Medicine by the Numbers

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Hyaluronic Acid Products for Chronic Wound Healing

Melinda W. Ng, MD, David Grant Medical Center, Travis Air Force Base, Fairfield, California
Christina Valerio, MD, Uniformed Services University of the Health Sciences, Bethesda, Maryland, and David Grant Medical Center, Travis Air Force Base, Fairfield, California

Details for This Review

Study Population: Adults in any care setting (e.g., hospital, outpatient, long-term care facility, home care) who presented with pressure ulcers, leg ulcers (venous, arterial, or mixed etiology), and diabetic foot ulcers

Efficacy End Points: Primary outcomes: complete wound and ulcer healing, time to complete wound healing; secondary outcomes: health-related quality of life; pain; wound recurrence rate; change in wound size and area

Harm End Points: Adverse events

Narrative: Chronic wounds are defined as wounds that do not heal as expected. They are extremely common worldwide and are often related to underlying disease (e.g., diabetes mellitus, vascular disease), can decrease quality of life, and are costly to manage.[1] Some evidence suggests that application of hyaluronic acid, most commonly in an aqueous gel formulation, to chronic wounds may promote healing during the inflammation and granulation phases of wound healing.[2] Hyaluronic acid is proposed to maintain a moist wound environment that helps cell migration in the wound bed. This process is thought to reduce scarring and fibrosis, improve angiogenesis, and reduce overall inflammation.[2-5]

A 2023 Cochrane review evaluated hyaluronic acid application (and its derivatives) for chronic wound healing.[6] This review included 12 randomized controlled trials (RCTs) with 1,108 adult participants (mean age 69.6 years) in seven countries (France, Italy, Korea, Morocco, Poland, Spain, and Switzerland). Most of the participants were female (57%); participants presented with 178 pressure ulcers (as defined by European Ulcer Advisory Panel Stages I to III[7]), 896 leg ulcers (defined as being present for 2 months or longer), and 54 foot ulcers (defined as being present for 6 weeks or longer). Studies compared hyaluronic acid or its derivatives as a dressing or topical agent with another type of dressing, placebo, topical agent, or standard treatment. Primary outcomes studied included complete wound healing, time to complete wound healing, and adverse events. Complete wound healing was defined as the proportion of wounds that healed during study follow-up based on study author documentation. Secondary outcomes included health-related quality of life, pain, wound recurrence rate, and change in wound size and area.

In the review, moderate-certainty evidence showed that hyaluronic acid compared with a neutral vehicle (i.e., inactive dressing component or substance normally used to deliver hyaluronic acid) for leg ulcers probably improved complete wound healing at 60 days (four RCTs; N = 526; risk ratio = 2.11; 95% CI, 1.46 to 3.07; absolute risk difference = 13.7%; number needed to treat = 8). Low-certainty evidence demonstrated that hyaluronic acid compared with a neutral vehicle may slightly reduce pain from baseline on a visual acuity scale (three RCTs; N = 337; mean difference = 8.55 mm lower; 95% CI, 14.77 mm to 2.34 mm lower) and may slightly improve ulcer size at 45 days (two RCTs; N = 190; mean difference = 30.44% smaller; 95% CI, 15.57% to 45.31%). The evidence was uncertain for whether hyaluronic acid increased the incidence of infection compared with a neutral vehicle for leg ulcers.

In all other studies in the Cochrane review, when comparing hyaluronic acid and its derivatives with a control for pressure, leg, and foot ulcers, very low-certainty evidence demonstrated uncertainty for any improvement or change in

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Benefits

1 in 8 was helped (complete wound healing)

Harms

Insufficient evidence to determine

The NNT Group Rating System

Green	Benefits greater than harms
Yellow	Unclear benefits
Red	No benefits
Black	Harms greater than benefits

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the primary outcomes of complete wound healing, time to wound healing, or adverse events, as well as secondary outcomes of pain and change in wound size. No trials reported on the other secondary outcomes of health-related quality of life or wound recurrence.

Caveats: Most studies had a small sample size and high risk of bias (major limitations included lack of blinding of participants and personnel as well as outcome assessment). Significant heterogeneity occurred in the type of hyaluronic acid product and the comparators used for wound interventions. In addition, the follow-up duration for most studies was short (nine of 12 RCTs followed participants for 60 days or fewer), making it difficult to evaluate whether a chronic wound would eventually heal with a longer intervention. Only one RCT followed participants until it was determined that all participants had complete wound healing.

Conclusions: Despite these limitations, moderate-certainty data showed that hyaluronic acid may slightly improve complete leg ulcer healing compared with a neutral vehicle. However, there is insufficient evidence to determine any benefit from hyaluronic acid for pressure ulcers or foot ulcers in people with diabetes. Because of the significant risk of blinding bias and imprecision in the results as well as inadequate assessment of harms, we have assigned a color recommendation of yellow (unclear benefits) for use of hyaluronic acid for chronic wounds. Future research should focus on increasing sample size, reducing bias, and improving heterogeneity in interventions while also reporting data on adverse events.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Uniformed Services University of the Health Sciences, U.S. Department of Defense, U.S. Air Force, or U.S. government.

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