Bioengineered skin substitutes for the management of wounds: a systematic review

CRD summary
This well-conducted review evaluated safety and efficacy of bioengineered skin substitutes for wound management. The authors concluded that short- and long-term efficacy of bioengineered skin substitutes for management of venous leg ulcers, diabetic foot ulcers and other wounds could not be determined, but they appeared at least as safe as standard therapies. These conclusions are likely to be reliable.

Authors' objectives
To evaluate safety and efficacy of bioengineered skin substitutes for wound management.

Searching
MEDLINE, EMBASE, The Cochrane Library, Science Citation Index and Current Contents were searched from inception to April 2006. ClinicalTrials.gov, CRD databases and the databases of Health Technology Assessment, National Research Register, National Institute of Health and Meta Register of Controlled Trials were also searched. Searches were conducted without language restrictions. Search terms were reported. Foreign-language papers were subsequently excluded unless they contained information not reported in well-designed English-language papers. Bibliographies of retrieved papers were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) of adults and children with venous leg ulcers, diabetic foot ulcers or a combination of wounds suitable for treatment with bioengineered skin substitutes (BSS) that reported efficacy and or safety data were eligible for inclusion. Studies that compared biosynthetic skin substitutes or autologous cultured and non-cultured skin engineering products with the comparators biological skin replacements or standard methods (dressings and/or topical agents or compression therapy) and studies that compared two new interventions were eligible for inclusion. The outcomes of interest related to: extent of wound healing; acceptance/rejection of graft; convalescence of patients; peri-operative and postoperative morbidity and mortality, patient satisfaction and cost/resource use.

The patients in the included studies had venous leg ulcers, diabetic foot ulcers and other wounds (such as skin graft donor sites and wounds resulting from excisional or Mohs micrographic surgery to remove cutaneous malignancies). A variety of bioengineered skin substitutes was included (such as Apligraf, Cryopreserved cultured allografts and Dermagraft) and a variety of comparators were employed (such as compression of different types, saline and/or gauze and petrolatum gauze). Follow up ranged from at least four weeks to 14 months. Efficacy outcomes reported included wound closure, wound healing time, pain, exudate and cosmesis. Safety outcomes included infection and local allergic reaction.

Studies were selected independently by two reviewers. Disagreements were resolved by discussion.

Assessment of study quality
Methodological quality was assessed using the criteria in the Cochrane Reviewers Handbook, which included quality of reporting, randomisation, allocation concealment, blinding, sample size and statistical methods. The evidence was classified according to the National Health and Medical Research Council Hierarchy of Evidence according to study design. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data for outcomes was extracted from primary studies using a data extraction table. If no data were reported for an outcome no value was assigned. Data were extracted by one reviewer and checked by another.

Methods of synthesis
Data were combined in a narrative synthesis, categorised by indication for treatment (venous leg ulcer, diabetic foot
ulcer and other wounds) and by brand of skin substitute.

**Results of the review**

Twenty three RCTs were included (n=2,063). The authors reported that reporting of methodological detail was generally inadequate (several studies did not report method of randomisation or blinding and almost half did not report an intention to treat analysis). The evidence base was rated as average (limited by small samples, short follow-up periods and lack of methodological rigour).

**Venous leg ulcers** (nine RCTs, n=708): There were no differences between Apligraf, cryopreserved cultured allografts, cultured keratinocyte allografts, Dermagraft, EpiDex, OASIS Wound Matrix and Promogran against standard treatment in the efficacy measures of wound healing time, wound closure and decreased ulcer area and for pain, recurrence and wound infection.

**Diabetic foot ulcers** (eight RCTs, n=1,173): Apligraf, Dermagraft, GraftJacket, Hyalograft, Laser Skin, OrCel and Promogran were associated with improved wound healing time and improved wound closure was associated with Apligraf, GraftJacket and OrCel compared against standard care. Bioengineered skin substitutes were also associated with lower infection rates. There was no difference in recurrence between bioengineered skin substitutes and comparator, where reported.

**Other wounds** (six RCTs, n=182): Bioengineered skin substitutes and comparator were similar in healing efficacy across different types of wound. Postoperative pain was low in both groups.

**Authors’ conclusions**

The short- and long-term efficacy of bioengineered skin substitutes for the management of venous leg ulcers, diabetic foot ulcers and other wounds could not be determined based on the available evidence. Bioengineered skin substitutes appeared to be at least as safe as standard therapies for these indications.

**CRD commentary**

The research question was well defined with inclusion criteria for participants, intervention, outcomes and study design. Searches for published and unpublished studies in any language were conducted, which minimised the possibility of language and publication biases. Validity of the primary studies was assessed and taken into consideration. Study selection and data extraction were performed by two reviewers, which reduced the risk of error and bias. The process of validity assessment was not described, so it was unknown whether similar steps were taken. The primary studies were heterogeneous and synthesised narratively, which appeared to be appropriate. This review appeared to be generally well-conducted and the authors’ conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that high-quality prospective RCTs of the use of bioengineered skin substitutes (particularly in terms of recurrence) with longer follow-up periods were needed and standard outcome measures should be developed. Cost-effectiveness studies that took the Australian healthcare context into consideration should be considered.

**Funding**

Australian Safety and Efficacy Register of New Interventional Procedures, Surgical.

**Bibliographic details**

Original Paper URL
http://www.surgeons.org/AM/Template.cfm?Section=ASERNIP_S_Publications&Template=/TaggedPage/TaggedPageDisplay.cfm&TPLID=17&ContentID=3297

Indexing Status
Subject indexing assigned by CRD

MeSH
Administration, Topical; Biocompatible Materials /therapeutic use; Skin Transplantation /methods; Skin, Artificial; Treatment Outcome; Wound Healing

AccessionNumber
12007008446

Date bibliographic record published
13/12/2007

Date abstract record published
26/08/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.