

## Title page

Title:

**Systematic review and meta-analysis of the efficacy of epidermal grafting for wound healing**

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### Short running title

Systematic review on epidermal grafting

### Key words

Epidermal graft, skin graft, wound healing, systematic review

### Key messages

- The use of EG for wound healing has been on the rise of late, however, data to date on the outcome and treatment group has been heterogeneous
- This systematic review synthesises the current evidence on EG for wound healing to establish the efficacy of this technique in the clinical setting, by measuring the proportion of wounds healed and the mean wound healing time.
- EG offers a healing rate of over 70 percent with mean healing time of five weeks and allows painless autologous skin grafting to be performed without donor site morbidity.

## Abstract

Autologous skin grafting is an important method for wound coverage; however, it is an invasive procedure and can cause donor site morbidity. Epidermal grafting (EG) enables epidermal transfer to wound with minimal donor site morbidity. However, data to date has been heterogeneous. This study aims to synthesise the current evidence on EG for wound healing to establish the efficacy of this surgical technique. A comprehensive search in the MEDLINE, EMBASE and CENTRAL database was conducted. The endpoints assessed were; proportion of wounds healed and mean wound healing time. This systematic review was conducted and reported according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We identified 1568 articles, of which 7 articles were included in this review; a total of 209 wounds in 190 patients. The mean wound duration was 17.06 weeks (95% c.i. 8.57 to 25.55). Of these, 71.5%(95% c.i. 56.7 to 84.2) of the wounds achieved complete healing. Mean time for complete wound healing was 5.53 weeks (95% c.i. 3.18 to 7.88). The mean donor site healing time was 7.48 days (95% c.i. 4.83 to 10.13), with no reported donor site morbidity. The current data are small and lacks level 1 evidence.

## Introduction

Wound care presents a significant financial and resource burden to the healthcare system, reported to account for over 5 percent of National Health Service (NHS) expenditure. Between £2.3–£3.1 billion is spent in caring for patients with chronic wounds in the United Kingdom alone (1). Chronic wounds account for a burdening problem with over 100,000 new ulcers anticipated every year, with an ageing population and rising prevalence of obesity and diabetes (2).

In most cases management is conservative, by wound care and dressings. Intervention by autologous skin grafting is an important modality for wound coverage (3). Skin grafting can be classified based on the thickness of the harvested skin, namely, full thickness skin graft (FTSG), split thickness skin graft (SSG) and epidermal graft (EG) (4, 5).

FTSG consists of the epidermis and the entire dermis of the skin. FTSG is normally reserved for smaller wounds as the donor site must be closed primarily. Thus, only selected areas with sufficient skin laxity is suitable for skin harvest, commonly the retroauricular area, cervicopectoral area, and groin (3). Larger areas can be managed by SSG which involves shaving the epidermis and part of the dermis of the skin. This is best performed by an electric air dermatome and the donor site regenerates by secondary intention from the residual reticular dermis (3). SSG is the commonest form of autologous skin grafting performed and can be meshed to cover a wide surface area. A major consideration for SSG is that the donor site may itself develop as a second, often painful wound, which may take more time to heal than the graft site itself and holds the risk of infection and scarring (6). Both the FTSG and SSG

often require hospital admission, even as a day case, anaesthesia, and a period of immobility for some patients.

EG, on the other hand, is an emerging and promising option. EG involves harvesting only the epidermal layer of the skin from the donor site by applying continuous negative pressure on the normal skin to raise blisters (Figure 1). The roof of the blister, which is the epidermis, is then excised and transferred onto the wound. As the dermis in the donor site remains untouched, the skin regenerates itself without scar. This procedure is also often painless as the pain fibres in the dermis are unstimulated, allowing autologous skin grafting in the outpatient setting without administration of anaesthesia and with minimal donor site morbidity(7).

The use of EG for wound healing has been on the rise of late, with several recent publications in the last couple of years. However, data to date have been heterogeneous on the outcome and on when and in which patient group this surgical technique should be employed. This systematic review synthesises the current evidence on EG for wound healing to establish the efficacy of this technique in the clinical setting, by measuring the proportion of wounds healed and the mean wound healing time. It is timely that the evidence is assessed to guide clinical decision making and to further facilitate future research.

## Materials and methods

The protocol for this systematic review was registered with the PROSPERO international prospective registration of systematic reviews (registration number: CRD42016033051), and a detailed protocol was peer reviewed and published(8). There is no deviation from the

published protocol. This systematic review was conducted and reported according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (9).

### Search strategies

We searched the MEDLINE (OvidSP), EMBASE (OvidSP), and Cochrane Central Register of Controlled Trials (CENTRAL) database from 1946 until December 2016 to identify studies of relevance to this review. The search strategy included a combination of text words and Medical Subject Headings (MeSH) terms relating to the use of EG for treating wounds. No language or publication restrictions were applied. The reference list of all articles included were cross-checked for further articles of relevance. A sample search strategy for MEDLINE (OvidSP) is shown and similar strategy was adapted for other databases.

1. [epidermal graft\*] OR [blister graft\*] OR [suction blister\*] OR [suction graft\*]
2. Epidermis/su, tr [Surgery, Transplantation]
3. [1] or [2]

### Inclusion criteria

The inclusion criteria used were: (i) studies involving adult patients above 18 years old; (ii) EG for wound healing; (iii) English language; (iv) available information containing at least the following: number of subjects, method of EG harvest, and healing time.

### Exclusion criteria

The exclusion criteria were: case reports or case series of ten or lesser patients; studies describing the use of EG in skin pigmentation disorder such as vitiligo; studies combining EG with other treatments such as stem cells or dermal substitutes; and studies describing only the harvest technique without treatment outcome.

### Outcome measures

The primary efficacy outcomes measured were the proportion of wounds healed and the mean wound healing time (time for complete healing). Secondary outcome measures were the mean donor site healing time, need for anaesthesia, economic evaluation based on the cost associated with resources used, health-related quality of life, and proportion of patients with adverse event. Subgroup analysis was performed for the proportion of wounds with complete healing based on the wound aetiology.

### Study selection

The retrieved articles' titles and abstracts were scanned for potential eligibility, using the predetermined selection criteria, after excluding duplicate records. Full-text review was undertaken for studies that met the inclusion criteria. Abstracts and conference proceeding without full text were not included because of the difficulty in evaluating incomplete information. Ongoing trials without complete data were not included.

### Data extraction

Data from all full-text articles accepted for final analysis were independently retrieved by two authors (M.K. and O.J.S.) using a standardised data extraction form. Discrepancies were resolved by discussion. The following data were extracted: study characteristics (first author, year of publication, country, study design), patient demography (number of studied subjects, sex, mean age, comorbidity, number of wounds treated), wound characteristics (wound aetiology, mean wound duration, mean wound size, pre-grafting wound quality), characteristics of EG harvest technique, use of anaesthesia, outcomes (wound healing time, number and type of wounds with 100 percent healing, number of wounds with 50-99 percent healing, number and type of wounds failed to heal, donor site healing time), and

complications or adverse events. Data were extracted from the studies as presented or were calculated (e.g.: mean age and mean wound size).

#### Assessment of risk of bias of included studies

A formal risk of bias assessment was not performed as the included studies were mostly small case series.

#### Data analysis and synthesis

The main outcome measures of the included studies were the pooled estimate of the proportions of wounds healed, the mean wound healing time, and the mean donor site healing time with the corresponding 95 percent confidence intervals (c.i.). Meta-analysis of proportion was performed for the proportion of wounds healed. Meta-analysis of summary was performed for the mean wound and donor site healing time, mean wound size, mean wound duration and mean age of the patients. The clinical and methodological heterogeneity were assessed. Random effects model was used for the pooled estimates as the included studies demonstrated high clinical and statistical heterogeneity (10). The outcomes were analysed using StatsDirect Statistical software (StatsDirect statistical software, version 2.8.0; StatsDirect, Altrincham, UK).

## Results

#### Literature search results

We found 1102 articles in the MEDLINE database search, 961 articles in the EMBASE database search, and 271 articles in the CENTRAL database search. References from these three searches were combined and after removing the duplicates, 1568 articles were available for

title and abstract reviewing. Of these, 1395 articles did not meet the inclusion criteria and were excluded. Following full text review of the remaining 173 articles, 166 articles were excluded as the inclusion criteria was not met. A total of 7 articles were included and formed the basis of this systematic review(7, 11-16) (Figure 2). Cross-checking of the reference list revealed that no article was missed by the initial search. Details of the included studies are summarised in Table 1.

### Wound healing outcome

A total of 209 wounds in 190 patients were treated with EG, with the average wound size of 20.18 cm<sup>2</sup> (95 percent c.i. 8.19 to 32.17). The mean age of the patients was 62.62 years (95 percent c.i. 55.56 to 69.69). The mean wound duration of the 128 reported wounds was 17.06 weeks (95 percent c.i. 8.57 to 25.55).

The number of wounds that achieved complete wound healing was reported in six studies involving 137 wounds. The proportion of wounds that achieved complete healing was 71.5 percent (95 percent c.i. 56.7 to 84.2) (Figure 3), with the mean time for complete wound healing of 5.53 weeks (95 percent c.i. 3.18 to 7.88) (Figure 4). The proportion of complete healing for the CelluTome Epidermal Harvesting System alone, which was used in 4 of the studies, was 73.5 percent (95 percent c.i. 54.0 to 89.1), with the mean healing time of 5.91 weeks (95 percent c.i. 3.81 to 8.05).

EG was used to treat wounds of various aetiologies, duration and size. The following wide range of wounds were treated: venous ulcer (n=34), arterial ulcer (n=4), mixed arteriovenous ulcer (n=3), diabetic ulcer (n=7), rheumatoid ulcer (n=9), vasculitis (n=9), trauma (n=18), burns (n=1), SSG donor site (n=3), pyoderma granulorum (n=1), and lymphoedema (n=1) (Table 2). Most of the treated wounds were chronic wounds (more than or equal to three months in

duration), except for 13 wounds that were acute wounds (less than three months in duration). All treated diabetic foot ulcer, SSG donor site, and burns wounds achieved complete healing (Table 2). Wounds of other aetiologies demonstrated a lower success rate (Table 2).

Partial healing of between 50-99.9 percent healing was achieved by 14.0 percent (95 percent c.i. 2.7 to 31.9) of the wounds within the follow up duration while failure or no healing (0-49.9 percent healing) was reported in 13.5 percent (95 percent c.i. 8.3 to 19.8) of the wounds. The failures were mainly attributed to wound infection. There was lack of reporting on the time for partial healing and there was no consistency in the follow up duration in the included studies.

#### Donor site healing

Three different EG harvesting systems were used: Dermovac (Oy Instrumentarium, Helsinki, Finland), the syringe system, and the CelluTome Epidermal Harvesting System (Acelity, San Antonio, Texas). Although these systems harvest different sizes of grafts, they share the similar harvest principle that applies continuous negative pressure on normal skin to raise blisters. The donor site healing time was reported in three studies involving 59 patients, whereby one study used the Dermovac system while two studies used the CelluTome Epidermal Harvesting System.

The pooled mean donor site healing time was 7.48 days (95 percent c.i. 4.83 to 10.13). The donor site healing time of the CelluTome Epidermal Harvesting System alone, which is the latest EG harvesting system, is 6.21 days (95 percent c.i. 4.73 to 7.68). The Dermovac system, which raises blisters measuring 5-15 mm, has a donor site healing time of 10 days (13).

Hentzer et al. reported slight diffuse pigmentation at the donor site while Costanzo et al. reported occasional hypopigmentation by the Dermovac system, but all donor sites healed

without scar (11, 13). The donor site healing time and quality of the donor site healing by the syringe system was not reported by any of the included studies.

#### Use of anaesthesia

Only one study reported on the use of local anaesthesia during graft harvest which used the syringe system. In this retrospective study, Hanafusa et al. compared pain during harvest using syringes of different sizes (5ml, 10ml and 20ml) with and without the use of anaesthesia (12). Pain at graft harvest was eliminated among patients that received local anaesthesia (n=27), while 50 percent of patients (n=34) without local anaesthesia felt pain. However, the pain severity at harvest was not reported using a validated pain measurement scale. By contrast, the CelluTome Epidermal Harvesting System and the Dermovac system, which harvests multiple small blisters, were reported to be painless even without the administration of local anaesthesia although this was also not reported using a pain measurement scale.

#### Cost, quality of life and adverse events

None of the included articles measured the health-related quality of life or patient satisfaction. The economic evaluation of the various harvesting systems was also not reported. No adverse events were reported in any study.

## Discussion

The aim of this systematic review was to evaluate the efficacy of epidermal grafting for wound healing. We found 7 articles, no randomised controlled trials exist now. The current evidence on the efficacy of epidermal grafting involves small case-series with huge heterogeneity in the study population.

We found that complete healing was achieved by 71.5 percent (95 percent c.i. 56.7 to 84.2) of the wounds with the mean time for complete healing of 5.53 weeks (95 percent c.i. 3.18 to 7.88). Although none of the studies compared the healing outcome with conservative management or SSG, previous data suggests that the healing outcome is comparable with SSG which has a healing rate of 73 percent (17). The average time for complete donor site healing was 7.48 days (95 percent c.i. 4.83 to 10.13), with no reported donor site morbidity. EG was performed on wounds of various aetiologies, duration and size. The diabetic foot ulcer, burn wound, and SSG donor site wounds achieved complete healing while wounds due to lymphoedema and pyoderma granulosum failed to heal. Despite demonstrating the wide applicability of this technique, there was a lack in the consistency in between studies to make a strong recommendation on the type of wound that would best benefit from this treatment. In this review, we managed to highlight the overall success rate of EG for wound healing and the mean wound and donor site healing time which was previously unclear. Although the success rate of EG in direct comparison to SSG is yet to be not known, the lack of donor site morbidity and the ability to perform this procedure in the outpatient setting without the use of local anaesthesia are the major advantages that this technique offers over conventional techniques. The mechanism of healing between EG and SSG is expected to be different, whereby EG is expected to behave more like a bioactive dressing which stimulates the wound bed to regenerate (reviewed in ref. (5)). The difference in the success rate between the various wound aetiologies suggest that the EG is sensitive to the microenvironment of the wound. This also suggests that post grafting wound care should be specific to the wound aetiology.

The various EG harvesting systems used in the included studies varied in the amount of negative pressure generated and the size of graft harvested despite relying on the similar principle. The EG harvesting system that was most widely used in the included studies was the CelluTome Epidermal Harvesting System, which was used by four of the studies. This system has the shortest graft harvest time, fastest donor site healing, no reported donor site morbidity, and can be performed in outpatient setting without anaesthesia. Being an automated system, the procedure is easily reproducible with consistent graft quality. The shorter harvest time is contributed by the high negative pressure which is applied concurrently with the thermal energy of 40°C and its design which harvests an array of 128 micro-blisters, each of 2mm diameter and spaced 2mm apart, within an area measuring 5cm x 5cm (18). The earlier systems used to harvest EG, which is the Dermovac and the syringe system faced several challenges which limits its clinical applicability. The Dermovac, which has an adapter plate that allows user to determine the number and size of blisters to be harvested, has a long harvest time and requires a large equipment(19). The reliability of the syringe system, on the other hand, had been described to depend on numerous patient and environmental factors, requires skill, time consuming, causes pain and tedious to use with often inconsistent blister shape and size formation (18).

The evidence in this study is limited by the lack of high-quality, level-1 evidence. The existing studies were mostly small, retrospective case-series and single-centre cohort studies that are often at risk of bias. There were no comparative data to evaluate that healing outcome of EG against the current standard of care such as advanced dressings or SSG. Formal bias assessment was not performed due to the study design of the included studies. In terms of the search strategy, as there is no Medical Subject Heading (MeSH) term available for EG, potentially valuable and informative studies published with other keywords may therefore

been missed. Further, several different harvesting systems were used in the included studies. Proportion of healing based on the size and depth of wound as well as device utilized were not performed due to incomplete reporting in most of the studies. Similarly, subgroup analysis for healing based on the wound aetiology was not performed due to the broad heterogeneity in the study population. The EG harvested by the different harvest systems were assumed to produce similar graft quality for the purpose of this review as the grafts were all harvested by blister formation.

In conclusion, EG offers a healing rate of over 70 percent and allows painless autologous skin grafting to be performed without donor site morbidity. The rapid donor site healing could have a major impact in the patient's quality of life. Our conclusions are limited by the small size and heterogeneity of the studies and the different techniques of EG. Methodologically sound randomised controlled trials to compare EG against SSG or conservative treatment are necessary.

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#### Competing interests

The author declares that they have no competing interests or financial disclosures.

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Table 1

Overview of the included studies

Citation	Hentzer B et al, 1975(13)	Costanzo U et al, 2006(11)	Hanafusa T et al, 2008(12)	Bhatia A, 2016(16)	Cai SS et al, 2016(15)	Hachach-Haram N et al, 2016(7)	Prakash TV et al, 2016(14)
Year	1975	2006	2008	2016	2016	2016	2016
Country	Denmark	Switzerland	Japan	India	USA	UK	India
Study type	Case series	Case series	Case series	Case series	Case series	Case series	Case series
Number of patients	12	18	61	34	12	35	18
Male	N/R	5	N/R	17	6	16	9
Mean age (year)	N/R	76.5	I/R	67.1 ± 13.8	57.1 ± 19.1	66.1 ± 21.1	54.1 ± 10.8
Number of wounds	12	29	69	34	12	35	18
Mean wound duration (week)	N/R	21±178.7	I/R	13.7 ± 15.0	14.6 ± 18.3	19.4±24.0	147.2 ± 194
Average wound size (cm <sup>2</sup> )	N/R	6.70 ± 5	27.80 ± 7.10	N/R	49.1 ± 77.6	20.5 ± 22.4	N/R
Epidermal graft harvesting technique							
<i>Device</i>	Suction device Dermovac®	Suction cups with oil rotary vacuum pump	Syringe	CelluTome	CelluTome	CelluTome	CelluTome
<i>Negative pressure (mmHg)</i>	250-300 mmHg	200-300	N/R	400-500	400-500	400-500	400-500
<i>Duration</i>	1-2 Hours	2 to 3 hours	16-128 minutes	30-45 minutes	30-45 minutes	30-50 minutes	20-45 minutes
Use of anaesthesia	No	No	LA in 27 patients	No	No	No	No
Donor site dressing	N/R	Antiseptic cream and gauze	N/R	N/R	Tegaderm	Tegaderm	Gauze or Tegaderm
Wound site dressing	Gauze + wet dressing with 2% boric acid.	Non-adherent dressing (Sofra- Tulle), gauze, compression bandage	N/R	N/R	Negative pressure wound therapy	Adaptic Touch + secondary dressing (iNadine or Aquacel)	Gauze

Wounds with complete healing	10	16	18	28	4	22	16
Duration for complete healing (week)	2 ± 1.98	3.6 ± 1.98	8.3 ± 0.9	7 ± 6.6	10.6 ± 5.28	5.91 ± 3.48	3.7 ± 1.8
Wounds with 50-99% healing	1	10	N/R	0	5	6	0
Number of failure	1	3	N/R	4	0 (3 patients lost to follow up)	7	1
Donor site healing	10 days	N/R	N/R	N/R	1 week	5.49 ± 1.48 days	N/R

**Legend:** N/R=Not reported I/R=Incomplete reporting

Table 2

Healing by wound aetiology

Wound aetiology	Number treated	Completely healed wounds	Percentage healed (%)
Diabetic foot ulcer	7	7	100.00%
SSG donor site	3	3	100.00%
Burn	1	1	100.00%
Venous	34	33	97.06%
Arterial	4	3	75.00%
Mixed	3	2	66.67%
Rheumatic disease	9	6	66.67%
Trauma	18	12	66.67%
Vasculitis	9	5	55.56%
Pyoderma granulorum	1	0	0.00%
Lymphatic	1	0	0.00%

Figure 1

Illustration of the skin layers involved in autologous skin graft harvest.

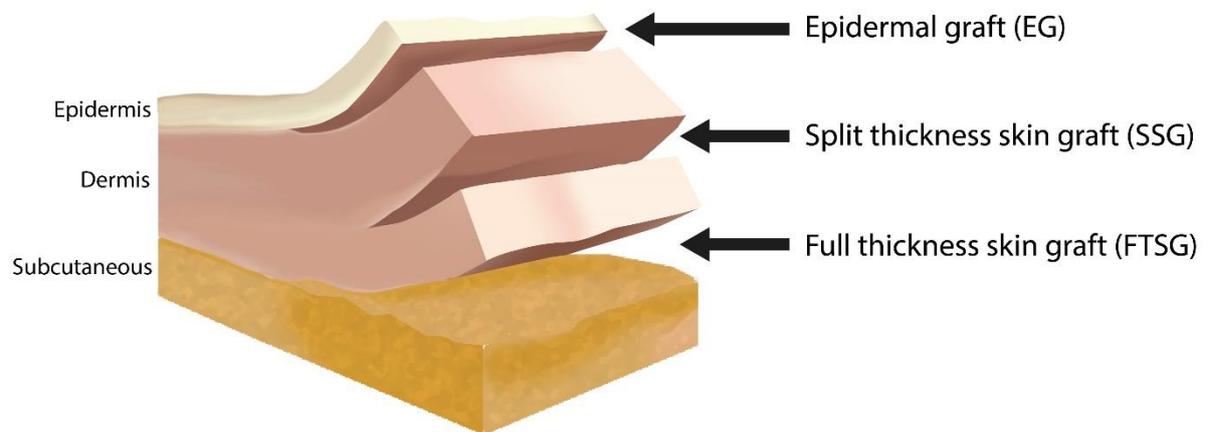


Figure 2

Flow diagram of literature search

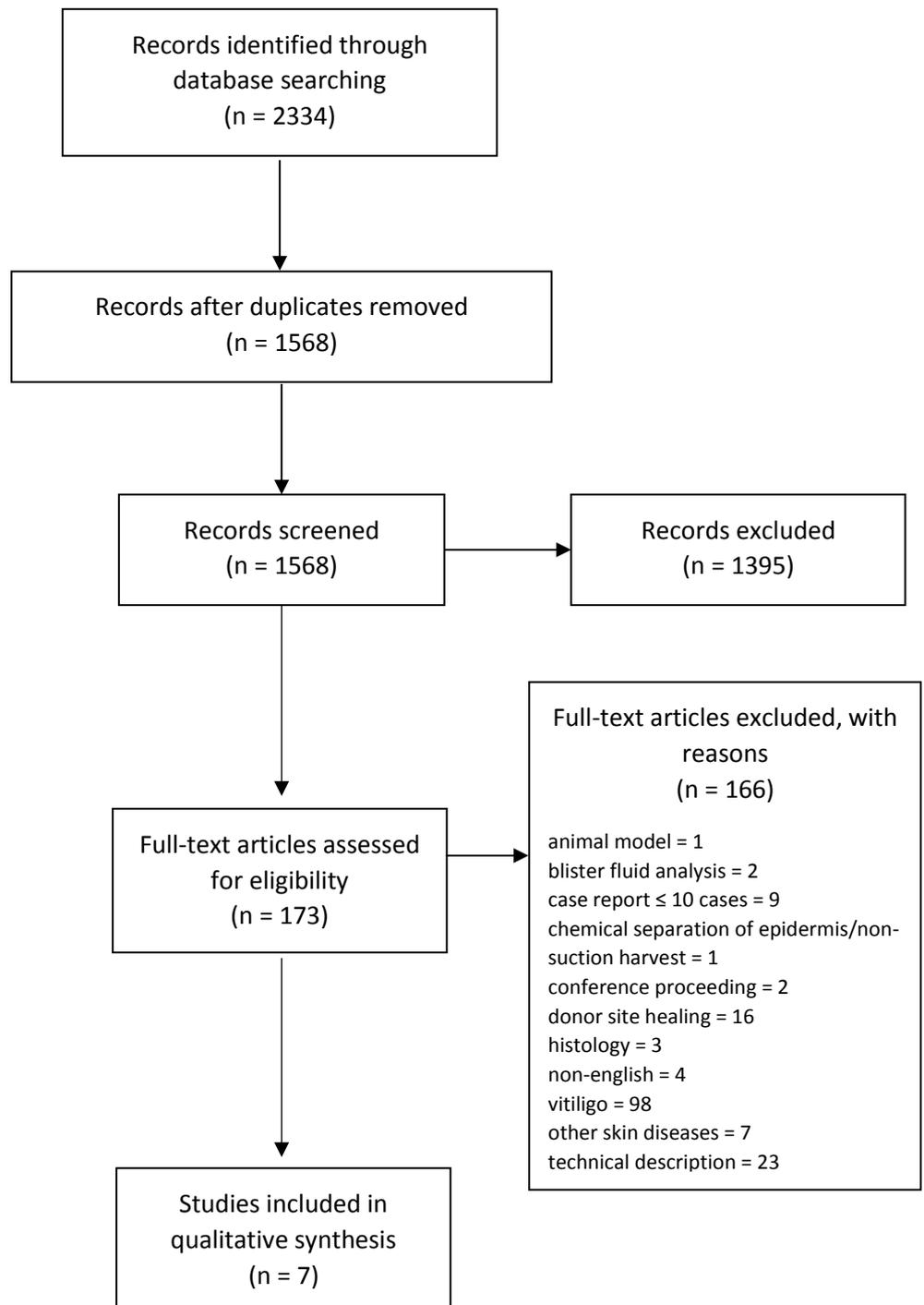


Figure 3

Meta-analysis of proportion of wounds with complete healing (random-effects plot). Proportions are shown with 95 per cent confidence intervals.

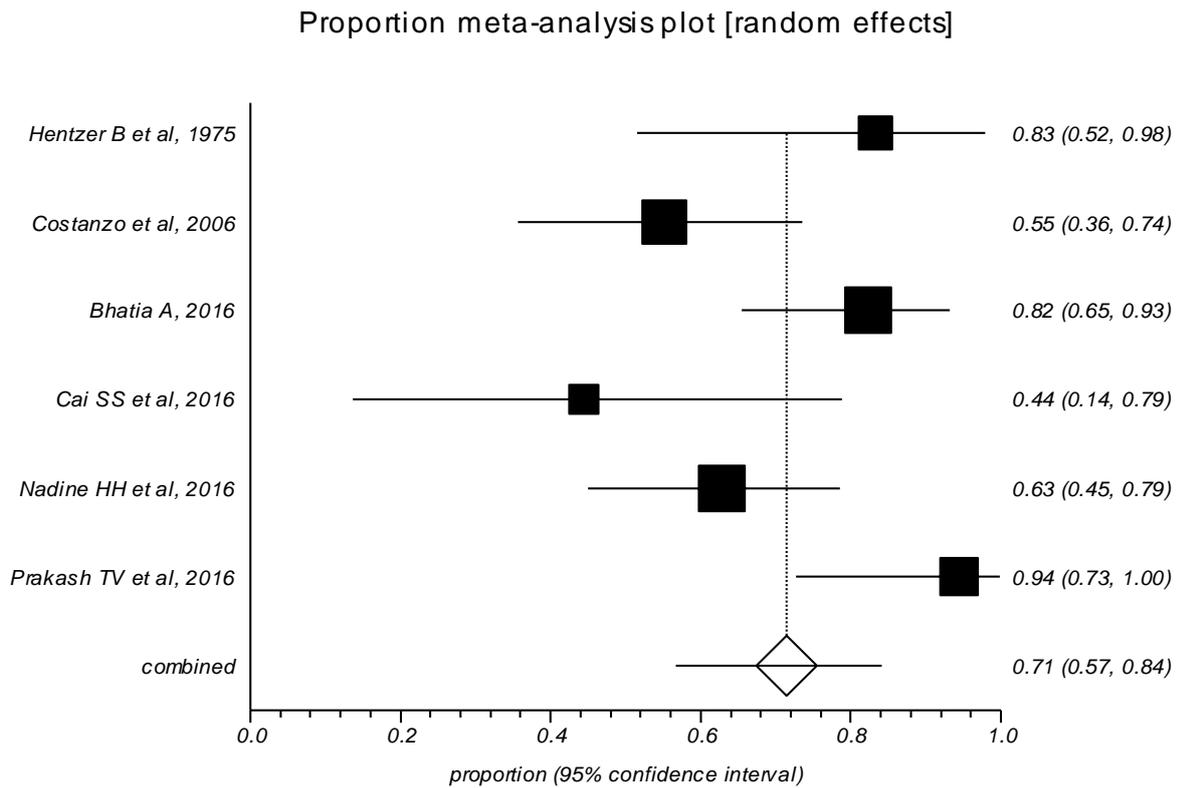


Figure 4

Meta-analysis of summary of time for complete wound healing (random effect plot).

Proportions are shown with 95 per cent confidence intervals.

