Bioengineered skin substitutes for the management of burns: a systematic review
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CRD summary
This review evaluated safety and efficacy of bioengineered skin substitutes compared with biological skin replacements and/or standard dressing methods in burn management. The authors were unable to formulate conclusions because skin substitutes and methods for burn management were diverse. Methodological and primary study limitations made it difficult to determine the reliability of the conclusions, but they seem suitably cautious.

Authors' objectives
To evaluate the safety and efficacy of bioengineered skin substitutes in comparison with biological skin replacements and/or standard dressing methods in the management of burns.

Searching
The Cochrane Library, Current Contents, EMBASE, PubMed/MEDLINE and CINAHL were searched from inception to 2006 (it also appeared that Science Citation Index was searched). NHS CRD, NHS HTA, National Research Register, National Institute of Health, meta Register of Controlled Trials and clinicaltrials.gov were searched in April 2006. Searches were conducted without language restrictions, but foreign language articles were excluded unless they provided information not available in well-designed English-language articles. Search terms were reported. Bibliographies of all publications were handsearched.

Study selection
Systematic reviews of randomised controlled trials (RCTs) and RCTs of adults and children with burns (or donor sites used to treat burn wounds) suitable for treatment with bioengineered skin substitutes and reporting efficacy and/or safety data were eligible for inclusion. Included studies were mainly with partial (less than 15%) total body surface area (TBSA) and/or full thickness burns treated with the bioengineered skin substitutes Biobrane, TransCyte, Dermagraft, Integra, Apligraf, autologous cultured skin and allogeneic cultured skin compared with various other methods. The follow-up period varied from 11 days to two years. Eligible studies were required to report at least one of the following outcomes: extent of wound healing; acceptance or failure of graft; convalescence of patients; perioperative and postoperative morbidity and mortality of patients; patient satisfaction or cost/resource use. Pain-related outcomes included pain, pain medication and dressing changes.

Assessment of study quality
Methodological quality was assessed according to the criteria published in the Cochrane Reviewers' Handbook, which included assessment of: reporting of methodology; randomisation; allocation concealment; blinding of patients and assessors; attempts to minimise bias; sample size; generalisability; and statistical methods. The authors did not state how the validity assessment was performed.

Data extraction
Data for the outcomes of wound infection, wound healing time, wound closure, wound exudate, patient-related outcomes (including pain and cosmesis) and safety outcomes such as complications and mortality were extracted for burns management and management of donor site (where available) by one reviewer into standardised data extraction tables (developed a priori) and checked by another reviewer.

Methods of synthesis
Studies were combined in a narrative synthesis categorised into type of bioengineered skin substitute, then by management of donor site and management of burns and by adult or paediatric population.

Results of the review
Twenty RCTs were included in the review (n was unclear but seemed to be approximately 881). Sample sizes ranged from 10 to 149 patients, where reported. Sixteen studies were of burns management. Four studies were of management of donor sites.
The quality of the included studies was average. The RCTs that were included had small sample sizes and methodological detail was poorly reported.

**Burns Management:**

Biobrane and TransCyte were found to be more effective than silver sulfadiazine for partial thickness burns (less than 15% total body surface area). Wound infection was similar in Biobrane and silver sulfadiazine groups (two studies). Biobrane was significantly more effective than silver sulfadiazine for wound healing time (four studies) and wound closure (two studies) (there were similar results for TransCyte). TransCyte was more effective for wound healing time compared with silver sulfadiazine and topical antibiotics (three studies). Good adherence was reported for treating facial burns with TransCyte (three studies). There was no wound infection in TransCyte patients, compared with mild cellulitis in six patients with silver sulfadiazine (one study). Two studies reported no wound infections in either the TransCyte or topical antibiotics groups. Skin grafts were not needed for patients treated with TransCyte (two studies), but were required for 14% of patients treated with silver sulfadiazine (one study).

For wound closure, full thickness burns showed more granulation with allograft (74%) compared with Dermagraft (51%) (two studies). There were no significant differences between dermagraft and allograft for partial or full thickness burns for wound infection (two studies), healing time (one study) and graft uptake (wound closure) (two studies). Biological skin replacements were more efficacious than Integra in wound closure, but had a significantly longer wound healing time than Integra (one study). There were high rates of infection with Integra in one study in which patients had burns that were greater than 45% total body surface area.

Apligraf combined with autograft were effective for burns between 20% and 50% total body surface area. Apligraf and autograft was more effective than autograft in wound healing time greater than 75% (one study). There was no significant difference in wound closure with greater than 75% graft take (one study).

**Management of donor sites:**

Wound healing time was significantly longer for wounds covered with Biobrane compared with sites treated with allogeneic cultured keratinocytes (two studies). Wound closure post-surgery was significantly faster with OrCel compared with Biobrane. There was no difference between Biobrane and OrCel in wound infection (one study). There was no difference in wound infection, but wounds treated with OpSite took longer to heal compared to allogeneic cultured skin treatment.

Mortality rates were high. It was unclear whether this was due to the use of bioengineered skin substitute or actual burn injury.

Patient-related outcomes and further results were reported in the paper.

**Cost information**

Assuming that patients followed all of the instructions for wound dressing and kept all of their clinic follow-up visits, the costs reported in three of the included studies were: OrCel $US 27.80 per cm$^2$ and Biobrane $US 0.16$ cm$^2$. The mean cost of Biobrane ($US 434$) was significantly lower than treatment with silver sulfadiazine ($US 504$) in paediatric and adult patients with partial thickness burns with 44 weeks follow up. One study reported significantly lower costs using TransCyte for partial thickness facial burns compared with antibiotic ointment and creams. The cost of TransCyte was lower than that of antibiotics ($210$ compared with $390$), but this was not significant. Conventional meshed autografts were found to be superior to cultured epidermal autografts with regard to the total number of operations, length of hospital stay and cost per patient in a study of paediatric patients with full thickness burns to 90% total body surface area.

**Authors' conclusions**

Overall conclusions for suitability of bioengineered skin substitutes could not be formulated due to the diversity of skin substitutes and methods for burn management. The evidence suggested that for management of partial thickness burns Biobrane, TransCyte, Dermagraft and allogeneic cultured skin were at least as effective as topical agents, wound dressings or allograft. Management of full thickness burns could not be determined.
The research question was well-defined and there were inclusion criteria for study design, participants, outcomes and intervention. Published and unpublished sources were searched for studies in all languages, reducing the possibility of publication and language bias. There were inconsistencies in reporting of the databases that were searched. Validity of the primary studies was assessed and taken into account by the authors when assessing the evidence. Nonetheless, the studies were only of average quality and the evidence presented was based on a small number of studies often with small sample sizes (acknowledged by the authors). Study selection and data extraction were performed in duplicate, minimising the risk of reviewer bias and error. The process of validity assessment was not described, so whether steps were taken to reduce bias and error was unknown. Studies were combined in a narrative synthesis, which was appropriate given the heterogeneity of the study interventions, comparators and outcomes. The authors stated that they categorised the studies by age, but this was not apparent in the review. Given the number of limitations with the included studies (particularly the small number of studies) and the potential for bias, it is difficult to determine the reliability of the authors' conclusions. But, the conclusions seem suitably cautious.

Implications of the review for practice and research

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

Research: The authors stated that more rigorous randomised controlled trials of patients with smaller burns should be undertaken as these burns were more common. Studies with sufficient follow-up should be conducted to assess the long-term safety of bioengineered skin substitutes. Future studies should document outcomes for partial and full thickness burns separately. Randomised controlled trials on cultured epithelial autograft (particularly cultured epithelial autograft suspension) were also needed.

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Other publications of related interest

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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.