Advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers: a systematic review

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CRD summary
This review concluded that, compared with standard care, some advanced wound care therapies could increase the proportion of diabetic or venous ulcers healed and reduce the time to healing, but the evidence was limited. This conclusion is an accurate representation of disparate evidence, composed mostly of small trials of varying quality.

Authors’ objectives
To evaluate the benefits and harms of advanced wound care for non-healing, diabetic, venous or arterial ulcers.

Searching
MEDLINE and The Cochrane Library were searched up to June 2013, for studies reported in English. References of relevant studies were checked, and experts were consulted.

Study selection
Randomised controlled trials (RCTs) of adults with non-healing diabetic, venous or arterial ulcers were eligible for inclusion. Trials needed to compare an advanced wound care, with standard care or another advanced care. The primary outcome was the percentage of ulcers healed at trial completion. Secondary outcomes included time to complete ulcer healing, patient global assessment, and return to daily activities. Adverse events, mortality, hospitalisation, pain, infection, amputation, revascularisation, recurrence, and adverse responses to treatment were also assessed.

Most of the included trials were of patients with diabetic ulcers; all except one of the others were of patients with venous ulcers. Most had a standard care or placebo comparison group. Nine therapies were evaluated for diabetic ulcers, and nine for venous ulcers. Therapies included collagen, hyperbaric oxygen therapy, silver products, biological skin equivalents and dressings, keratinocytes, and plasma products. Most patients with diabetic ulcers were middle-aged, White, and male; most patients with venous ulcers were older, White and female. Where described, most ulcers were on the legs or feet. Mean ulcer size ranged from 1.9cm² to 41.5cm² for diabetic ulcers, and from 1.2cm² to 11.1cm² for venous ulcers. Ulcer duration ranged from two to 94 weeks for diabetic ulcers, and from 12 to 207 weeks for venous ulcers.

The full report, related to this article, included eight trials of patients with mixed-aetiology or amputation ulcers (see Other Publications of Related Interest). It appears that more than one reviewer was involved in selecting the trials for inclusion.

Assessment of study quality
The studies were assessed for quality using the modified Cochrane risk of bias tool. This assessed allocation concealment, blinding, the approach to analysis, and the description of withdrawals. Trials were given an overall rating of good, fair, or poor. The strength of evidence, for each comparison, was rated as high, moderate, low or insufficient.

One reviewer carried out these assessments, and a second reviewer checked them.

Data extraction
The data were extracted to calculate relative risks, with 95% confidence intervals. Absolute risk differences were also calculated.

The data were extracted by one reviewer and checked by a second reviewer.

Methods of synthesis
Diabetic, venous and arterial ulcers were considered separately. A random-effects meta-analysis was used where multiple trials assessed the same comparison, otherwise a narrative synthesis was reported. Statistical heterogeneity was
assessed using $X^2$ and $I^2$.

**Results of the review**

Fifty-six RCTs, with 5,869 patients, were included in the review. Sample sizes ranged from nine to 382. Most trials were rated as fair. Trials lasted between four and 26 weeks.

**Diabetic ulcers:** There were 35 RCTs, with 3,773 patients, reporting on nine therapies. Moderate strength evidence favoured two therapies (biological skin equivalent – Apligraf – and negative pressure wound therapy). Low strength evidence favoured the other seven therapies, compared with standard care. The relative risk, for the proportion healed, at study completion, was 1.49 (95% CI 1.11 to 2.01) based on one good-quality trial of negative pressure therapy; and 1.58 (95% CI 1.20 to 2.08) based on two fair-quality trials of Apligraf. The results for other therapies, comparisons between therapies, and secondary outcomes were reported.

**Venous ulcers:** There were 20 RCTs, with 2,065 patients, reporting on nine therapies. There was moderate strength evidence (two fair-quality trials) favouring keratinocyte therapy over standard care. The relative risk for the proportion of ulcers healed at study completion was 1.57 (95% CI 1.16 to 2.11). Full results for other therapies, comparisons between therapies, and secondary outcomes were reported.

**Arterial ulcers:** There was one RCT, with 31 patients, which showed a benefit of biological skin equivalent over standard care.

**Authors' conclusions**

Some of the advanced wound care therapies could increase the proportion of ulcers healed and reduce the time to healing, compared with standard care, but the evidence was limited.

**CRD commentary**

This review addressed a clear question, supported by specific inclusion criteria. The search was adequate. The authors used methods designed to reduce reviewer error and bias throughout the review. The quality of the trials was appraised, using appropriate methods; the results were not reported in detail, but they were an integral part of the synthesis. The synthesis seems to have been appropriate, in its limited use of meta-analysis.

The authors' conclusions are an accurate representation of disparate evidence, composed mostly of small trials of varying quality.

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

**Practice:** The authors stated that the results for standard care suggested that a more rigorous approach than was usual in clinical practice might be beneficial for many patients.

**Research:** The authors stated that additional RCTs comparing advanced wound care with standard care were needed, with comparisons of different advanced therapies, and cost-effectiveness analyses. Trials should have sufficiently large samples to allow outcome reporting by key patient and ulcer characteristics, with long follow-up sufficient to assess whether healing was maintained.

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