Influence of bioengineered skin substitutes on diabetic foot ulcer and venous leg ulcer outcomes


CRD summary
This review evaluated the safety and effectiveness of bioengineered skin substitutes compared with standard dressings and/or autografts when used on chronic wounds. It found that bioengineered skin substitutes (with a dermal component) may improve healing outcomes in diabetic foot ulcers and venous leg ulcers. Lack of reporting of statistical tests means the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the safety and effectiveness of bioengineered skin substitutes compared with standard dressings and/or standard autografts when used on chronic wounds.

Searching
MEDLINE, EMBASE, the Cochrane Library, Science Citation Index and Current Contents were searched, without language restrictions, from inception to July 2008. The Clinical Trials database (USA), CRD databases (not specified), HTA database, NRR (National Research Register), National Institute of Health (USA) and Meta Register of Controlled Trials were also searched (June 2008). Search terms were reported. Additionally, bibliographies of retrieved articles were scanned.

Study selection
Randomised controlled trials (RCTs) and systematic reviews of RCTs that compared bioengineered skin substitute (as a physical layer that would integrate into the wound and not lysate) were eligible for inclusion. Eligible trials had to report effectiveness and/or safety outcomes.

The outcomes evaluated were days to complete closure, rate of healing and percentage decrease in ulcer surface area.

The included trials were of patients with venous leg ulcers and diabetic foot ulcers. The trials compared Apligraf (Graftskin), Dermagraft, OASIS Wound Matrix, Promogran, EpiDex, cryopreserved cultured allografts, cultured keratinocyte allografts, GraftJacket, OrCel, Hyalograft and Laserskin with various gauze and gel dressings.

Studies were selected independently by two reviewers and disagreements resolved by discussion.

Assessment of study quality
Methodological quality was assessed using criteria published in the Cochrane Reviewer's Handbook. Trials were assigned a level of evidence according to the National Health and Medical Research Council Hierarchy of Evidence.

The authors did not state how many reviewers were involved in validity assessment.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes. Absolute differences between categorical variables (healing rates) and 95% confidence intervals were calculated for outcomes not suitable for statistical pooling.

Data were extracted by one reviewer and checked by another.

Methods of synthesis
Odds ratios and 95% confidence intervals were pooled in meta-analyses. Statistical heterogeneity was also assessed (test not reported). Outcomes not suitable for meta-analysis were reported narratively according to condition (diabetic foot ulcer and venous leg ulcer).
ulcer or venous leg ulcers), then by bioengineered skin substitute used.

**Results of the review**

Eighteen RCTs were included in the review (n=1,909 patients). All RCTs appeared comparable at baseline. Follow-up ranged from four to 32 weeks.

Nine RCTs reported venous leg ulcers (n=708 patients); six described randomisation method; four allocation concealment; three blinding; and five performed intention-to-treat analysis. Four trials reported a power calculation was performed.

Nine RCTs reported diabetic foot ulcers (n=1,201); two described randomisation method, three gave detail on allocation concealment; five provided data on blinding; and five provided intention-to-treat analysis. Two trials reported a power calculation was performed.

**Venous leg ulcers:** Two RCTs reported that bioengineered skin substitutes significantly improved 100% wound closure (Apligraf and OASIS Wound Matrix), two did not report significance and five found no significant difference (cultured keratinocyte allografts, Dermograft, Promogran and EpiDex). Healing time was reported to be significantly better with bioengineered skin substitutes in two RCTs (Apligraf and Dermagraft), but no significant difference was reported in two RCTs for cryopreserved cultured allografts and cultured keratinocyte allografts). Percentage decrease in surface area were found to be better than standard therapy with Promogran (one RCT) and Dermagraft (one RCT), whereas EpiDex (one RCT) and cultured keratinocyte allografts (two RCTs) were no better than standard therapy. Results for ulcer size for cryopreserved cultured allografts were conflicting (two RCTs). Patient-reported pain and infection was largely similar between bioengineered skin substitute and standard therapy groups. Infection appeared to be the main adverse event.

**Diabetic Foot Ulcers:** The incidence of 100% wound closure was significantly better for bioengineered skin substitutes than with standard therapy in five RCTs (Apligraf, Dermagraft and GraftJacket), but no significant difference was found for Promogran or Hyalograft with Laserskin. Healing times were better with bioengineered skin substitutes than standard therapy with Apligraf, Dermagraft, GraftJacket, Hyalograft with Laserskin and OrCel. Two RCTs found the percentage decrease in ulcer area was larger with bioengineered skin substitutes Dermagraft and GraftJacket than with standard therapy. Pain outcomes were not generally reported and no major complications were identified, although in two of eight RCTs that reported adverse events, adverse events were significantly lower in the Apligraf and Dermagraft groups compared with standard therapy (the remaining RCTs found similar infection and adverse event rates).

**Authors’ conclusions**

Bioengineered skin substitutes with a dermal component may improve healing outcomes in diabetic foot ulcers and venous leg ulcers.

**CRD commentary**

The research question was supported by inclusion criteria for study design, intervention and outcomes. All languages and unpublished sources were searched, reducing the possibility of language or publication bias. Study selection and data extraction were performed in duplicate, minimising the chance of possible reviewer bias and error, but this was not reported for validity assessment.

Validity was assessed using an appropriate tool and taken into account in the analysis. It appeared that the authors took steps to combine trials in an appropriate manner, but results of tests for statistical heterogeneity were not reported, so it was unclear whether the results of meta-analyses were reliable.

Although many aspects of this review were well-conducted, lack of reporting of statistical tests means the reliability of the authors’ conclusions is unclear.

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

**Practice:** The authors stated that bioengineered skin substitutes could be considered at least as safe as standard therapies.
Research: The authors stated that better designed trials with longer follow-up periods (of at least one year) are needed. A study is needed to develop and standardise outcome measures for wound closure assessment and cost-effectiveness studies should be considered.

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