RESEARCH
www.commprac.com
ISSN 1462 2815

# A RANDOMISED CONTROLLED TRIAL ON EVALUATING EFFECTIVENESS OF HYALURONIC ACID DRESSING ON HEALING OF DIABETIC ULCERS

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**DOI: 10.5281/zenodo.10989965**

**Abstract**

**Background & Aim:** This study is to evaluate the effectiveness and safety of using hyaluronic acid (HA) dressings in the management of diabetic foot ulcers in comparison with conventional dressing materials. **Methods:** A total of 110 diabetic foot ulcer patients were randomly assigned to one of two groups: the control group (55 patients) or the experimental group (55 patients) receiving HA dressings (Healoderm TM). Two patients in conventional and three patients in experimental group were lost to follow up after 2nd week of visit. During this study, a single investigator recorded weekly wound length and depth, wound characteristics, adverse events, and gross photographs of the wounds. **Results:** Patients were measured according to the percent reduction of wound area and the percent increase of healthy granulation tissue. During week 3, the experimental group reduced wound area by 53.8%, while the control group reduced it by 31.9%. The experimental group reduced wound depth by 61.5% while the control group reduced wound depth by 52.9%. Furthermore, the experimental group increased healthy granulation tissue area by 53.9% while the control group increased it by 16.8% (P=0.62). **Conclusion:** The study treatment did not cause any adverse events. Diabetic wound healing may be accelerated by hyaluronic acid dressings.

**Keywords:** Hyaluronic Acid, Diabetic Ulcers, Wound Healing, Immunosuppressive, Foot Ulcers.

## INTRODUCTION

Wound healing is important to restore the lost skin which is the primary immunological barrier. It is an interactive process with inflammatory, proliferative and remodelling phases. An optimal wound healing environment is obtained and maintained through active wound dressings. Since their inception in 1960s, wound dressings have undergone significant development in techniques and materials with active ingredients such as hyaluronic acid(HA) and collagen.[1] The HA is a linear glycosaminoglycan(GAG) which plays an important role in all phases of wound healing. As HA binds to fibrinogen during phase of haemostasis and aids in effective clot formation. With its immunosuppressive properties, HA suppresses protracted inflammation and increases proliferative activity .Angiogenesis, proliferation and migration of keratinocytes are promoted by HA in the proliferative phase. During the remodelling process, HA contributes in production of type 1 collagen, wound regeneration and scar formation.[2] Diabetic foot ulcers are treated with hyaluronic acid

containing dressings and conventional dressings. We compare their efficacy and safety.

## METHODOLOGY

In the following single blinded clinical study, patients attending OPD with diabetic foot ulcers were recruited and randomized into experimental and conventional groups till sample size of 110 was achieved. The study included people with type 1 or type 2 diabetes, ulcers greater than 1.0 cm2, that have not healed after six weeks, and who have more than one intact artery on a Doppler ultrasound or with a transcutaneous oxygen pressure of 30mmHg.The dressing in experimental group of diabetic foot ulcer patients were performed using Healoderm$^{TM}$ which contains sodium hyaluronate in a porous spongy biologic material. The allocation of a particular group was not known to the patients. Patients' demographic details and wound characteristics were collected, recorded and stored in a personal computer by a single investigator.

### Techniques

The greatest width, longest length, and deepest depth of the target wound were measured. The circumference of the ulcer was marked with the Opsite and the traced area was measured. Additionally, slough, granulation tissue, edge characteristics of a wound were assessed and photographed. A thorough cleaning of the wound was performed before hyaluronic acid dressing was applied to the experimental group. Primary wound dressing was then applied by cutting Healoderm$^{TM}$ sheets to the wound's size, covering the raw surface. This was covered with a secondary dressing made of hydrophilic polyurethane foam. All patients attended OPD at 2- to 3-day intervals for a minimum for 3 weeks or until wound healed. Off-loading dressing was performed on patients with pressure ulcers. Hydrophilic polyurethane foam alone was used in the control group with a similar follow up schedule.

### Evaluation

A weekly follow-up evaluation was conducted for a period of three weeks or until healing of wound by investigator recording the wound condition, number and frequency of dressing changes, compliance with appropriate off-loading devices, and any adverse events. A complete healing of the wound was evaluated on the basis of two criteria. Within the three-week study period, effectiveness was measured by the percentage reduction in area and depth relative to baseline planimetry. During a 3-week study period, granulation tissue was measured in relation to total wound size as a secondary efficacy criterion. In this study, granulation tissue is defined as the dark pink or light red tissue that forms at the base of a wound and is moist and healthy in appearance. Means and standard deviations were used to calculate the quantitative values. For comparing wound reduction and granulation tissue area, the Mann-Whitney U-test was used. A 5% level of confidence was used in order to determine statistical significance.

## RESULTS

There were 105 participants who completed the study, five of whom dropped out due to unknown reasons. Clinical laboratory parameters, as well as patient characteristics, were recorded. Both groups had similar clinical characteristics at baseline. In the final measurement (after 3 weeks), the ulcer size ranged from 0 to 30.3 $cm^2$ (mean, 6.60±11.63 $cm^2$) in the experimental group, and ranged between 0.2 and 54.7 $cm^2$

(mean, 15.15±21.47 $cm^2$) in the control group. Every week, wound area and depth were calculated by comparing them to baseline planimetry wounds. We found that the mean percentage of wounds reduced by 51.60±36.83% in the experimental group and 29.68±35.48% in the control group (P=0.186). As for wound depth reduction, it was 59.29±28.91% in the experimental group and 50.74±40.37% in the control group (P=0.714) which is not statistically significant. According to the comparison between the experimental and control groups, the mean percentage increase of healthy granulation tissue area was 51.75±33.89% in the experimental group and 14.59±49.59% in the control group (P=0.62). The study period was not adversely affected by any adverse events in either group. In both groups, no overt infections were observed. Clinically meaningful differences were not observed during the study regarding serum albumin, haematology or vital signs.

**Table 1: Demographic characteristics of patients in either group**

| | Hyaluronic Treatment group (n=50) | Control group (n=55) |
|---|---|---|
| Age (years) | 63±14.4 | 65.4±4.81 |
| Type1:Type2 (n) | 0:50 | 0:55 |
| Male: Female | 50:0 | 40:15 |
| HbA1c(%) | 6.98±2.0 | 7.84±0.86 |
| Hb(g/dl) | 10.43±1.53 | 10.85±1.8 |
| WBC(×$10^3$/ml) | 7.68±2.48 | 8.35±3.72 |
| Albumin(g/dl) | 3.83±1.68 | 3.99±1.62 |

**Table 2: Baseline clinical characteristics of either group**

| | Experimental Group | Control. Group |
|---|---|---|
| Depth of ulcer(mm) | 7.6±2.42 | 9.84±12.82 |
| Ulcer size($cm^2$) | 7.82±7.42 | 13.18±17.27 |
| Duration of ulcer(months) | 15.4±3.47 | 16.3±4.6 |
| Percentage of granulation | 14.82±26.25 | 16.27±12.26 |
| Plantar(fore foot: mid-foot: hind foot) | 6 (2:0:4) | 4(2:1:1) |
| Dorsal(fore foot: mid foot: hind foot) | 4(2:1:1) | 5(2:1:2) |
| $TcpO_2$(mmHg) | 46.34±12.85 | 50.82±14.65 |

**Table 3: Outcome characteristics in either group**

| | Experimental group | Control group | P-value* |
|---|---|---|---|
| Final ulcer size ($cm^2$) | 6.72±8.71 | 15.17±17.27 | |
| Final depth (mm) | 6.8±5.29 | 8.62±15.98 | |
| Final percentage of granulation tissue area (%) | 67.42±33.85 | 33.48±36.92 | |
| Mean percentage of wound area reduction (%) | 50.27±33.81 | 28.51±88.23 | 0.112 |
| Mean percentage of wound depth reduction (%) | 58.27±34.22 | 49.23±22.17 | 0.314 |
| Mean percentage of granulation tissue area increment (%) | 50.13±25.17 | 13.62±27 | 0.459 |

*Significant difference, P＜0.05

## DISCUSSION

An HA-benzyl alcohol binding method was developed in the 1990s. HA became manageable in other forms without losing its identity or function as a result of this work. A variety of wounds of different aetiologies have been treated with HA and its derivatives.[3] Human body tissues such as connective tissues, epithelial tissues, and neural tissues contain HA polysaccharides. Cell proliferation and migration are two of

HA's key functions in wound healing. HA, as a temporary structure, facilitates the diffusion of nutrients to the wound and helps eliminate waste products resulting from cellular metabolism.[4] For this reason, HA is often used to treat wounds at the beginning of their healing process. Also, HA is closely related to keratinocyte proliferation and migration, which are the cells that make up the epidermis or outermost layer of the skin.[5] As the wound matures, protein molecules (proteoglycans and collagen) replace this temporary structure. Additionally, HA is a highly osmotic macromolecule, allowing it to control hydration during wound repair and associated inflammatory processes, since it is a hygroscopic macromolecule. Proliferation and migration of cells are also affected by elevated HA during this process. It is believed that HA weakened cellular anchoring to extracellular matrix, which provided a pathway for detachment of cells and their migration and division.[6] A greater amount of protein is produced as granulation tissue matures as HA is degraded. In order to build up tissue resilience, proteins bind to HA molecules and become proteoglycans.[7] Up to 3,000 times the weight of these molecules can be absorbed by water by these molecules. Due to this, HA also has the ability to hydrate the aforementioned tissues in addition as a hydrating agent.[8-12]

In the Caravaggi 2003 trial, dorsal foot ulcers in Wagner classes I-II diabetic patients were significantly healed quicker with HA pads that contained keratinocyte seeds, compared with standard therapy.[13] HA matrixes and standard care therapy were compared with Wagner class IV diabetic foot ulcers in the Edmonds trial to determine how fast they healed. In the Abbruzzese trial, patients on HA plus standard care therapies were also compared to those on placebo plus standard care therapies, and HA showed statistically significant reductions in ulcer area size over a 2-week period.[14] It has also been proven that HA dressings maintain wound moisture better than conventional dressings, and that they are more comfortable too.[15]

In our study, diabetic foot ulcer patients treated with HA dressing did not experience faster wound healing compared with those treated with conventional dressings. Although the experimental and control groups did not show statistically significant differences, the HA dressings showed a trend towards positive healing effects. Several valuable conclusions were drawn from the current study. Diabetes-related foot ulcers may benefit from its use as an ideal dressing.

## CONCLUSION

It has been shown that diabetic wounds may heal faster with dressings made from HA. It will be necessary to study larger samples in order to determine the effectiveness of this treatment.

**Conflict of Interest:** No conflicts of interest exist between the authors

**Funding: Nil**

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