}. A cautious overall conclusion might be that early excision reduces the length of hospital stay, whereas conservative treatment reduces the proportion of participants that receive a surgical intervention and reduces blood loss as a result of the operation. A reason for our caution is that heterogeneity of studies prevented pooling for most outcomes and therefore none of the results were sufficient to support any definite conclusions.

**Overall completeness and applicability of evidence**

The objective of this review was to assess the effectiveness of early excision and grafting on scar quality in people with burns of any depth. Unfortunately, only three out of ten studies addressed scar quality as an outcome and differed in outcome measurement. With regard to mortality, major improvements in burn care in the twentieth century have decreased mortality rates. One of those major improvements is early excision in major burns, but other more recent improvements in newly developed topical antibiotics and critical care might diminish the effect of early excision on mortality. Since three out of four studies that reported mortality were conducted more than 25 years ago, this raises the question whether the results of those older studies are still applicable to present-day burn care. In addition, none of the included studies addressed the patient reported outcomes of pain, 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, the cautious conclusion that there appears to be no clinically significant reduction in wound infection between early excision and conservative treatment might be applicable to specialised burn centres in developed countries only. In contrast to most health care facilities in developing countries, those burn centres have the facilities and resources that are necessary to prevent wound infection.
Quality of the evidence

The evidence combined in this review was of insufficient quality to allow definite conclusions to be drawn. Most of the ten included studies had relatively small sample sizes, ranging from 13 to 85, and the total of 416 participants might be lower due to a possible overlap of participants between three studies \[46,54,57\]. While pooling data from small trials could increase statistical power and give a more precise overall estimate of effect size, most of the studies in this review did not compare similar interventions or differed in outcome measures, which generally prevented pooling. Most of the included studies had methodological limitations regarding sequence generation, allocation concealment and blinding of outcome assessment. Only two studies described sequence generation and allocation concealment adequately \[45,53\] and one study provided this information in personal communication \[56\]. One study described sequence generation adequately but did not provide information about the allocation concealment \[46\] and the other six studies only stated that participants were randomised. The nature of the interventions made blinding of participants and care providers not possible, but outcome assessors could have been blinded. This was done in six out of ten studies, whereas three studies did not describe blinding of outcome assessors \[47-53\] and one study did not blind the outcome assessor \[45\]. Furthermore, drop-out rate in two studies was unacceptable high without reasons given \[45,55\], one study did not perform intention-to-treat (ITT) analysis \[55\] and one study had a minor discrepancy between the number of participants in the text and the number of participants in the tables \[46\]. 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 occurred due to a possible participant overlap between three studies \[46,54,57\] that were conducted in the same hospital with an overlapping study period. We were unable to confirm whether there was a participant overlap, or determine how this would alter our conclusions, should it indeed be the case. Another potential bias 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. No contact details were retrieved of Jackson et al. (1960) and Salisbury et al. (1982) \[47,55\]. Despite issuing a reminder, we received replies only from Engrav et al. (1983), Maslauskas et al. (2005) and Subrahmanyam et al. (1999) \[45,48-52,56\]. As a result of those answers, we judged the sequence generation and allocation concealment of Subrahmanyam et al. (1999) to be of “low risk of bias” instead of “unclear risk of bias” and we judged the blinding of outcome assessment of Engrav et al. (1983) to be of “high risk of bias” instead of “unclear risk of bias”. Maslauskas et al. (2005) provided information on citations only.
Agreements and disagreements with other studies or reviews
The results of this review are largely in accordance with the results of Ong et al. (2006), but some conclusions in that non-systematic and not up-to-date review were slightly premature. Ong et al. (2006) states that “early excision of burns reduces mortality in patients without inhalational injury, increases blood transfusion requirements and reduces the length of hospital stay in patients”. These conclusions were based on six studies, all with methodological limitations and including one study that was excluded in this review because it was not a RCT. Since none of the included studies provided firm evidence, conclusions by Ong et al. (2006) should have been more cautious. Furthermore, the small number of included studies in this review is in accordance with two Cochrane reviews that focused on wound dressings and topical silver that included 26 and 20 RCTs, respectively. Those reviews included more studies, which was expected considering the broader search with regard to the intervention. Wasiak et al. (2008) included all RCTs that assessed burn wound dressings and Storm-Versloot et al. (2010) included all RCTs that assessed silver containing wound dressings and topical agents. Another review investigated the methodological quality of randomised controlled trials in burn care. 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”. Furthermore, their results showed an increase in RCTs over time without a significant improvement in methodological quality. These findings are only partly in line with our results; methodological quality in the ten included RCTs is similar over time, but our review showed no increase in published RCTs over time as only two out of the ten included RCTs were performed in the 21st century.

Authors’ conclusions

Implications for practice
There is insufficient high quality research and evidence to enable definite conclusions to be drawn about the effects of early excision and grafting on scar quality in people with burns. Nonetheless, results indicate that early excision and grafting reduces positive wound swabs and length of hospital stay, whereas conservative treatment reduces the proportion of participants that receive a surgical intervention and reduces blood loss as a result of the operation.

Implications for research
There is a need for large, well-designed trials that compare early excision and grafting with conservative treatment in burns. In order to improve methodological quality, future studies should be designed in conjunction with a trials expert and a statistician and should follow the CONSORT guidelines on reporting. Appropriate sequence generation and allocation
concealment methods should be used in order to reduce the risk of selection bias, and blinding should be attempted to avoid performance and detection biases. 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 pain, patient satisfaction and quality of life to their outcomes of interest, as these outcomes are especially important for patients. In addition, future trialists should include scar quality as an outcome of interest, preferably measured with validated scar assessment tools that incorporate both the patient’s and professional’s perspective, like the Patient and Observer Scar Assessment Scale (POSAS)\textsuperscript{[72]} (www.posas.org) that has been found reliable and valid\textsuperscript{[73]}.

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**Declarations of interest**

No conflict of interest.

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References

Early excision and grafting for burns


Chapter 4


