

# Comparative Effects of Hyaluronic Acid and Corticosteroid on Post-Extraction Wound Healing in Diabetic Patients

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## ABSTRACT

**Background:** Diabetic patients undergoing tooth extraction are prone to many wound complications. As hyaluronic acid has anti-inflammatory properties, it is suggested for wound care. Similarly, corticosteroid is also used to reduce pain and enhance the healing process. The study objective is to compare the efficacy of hyaluronic acid and corticosteroid to improve wound healing in diabetic patients.

**Methods:** After sample size estimation of 128 via Open Epi, a randomized clinical trial was performed on the diabetic patients from the Oral and Maxillofacial Surgery Department in Madinah Teaching Hospital, Faisalabad, from March 01, 2024, to June 30, 2024. The trial was registered at clinicaltrials.gov (Identifier NCT06637384). Patients were divided into three groups. Group 1 was subjected as a control group; Group 2 was treated with 0.2 % Hyaluronic acid, and Group 3 was treated with a single dose of Hy-Cortisone Injection at the extraction site. Wound healing was assessed through the Landry Healing Index. Statistical analysis was done via IBM SPSS Software 20. P-value less than 0.05 was considered significant.

**Results:** The results showed higher mean values of the Landry healing index score for the group treated by HA. Also, a statistically significant difference was found for the pairwise comparison between the groups (p-value = 0.001). The corticosteroid-treated group was also statistically significant on an individual basis (p-value < 0.05), but upon comparison, HA had more promising results.

**Conclusion:** This study concluded that upon comparison of the HA and corticosteroid-treated group, the HA-treated group showed the highest mean Landry healing index score (4.05) among the groups, suggesting potentially better healing outcomes associated with this treatment.

**Keywords:** Wound healing, Diabetes Mellitus, Corticosteroid, Hyaluronic acid.

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## INTRODUCTION

Diabetes Mellitus (DM) is a chronic medical ailment that has characteristic features of high blood glucose levels and abnormal fat and protein metabolism<sup>1</sup>. According to estimates from the International Diabetes Federation, 700 million people worldwide will have diabetes by 2045<sup>2</sup>. Diabetes mellitus is broadly classified into several types, primarily Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types that include monogenic diabetes<sup>3</sup>. The complications associated with the disease contribute to higher rates of morbidity and mortality<sup>4</sup>. Cellulitis and osteomyelitis are among the local complications, whereas diabetic foot, sepsis, and bacteremia are among the systemic consequences of DM<sup>5,6</sup>. Among all these, a major complication of DM

includes delayed wound healing<sup>7</sup>. DM usually causes the basement membranes of the capillaries and arterioles to thicken, which impairs wound healing<sup>8</sup>. Hyperglycemia causes the generation of advanced glycation end-products (AGEs), which disrupt collagen synthesis and cause the inflammatory molecules like TNF- $\alpha$  and IL-1 to release<sup>7,8</sup>. Another way that hyperglycemia may impact wound healing is that it is linked to alterations in keratinocyte differentiation, reduced proliferation, and alterations in cellular morphology<sup>9</sup>. Diabetic patients may also experience poor wound healing due to altered immune function<sup>10</sup>. High blood glucose levels interfere with the function of growth factors essential for new blood vessel formation, such as vascular endothelial growth factor (VEGF) as shown in figure 1.11.

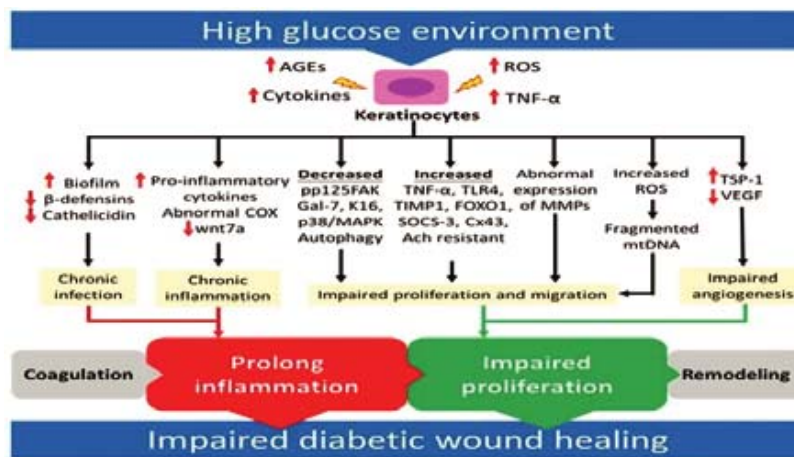


Figure 1. Scheme revealing different factors associated with dysfunctional keratinocytes in diabetic wound healing.

As an extracellular constituent of connective tissue, HA, commonly referred to as hyaluronan or hyaluronate, is a member of the family of glycosaminoglycan<sup>12</sup>. It is thought to be essential for tissue repair, wound healing, and promoting cell migration and differentiation during embryonic development<sup>13</sup>. HA's role in wound healing is multifaceted, involving modulation of inflammation, enhancement of cell proliferation and migration, and facilitation of tissue remodeling<sup>14</sup>. Similarly, the administration of corticosteroids is a strategy to reduce inflammation after extraction<sup>15</sup>. Corticosteroids exert their effects primarily by binding to glucocorticoid receptors, leading to the modulation of various inflammatory and immune responses. They play a role in tissue remodeling and degradation by reducing the activity of matrix metalloproteinase and inhibiting the production of pro-inflammatory cytokines<sup>16</sup>. These mechanisms can potentially influence the different phases of wound healing, including inflammation,

proliferation, and remodeling<sup>17</sup>.

There is a dearth of data that compares the efficacy of single-dose corticosteroid and hyaluronic acid in improving wound healing in diabetic patients after tooth extraction. The purpose of this study was to evaluate the relative effectiveness of corticosteroid and hyaluronic acid in the healing of diabetic patients' post-extraction wounds.

## METHODS

A single-blinded, randomized clinical trial was conducted in the Department of Oral and Maxillofacial Surgery, Madinah Teaching Hospital, Faisalabad, after Ethical Approval from the institution review board with reference number Tuf/IRB/293/24. The study duration was from March 01, 2024, to June 30, 2024. Data were collected from controlled diabetic patients undergoing tooth extraction in Madinah Teaching Hospital. The sample size was 128, calculated by online software

Open Epi Version 3. Two-sided significance level was 95, power level of 80, and the ratio of sample size was taken as 0.5<sup>18</sup>. The Kelsey method had been followed for total sample size estimation. Before each patient's tooth extraction, randomization and group assignment were carried out using computer software Research Randomizer. Signed informed consent from each patient was obtained. Three groups of patients were formed based on the inclusion and exclusion criteria:

Control Group 1 (n=42): The sockets untreated with hyaluronic acid and corticosteroid injection were designated as control group 1, where wound healing took place naturally via clot formation. Group 2 (n=43): Patients treated with 0.2 % Hyaluronic acid (Gengigel Gingival Gel 20ml, Ricerfarma, Milan, Italy) applied in the extraction socket. Group 3 (n=43): The extraction sockets of these patients were treated with a single dose of Hy-Cortisone Injection 250 mg (Generic name: Hydrocortisone Sodium Succinate, Cirin Pharmaceuticals, Pakistan).

The inclusion criteria of this study included controlled diabetic patients who had random blood glucose levels of 80 to 130 mg/dl, according to World Health Organization. Age was defined from 25-55, irrespective of the gender. Tooth extractions in maxilla or mandible without the presence of an acute infection or compromised periodontal state was among the inclusion criteria of the study. Contrary, the exclusion criteria included patients who declined to participate. Patients below the age of 25 and above the age of 55. Patients with

uncontrolled diabetes mellitus (blood sugar levels high than the defined range). Patients with history of adverse effects to local anesthetics or who are currently taking corticosteroids. Patients with unmaintained oral hygiene and smoking habits. Confirmation of any chronic illness, including those with hypertension or cardiac disorders. Patients who have undergone any recent major surgical procedure were also excluded from the study.

The wound healing after follow was assessed via the Landry Healing Index. This index had five grades: very poor (1), poor (2), good (3), very good (4), and excellent (5). Each grade further had five parameters that included tissue color, response to palpation, granulation tissue, incision margin, and suppuration. Daily follow-ups are ideal in some research settings (like intensive clinical trials), but in countries like Pakistan, they're often not feasible due to financial, logistical, and cultural realities. Due to resource constraints, the assessment of healing on the 6th day rather than daily monitoring is one of the limitations of this study. Future studies are recommended to ensure follow-up visits as frequent as possible.

Statistical analysis was done via IBM SPSS Software 20. One-way ANOVA test was applied for assessment of statistical significance of differences among groups. Post Hoc Tukey's test was applied for pairwise comparisons between the control and study groups. P-value less than 0.05 was considered significant

## RESULTS

Table 1: Comparison of Landry Healing Index

Parameters	Control Group (n = 42) Mean ± SD	HA-treated Group (n =43) Mean ± SD	Corticosteroid-treated group (n =43) Mean ± SD	P value
Tissue color	2.40 ± .077	4.05 ± .074	2.84 ± .081	< 0.001*
Bleeding on palpation	1.40 ± .077	2.00 ± .000	1.77 ± .065	< 0.001*
Granulation tissue	1.40 ± .077	2.00 ± .000	1.77 ± .065	< 0.001*
Incision margin	2.40 ± .077	4.05 ± .074	2.84 ± .081	< 0.001*
Suppuration	2.00 ± .077	2.00 ± .000	2.00 ± .000	< 0.001*
Cumulative Landry healing index score	2.40 ± .497	4.05 ± .486	2.84 ± .531	< 0.001*

All values are presented as mean ± standard deviation. \*P > 0.05 is considered significant

One hundred and twenty-eight patients from the Department of Oral and Maxillofacial Surgery of Madinah Teaching Hospital met the inclusion criteria and were included in the study. These patients were divided into three groups. The first was the control group in which no treatment modality was given; the second group was treated by 0.2% HA (Gengigel 20ml). The third group was administered a single dose of Hy-cortisone injection at the extraction site. Blood glucose levels of all these patients were controlled as per the inclusion criteria.

Concerning **Table 1**, the results indicated that the mean value of the Landry healing index of the group treated by HA was greater than the other groups. The group treated with corticosteroid had a mean value of 2.84, which was greater than that of the control group (2.40). The HA-treated group had a mean value of 4.05, which indicated that the healing index score for this group was better than others.

**Table 2: Comparison of Landry Healing Index by Post-Hoc Tuckey test**

Groups	Mean± SD	P-value
HA-treated Group and Corticosteroid-treated Group	1.209±.109	< 0.001*
Control group and HA-treated group	-1.642 ±.110	< 0.001*
Control group and Corticosteroid-treated group	0.432 ±.110	< 0.001*

\*P > 0.05 is considered significant

The comparisons of the five different parameters of the Landry healing index among the three groups also showed significant results. Tissue color, bleeding on palpation, granulation tissue, incision margin, and suppuration were the respective parameters. Parameter 1 and parameter 4 garnered significant effects of improved wound healing by HA. Corticosteroid-treated group, on the other hand, also had improved tissue color and the incision margin, but the mean values were lower as compared to the HA-treated group, indicating that HA has better healing outcomes.

Regarding **Table 2**, the post hoc tests applied for the multiple comparisons also showed statistically significant results. The comparison of Landry Healing Index between the HA-treated group and corticosteroid-treated group was statistically significant, as the p-value is .000, and the mean difference is significant at or less than a 0.05 level. Similarly, the comparison between the control group and the HA-treated group yielded a significant p value, and the comparison between the control group and corticosteroid-treated group also suggested a significant difference.

## DISCUSSION

The study focused on the effects of hyaluronic acid and single-dose corticosteroid injection in post-extraction wound healing of controlled diabetic patients. A total of 128 patients were included in the study who met the inclusion criteria. These patients were divided into three groups, namely the Control group, which had 42 patients, and the Hyaluronic acid-treated group and corticosteroid-treated group, which had 43 patients each.

In this study, based on the Landry healing index scores, the healing of the HA-treated group was higher than the corticosteroid-treated group. The comparison of Landry healing index among the control group, hyaluronic acid-treated group, and corticosteroid-treated group indicated a mean value of 4.05 highest for the HA-treated group, followed by 2.84 for the corticosteroid treated group, and 2.40, which was the lowest for the control group. These results may be attributed to the ability of HA to be involved in the modulation of inflammation and tissue regeneration. These properties make it particularly effective in the early

stages of wound healing, where rapid cell division and new tissue formation are critical<sup>19</sup>.

HA also promotes angiogenesis, which is vital to supply nutrients and oxygen to the healing site<sup>20</sup>. Previous studies have confirmed that HA provides beneficial effects in healing after extraction<sup>21</sup>. Hyaluronic acid gel was assessed to preserve the alveolar ridge. The results showed that the gel was effective in encouraging bone formation and lowering surgical complications<sup>22</sup>. Furthermore, studies have confirmed that HA helps to keep the surgical site moist, promoting cell viability and migration, which are essential for tissue repair<sup>23</sup>. HA also enhances both patient-reported outcomes and clinical wound healing at the graft donor site on the palate<sup>24</sup>. All these findings align with the findings of our current study in which a significant effect of HA on wound healing was observed. Evaluation of the effects of a single dose of corticosteroid in post-extraction wound healing of controlled diabetic patients was another aim of this study.

The corticosteroid group's mean value (2.84) was found to be higher than that of the control group

(2.40), suggesting that administering a single-dose injection can enhance wound healing and is preferable to providing no treatment modality at all. Corticosteroids like dexamethasone enhance healing by lowering inflammation. According to the findings of previous studies, dexamethasone can improve tissue healing and repair<sup>25</sup>. A clinical trial evaluated the preemptive use of different combinations of corticosteroids for third molar extractions. Results showed varying outcomes based on the drug combinations, with the majority of combinations providing better pain management and reduced inflammation<sup>26</sup>.

The results of the present study are in accordance with the fact that corticosteroids are effective in pain management after oral extraction. Recent research has shown that low-dose corticosteroid therapy can effectively balance inflammation without significantly impairing other phases of wound healing, such as proliferation and remodeling<sup>27</sup>. The mean values for the parameters of the Landry healing index for the corticosteroid group also showed significant fluctuations. Tissue color, bleeding on palpation, granulation tissue, incision margin, and suppuration were the respective parameters. Parameter 1 and parameter 4 garnered significant effects of improved wound healing by HA. The absence of granulation tissue also had similar outcomes as parameter 2. The subdivision of parameter 4 of the Landry healing index revealed that the majority of the patients had no connective tissue exposure, whereas only 35 patients had their incision margin epithelialized with connective tissue exposure. Parameter 5 of the Landry healing index, which is the most serious adverse effect after oral extraction, was absent in all the patients included in the study. Thus, on the basis of these results, we concluded that HA had more noteworthy effects to improve wound healing upon comparison with the corticosteroid-treated group and the steroid-treated group was better than giving no treatment modality at all.

The number of patients and a single corticosteroid injection dose are the study's primary limitations. Patients were assessed after six days instead of daily blood sugar assessments in this trial, which only included a single dose of corticosteroid medication. Participants who were too young or too old could not have their test product efficacy checked because this study only included participants within a specified age range. The results of this study need to be confirmed by larger sample sizes with uncontrolled diabetes in future research investigations. On the other hand, to rule out any adverse effects, wound healing should be evaluated by administering multiple doses of corticosteroid injections.

## CONCLUSION

This study concluded that the effect of hyaluronic acid and a single dose of corticosteroid to improve wound healing in controlled diabetic patients after oral extraction is significant. Upon comparison of the HA and corticosteroid-treated group, it was found that the HA-treated group showed the highest mean Landry healing index score (4.05) among the groups, suggesting potentially better healing outcomes associated with this treatment. The corticosteroid-treated group fell between the HA-treated group and the control group in terms of mean healing index score. The control group had the lowest mean score (2.40), indicating the least effective healing.

## LIST OF ABBREVIATIONS

**HA:** Hyaluronic Acid

**DM:** Diabetes Mellitus

## FUNDING

None

## PATIENTS' CONSENT

Informed consent was taken from the patients for the collection of data and publication of results.

## CONFLICT OF INTEREST

None

## ETHICAL APPROVAL

Ethical Approval was obtained from the institutional review board under reference number Tuf/IRB/293/24.

## AUTHORS' CONTRIBUTION

All authors contributed to the manuscript equally as per ICMJE.

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