Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review found that hyaluronic acid derivatives were associated with improved wound healing compared to usual care in chronic wounds, particularly burns and some ulcers. Reporting limitations and the small number of included patients make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To determine the effectiveness of hyaluronic acid and derivatives of hyaluronic acid in the healing of burns, epithelial surgical and chronic wounds compared to other therapies or placebo.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases and Google, technology assessment websites, clinical guideline websites and websites of manufacturers of hyaluronic acid were searched to November 2011; search terms were reported. Websites of 21 peer-reviewed journals were searched. The manufacturers of hyaluronic acid wound-healing products were contacted to identify unpublished trials and ongoing trials conducted after pilot studies were checked. References of trials identified through the electronic searches were checked for additional studies

Study selection
Randomised controlled trials that evaluated hyaluronic acid wound healing products in patients with diabetic foot ulcers down to and including bone (Wagner Class 4), diabetic and neuropathic lower extremity ulcers, venous leg ulcers, partial or full thickness burns or surgical removal of the epithelial layer of skin were eligible for inclusion. Eligible trials were required to evaluate the primary outcome complete wound healing (defined as complete epithelialisation of the wound without any septic drainage) and the secondary outcome of wound area reduction.

Patients in the included studies presented with superficial and deep dermal burns, dermal wounds from tattoo removal, leg ulcers, diabetic foot ulcers, venous and vascular ulcers, and neuropathic leg ulcers. The hyaluronic acid products included in the analysis were hyaluronic acid-impregnated inert pads, hyaluronic acid gel or cream, a pad or matrix composed entirely of hyaluronic acid (hyalofill or hyalomatrix) and hyaluronic acid pad used as a substrate for later autologous tissue grafts. Comparators were placebo, paraffin gauze, standard treatment, inert gels and silver sulphadiazine.

Two reviewers performed the study selection. Any disagreements between the reviewers were resolved by discussion.

Assessment of study quality
Methodological quality of the included studies was assessed by two reviewers who used the Cochrane collaboration tool for risk of bias in terms of random sequence generation, concealment of allocation to treatment, blinding, treatment of incomplete outcome data, selective outcome reporting and other risks of bias (such as imbalances of treatment groups at baseline). Any disagreements between reviewers were resolved by discussion or with a third reviewer.

Data extraction
Data were extracted to calculate risk ratios (RR) for dichotomous outcomes and mean differences for continuous outcomes and corresponding 95% confidence intervals (CIs). Trial authors were contacted for missing data where necessary.

One reviewer performed the data extraction, which was checked by a second reviewer.

Methods of synthesis
Pooled risk ratios, weighted mean differences (WMD) and 95% CIs for the summary estimates were calculated using
both fixed-effect and random-effects models. Statistical heterogeneity was assessed using the $I^2$ test. Where $I^2$ was greater than 60% for any outcome, sensitivity analyses were conducted to examine potential sources of heterogeneity. Potential for publication bias was evaluated by visual appraisals of funnel plots. The reviewers also assessed location and language biases.

**Results of the review**

Ten trials (599 participants, range 10 to 110 patients) were included in the review. Graphically-presented results of the quality assessment indicated that randomisation and blinding of participants and study personnel were adequately reported in less than half of the included trials and that allocation concealment was reported in two trials and blinding of outcome assessment was reported in one trial. All the trials reported incomplete outcome data.

**Leg ulcers (two trials):** One trial found the percentage wound area reduction was increased significantly with a hyaluronic acid-impregnated pad over a period of three to eight weeks compared to standard care. In the other trial time to skin grafting was significantly reduced when one side of a wound received hyaluronic acid pad compared to the other side of the wound which received a gel.

**Burns (three trials):** One trial showed that burns healed significantly faster with a placebo than a hyaluronic acid cream. In another trial radiotherapy-inflicted burns healed more quickly with hyaluronic acid cream than placebo. A third trial found faster healing with hyaluronic acid cream plus silver sulphadiazine than with silver sulphadiazine alone.

**Diabetic plantar and dorsal foot ulcers:** One study found hyaluronic pads seeded with keratinocytes plus autologous graft in Wagner Class 1 to 2 foot ulcers healed dorsal ulcers faster than usual care of paraffin gauze (p=0.049) but no differences were observed between groups for complete healing for both dorsal and plantar ulcers at 11 weeks. A second study with the same interventions and comparators found that reductions of 50% of ulcer area was achieved faster in the hyaluronic acid group compared to the paraffin gauze group (40 days compared to 50 days, p=0.018) and dorsal ulcers healed significantly quicker in the treatment group (p=0.047). Meta-analyses that examined all foot ulcers and dorsal ulcers only from the two studies found no differences between the hyaluronic acid groups and the paraffin gauze groups in healing.

**Neuropathic foot ulcers:** Hyaluronic acid derivatives had significant effects on healing at 12 weeks compared to usual care (RR 0.24, 95% CI 0.24 to 0.49; two trials, 60 patients; $I^2$=0%, random-effects model).

**Tattoo Removal:** One trial that examined the effect on healing of one formulation of hyaluronic acid compared to another in wounds from tattoo removal found no differences in healing rates between the two groups.

No evidence of publication bias was identified by visual appraisal of the funnel plots.

**Authors' conclusions**

Hyaluronic acid derivatives were associated with positive effects on wound healing compared to usual care or placebo for wounds from burns, venous insufficiency, diabetes and neuropathic insufficiency.

**CRD commentary**

The review addressed a clear question. Criteria for the inclusion of trials were well defined. Appropriate electronic databases journals and websites were searched for relevant studies. There were no language restrictions. Attempts were made to identify unpublished studies. Potential for publication bias was evaluated using validated methods. Steps were taken to minimise errors and biases at each stage of the review process. Methodological quality was assessed and for most quality items the risk of bias was judged to be uncertain to high across the studies. Results of the assessment were not clearly reported for each trial so it was difficult to see the quality of individual trials.

Little information was reported on some of the results of the included trials so it was difficult to judge the reliability of the results. The sample sizes of the included studies were small. Differences between wound types in the included studies meant that the decision to report the results stratified by wound type was justified.

Limitations in reporting of the results, a lack of clarity regarding the methodological quality of the trials the small number of included patients make the reliability of the authors' conclusions unclear.
Implications of the review for practice and research

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

Research: The authors stated that trials of longer duration were required particularly for treatment with larger wounds (>5cm²). Further research was required on the effects of hyaluronic acid on arterial ulcers and on complete healing of venous ulcers, more severe burns and epithelial surgical wounds.

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