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Effect of Hyaluronic Acid Mucoadhesives on Palatal Wound Healing and Postoperative Discomfort in Free Gingival Graft Surgery: A Clinical Trial

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ABSTRACT

Objectives: This study aimed to assess the effect of hyaluronic acid (HA) mucoadhesives with two different concentrations on palatal epithelial wound healing and postoperative discomfort following free gingival graft (FGG) surgery.

Materials and Methods: In this triple-blind, randomized, controlled clinical trial, 39 patients undergoing FGG surgery were randomly allocated to three groups (N=13). Following palatal graft harvesting, the two experimental groups received mucoadhesives containing 0.8% and 0.2% HA, while the control group received mucoadhesives without HA. In all groups, the donor site was protected with periodontal dressing. Epithelization, color match, contour, and distortion were assessed at 3, 7, 14, 21, and 42 days, postoperatively using the Landry's healing index and modified Manchester Scar Proforma (mMSP) index. Pain level and response to thermal stimuli were evaluated after 3, 7, 14, and 21 days using a visual analog scale (VAS). Data were analyzed by the Chi-square, Kruskal-Wallis, Mann-Whitney, Friedman, and Wilcoxon signed-rank tests (alpha=0.05).

Results: Significant differences were observed in the mMSP index scores among the groups at 3, 7, 14, and 42 days, favoring HA groups ($P<0.05$). The Landry's healing index score was significantly higher in 0.8% HA group on day 21 ($P=0.023$), compared to the control group. No significant differences were found in pain score or thermal stimulus responses among the groups ($P>0.05$).

Conclusion: Mucoadhesives containing HA were found to enhance palatal wound healing, leading to improved outcomes in terms of epithelization, color match, contour, and distortion reduction.

Keywords: Wound Healing; Hyaluronic Acid; Epithelium

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INTRODUCTION

Free gingival graft (FGG) surgery is a widely practiced procedure to increase the keratinized gingiva dimensions around teeth and dental implants. Typically, the palate serves as the primary donor site for harvesting a gingival graft, which then heals through secondary intention [1-3]. However, this procedure often has side effects such as bleeding, pain, burning sensation, sensitivity to thermal alterations, and delayed wound healing [4].

Over time, various approaches have been

explored to mitigate these complications, and enhance the healing process. These methods include the use of hemostatic agents, mechanical barriers, analgesics, antibacterial agents, and platelet-rich fibrin, among others. However, the search for an ideal solution remains inconclusive in the literature [4-8]. An optimal wound dressing for enhancement of the healing process should possess specific qualities, including the ability to reduce inflammation and maintain wound hydration, histocompatibility, biodegradability, absence of antigenicity, and appropriate mechanical properties [9-11].

Recent literature has highlighted the significant role of hyaluronic acid (HA) in wound healing, reducing postoperative inflammation, and alleviating the associated symptoms [1,11]. HA is a polysaccharide belonging to the glycosaminoglycan family, comprising of repeating units of glucuronic acid and N-acetyl-glucosamine [12]. This versatile molecule exists in two forms, either as an acid or a salt, collectively known as hyaluronan, and constitutes a major carbohydrate component within the extra-cellular matrix found in various tissues and body fluids [11,13,14]. It is notably abundant in all periodontal tissues, with a particular presence in non-mineralized tissues like the gingiva and periodontal ligament [1, 11]. HA possesses key attributes, such as viscoelasticity and hygroscopicity, which play a crucial role in tissue compatibility, resilience, hydrodynamics, and volume maintenance. Its multifaceted biological properties make it a promising candidate for aiding in wound healing processes. HA can induce early granulation tissue formation, inhibit detrimental inflammation during the healing phase, and promote re-epithelialization and angiogenesis. Furthermore, its hydro-philic nature creates an optimal environment for cell migration. In addition to biocompatibility, non-immunogenicity, and non-toxicity, HA also exhibits bacteriostatic, antifungal, anti-inflammatory, antioxidant, anti-edema, osteoinductive, and proangio-genic properties, all of which facilitate wound healing [10,14]. HA has applications in various clinical domains, including drug delivery, tissue engineering, and several medical specialties such as ophthalmology, dermatology, and rheumatology [1,6,10,13]. Its structural similarity to natural human body components makes it a favorable option for most patients, minimizing potential side effects. However, in rare instances, HA may lead to transient allergic reactions, including erythema, edema, itching, and mild swelling [15].

Several recent studies showed promising outcomes regarding the positive efficacy of HA in enhancing wound healing and reducing postoperative discomfort [1,10,11,16-18]. However, limited research has been conducted on the potential influence of HA on donor site healing in FGG surgery and patients' overall satisfaction.

Given the widespread application of FGG surgery in periodontology, and the significance of improving postoperative patient comfort, this study was conducted to assess the effects of HA mucoadhesives in two different concentrations on palatal epithelial wound healing and postoperative discomfort following FGG surgery.

MATERIALS AND METHODS

Ethical approval for this prospective triple-blind, randomized, controlled clinical trial was obtained from the ethics committee of the university (Approval number: IR.BABOL.REC.1400.262). The study protocol was also registered in the Iranian Registry of Clinical Trials (IRCT20100427003813N12).

Study population:

This study enrolled participants from the pool of patients requiring FGG surgery presenting to the Periodontology Department of School of Dentistry, Babol University of Medical Sciences. The prospective participants were provided with detailed information about the procedures and, upon their voluntary consent, proceeded to provide written informed consent.

Eligibility criteria:

The inclusion criteria encompassed patients aged 18 years or older who required FGG surgery and possessed adequate gingival tissue dimensions at the donor site (10-15mm

length, 5-8mm width, 1-1.5mm thickness).
The exclusion criteria were as follows: (I) presence of systemic diseases or conditions known to impact wound healing, such as uncontrolled diabetes mellitus, autoimmune diseases, or a history of alcoholism; (II) attachment loss exceeding 3 mm at the palatal gingiva of maxillary premolars and first molar; (III) current corticosteroid use; (IV) recent antibiotic use within the past month; (V) pregnancy or lactation; and (VI) active smoking.

Sample size:

The minimum sample size in each group was calculated to be 13 using the following formula, taking into account an alpha level of 0.05 (5%), a beta level of 0.20 (20%), standard deviation values of S_1=3.28 and S_2=1.24, and mean values of μ_1=3.33 and μ_2=0.58 according to similar previous studies [1,6]:

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \left[S_1^2 + S_2^2\right]}{\left(\mu_1 - \mu_2\right)^2} = 12.7 \approx 13$$

Randomization:

To achieve sample randomization, random numbers were generated via the website www.kitset.ir. The patients were then randomly allocated to either of the two intervention groups, one receiving 0.8% HA and the other 0.2% HA, or they were assigned to the control group, which did not receive HA. Allocation concealment was ensured through the use of coded mucoadhesives.

Interventions:

Preoperative phase: All patients received full-mouth supragingival and subgingival scaling and root planing, along with detailed oral hygiene instruction. The periodontal treatment, surgical procedure, and application of mucoadhesives were all carried out by the same clinician.

Surgical phase: Following local anesthetic infiltration with 2% lidocaine and 1: 80,000 epinephrine, the recipient site was meticulously prepared, ensuring adequate dimensions (10-15mm mesiodistally and 5-8mm width) supra-periosteally. Subsequently, the palatal donor site was anesthetized with 2% lidocaine and 1: 80,000 epinephrine. For FGG harvesting, the donor site was meticulously prepared, with the required dimensions extending from the mesial line angle of the second premolar to the distal finish line of the first molar. A horizontal, coronal incision, measuring 10-15mm in length with an apical distance of at least 2mm from the marginal gingiva, was carefully made. Two vertical incisions were then created at the mesial and distal sides of the initial horizontal incision. The second horizontal incision ran parallel to the first, with 5-8mm distance (measured from the central site and its edges using a probe with a stopper). Hemostasis at the donor site was achieved by applying a moist gauze with gentle pressure for 1 minute.
To prepare mucoadhesives, 95cc of distilled water was poured into a 500-cc Erlenmeyer flask. Subsequently, 0.1g of chitosan (CAS Number 9012-76-4; Sigma-Aldrich, MO, USA) was added, and the mixture was placed on a stirrer with a hot plate. Next, 5g of Carbopol was introduced, and the solution was heated to 50ºC. Next, 0.01g methyl paraben and 0.01 g propyl paraben were dissolved in 2mL of ethanol and added to the solution. Finally, 5mL of glycerin was incorporated into the sample. HA (CAS Number:9067-32-7; Sigma-Aldrich, MO, USA) was then blended into the mucoadhesive at the specified concentrations. The mucoadhesives, which contained 0.2% HA (experimental group 1), 0.8% HA (experimental group 2), or no HA (control group) were applied on the palatal donor site. Subsequently, the donor site was sutured in a bootlace style using 4-0 silk thread, and a periodontal dressing was applied to cover the area.

Postoperative care: Postoperative instructions included refraining from using a toothbrush or dental floss near the surgical site for 7 days post-surgery, adhering to a soft diet during the first week, and avoiding any actions that could cause mechanical trauma to the donor and recipient sites. Medications for all patients consisted of 500mg amoxicillin three times daily for one week, along with 400mg ibuprofen four times daily for 5 days, and rinsing 0.2% chlorhexidine mouthwash twice daily for 2 weeks. Patients with known allergies to the aforementioned medications were excluded from the study.
The patients subsequently underwent regular

examinations at 3, 7, 14, 21, and 42 days after surgery, all conducted by the same periodontist unaware of the group allocation of patients.

After 3 days, periodontal dressing was removed, and the donor site was thoroughly examined for pain, response to thermal stimuli, complete epithelialization, color match, contour, and distortion, in all patients. Subsequently, muco-adhesives with and without HA were re-applied on the donor site and covered with a new periodontal dressing.

After 7 days, the above-mentioned parameters were re-evaluated after removal of periodontal dressing and sutures. The patients were also assessed at 14, 21, and 42 days, postoperatively. The pain score and the patients' responses to thermal stimuli were quantified at 3, 7, 14, and 21 days using a visual analog scale (VAS), with score 0 indicating no pain or response to thermal stimuli, and score 10 representing severe pain or response to thermal stimuli.

To evaluate the response to thermal stimulus, saline refrigerated at 4°C was used. On examination days, 1 cc saline was poured on the wound site from approximately 1 cm distance using a syringe. Subsequently, the pain level was quantified using a VAS.

Complete epithelialization was evaluated according to the Landry's wound healing index [19,20] after 3, 7, 14, 21, and 42 days. This index includes parameters such as tissue color, bleeding, palpation response, epithelial-ization of the incision margins, and presence of suppuration and granulation tissue. Wound healing was graded on a scale of 1 to 5, with 1 indicating very poor healing, and 5 representing excellent healing.

To assess wound healing at 3, 7, 14, 21, and 42 days, the modified Manchester Scar Proforma (mMSP) was utilized [21], evaluating three parameters: Scar tissue color compared to the surrounding mucosa, categorized as a perfect match (0), slight mismatch (1), or obvious/gross mismatch (2); contour ranging from flush with the surrounding mucosa (0), slightly prominent or indented (1), to hypertrophic (2), and distortion varying from none/without distortion (0), mild to moderate distortion (1), and severe distortion (2). The mMSP scale score ranged from 0 (indicating excellent healing) to 6 (representing very poor healing).

Statistical analysis:

Statistical analyses were conducted using SPSS version 26.0 (SPSS Inc., IL, USA). Since data were not normally distributed as shown by the Shapiro-Wilk test, comparison of the mean values of the variables among the groups was performed with the Kruskal-Wallis test, while comparison of variables within each group across different time points was performed using the Friedman test. $P<0.05$ was deemed statistically significant.

RESULTS

In total, 39 patients participated in this study, consisting of 6 males and 33 females, with a mean age of 44.15±9.25 years. The participants who did not adhere to the postoperative guidelines and/or did not attend their follow-up visits regularly were excluded from the study (one patient due to long commute). Figure 1 shows the CONORT flow-diagram of the study.

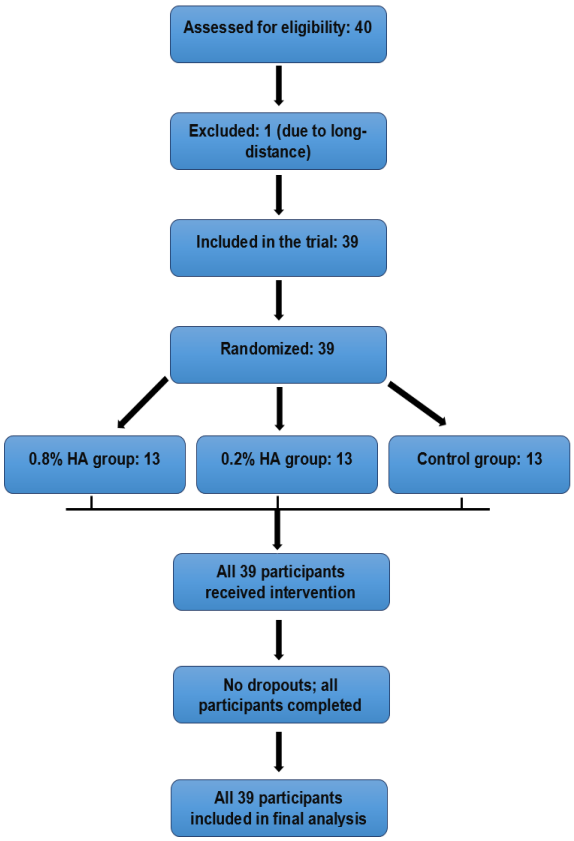

Fig 1. CONORT flow-diagram of the study

No significant differences were observed among the groups in terms of age or gender distribution (P>0.05). Additionally, there were no reported side effects associated with the use of HA.

Tables 1 to 4 provide a comparison of the measured variables across different time points in the study groups, while Figure 2 illustrates the healing process in all three groups at specific days.

Table 1. Mean and standard deviation values for the visual analog scale pain scores in the three groups at different time points

Group	Day 3	Day 7	Day 14	Day 21	P**
Without HA (N=13)	2.15±1.63	0.85±1.34	0.00±0.00	0.00±0.00	**<0.001**
0.2% HA (N=13)	2.62±1.45	1.69±1.03	0.23±0.44	0.00±0.00	**<0.001**
0.8% HA (N=13)	1.31±1.03	0.77±0.60	0.00±0.00	0.00±0.00	**<0.001**
P*	0.073	0.054	0.071	1.000	-

HA: hyaluronic acid
*Kruskal-Wallis test; **Friedman test

Table 2. Mean and standard deviation values for the visual analog scale thermal stimuli scores in the three groups at different time points

Group	Day 3	Day 7	Day 14	Day 21	P**
Without HA (N=13)	0.15±0.38	0.00±0.00	0.00±0.00	0.00±0.00	0.112
0.2% HA (N=13)	0.23±0.44	0.31±0.85	0.00±0.00	0.00±0.00	0.084
0.8% HA (N=13)	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	1.000
P*	0.209	0.128	1.000	1.000	-

HA: hyaluronic acid
*Kruskal-Wallis test; **Friedman test

Table 3. Mean and standard deviation values for the Landry's wound healing index scores in the three groups at different time points

Group	Day 3	Day 7	Day 14	Day 21	Day 42	P**
Without HA (N=13)	1.69±0.48	2.85±0.80	3.54±0.66	3.92±0.28^{D}	4.15±0.38	**<0.001**
0.2% HA (N=13)	1.77±0.44	3.23±0.73	3.62±0.51	4.08±0.28	4.31±0.48	**<0.001**
0.8% HA (N=13)	2.00±0.41	2.85±0.55	3.77±0.44	4.30±0.48^{d}	4.46±0.52	**<0.001**
P*	0.210	0.271	0.603	**0.036**	0.245	-

HA: hyaluronic acid
*Kruskal-Wallis test; **Friedman test. Different superscripted uppercase and lowercase letters in this table indicate statistically significant differences among the groups.

Table 4. Mean and standard deviation values of the modified Manchester Scar Proforma index in the three groups at different time points

Group	Day 3	Day 7	Day 14	Day 21	Day 42	P**
Without HA (N=13)	4.08±0.49^{a}	3.77±0.44^{B}	3.08±0.49^{C}	2.31±0.48	1.15±0.38	**<0.001**
0.2% HA (N=13)	4.08±0.49^{a}	3.23±0.60^{b}	2.38±0.51^{c}	2.15±0.38	0.85±0.38^{E}	**<0.001**
0.8% HA (N=13)	3.23±0.60^{A}	3.15±0.55^{b}	2.23±0.44^{c}	2.00±0.41	1.31±0.48^{e}	**<0.001**
P*	**0.001**	**0.012**	**<0.001**	0.201	**0.029**	-

HA: hyaluronic acid
*Kruskal-Wallis test; **Friedman test. Different superscripted uppercase and lowercase letters in this table indicate statistically significant differences among the groups

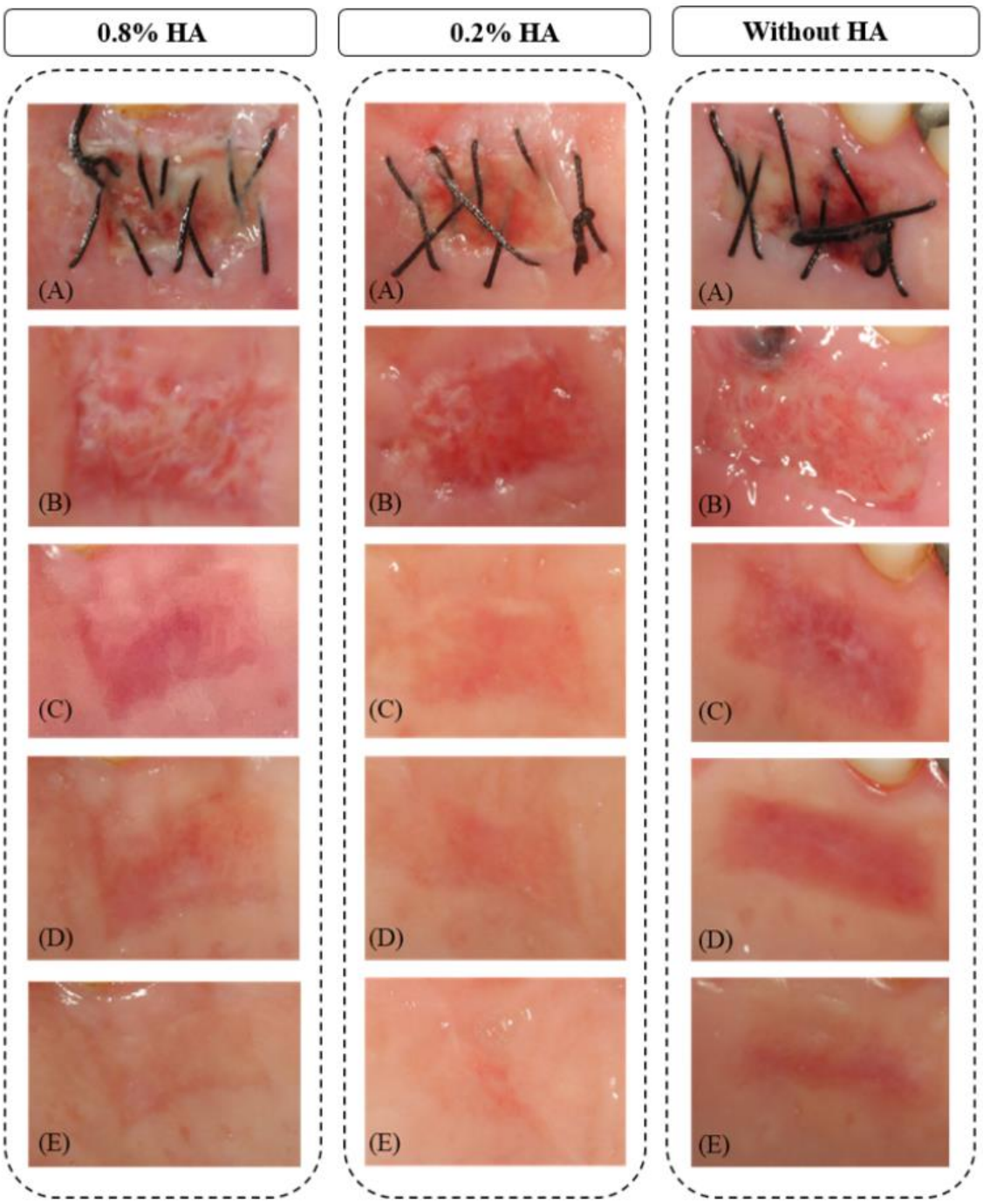

Fig. 2. Clinical palatal wound healing in 0.8% HA, 0.2% HA, and no HA groups at different time points after surgery: (A): day 3; (B): day 7; (C): day 14; (D): day 21; (E): day 42

A statistically significant descending trend in patients' pain score was observed in all three groups during the healing period ($P<0.001$), and none of the patients experienced pain after 14 days. Comparison of the pain scores among the specified postoperative days revealed a statistically significant difference ($P<0.05$), except for the 3 to 7 day period in 0.8% HA group ($P>0.05$), where the reduction in pain score was lower than that in other groups.

This study did not find a statistically significant difference in pain or patient

response to thermal stimuli among the three groups (P>0.05).

Changes in the Landry's wound healing index score over time within all three groups were statistically significant (P<0.001), showing an improvement over time. Comparison of the Landry's wound healing index score among all three groups during the healing period revealed a statistically significant difference (P<0.05), except for intragroup comparisons during the 7 to 14 day period in 0.2% HA group, and 21 to 42 day period in all three groups, where significant differences were not observed (P>0.05).

The Landry's healing index score exhibited a statistically significant difference between 0.8% HA group and the control group at 21 days (P=0.023) with a 95% confidence interval of 0.03-0.74 favoring 0.8% HA group. However, no significant differences were found in this index at the remaining time points (P>0.05).

The mMSP index, assessing color match, contour, and distortion during the healing phase experienced a significant change (P<0.001) and improved over time in all three groups except between 14 and 21 days in 0.2% HA group (P=0.083), and 3 and 7 days (P=0.317), and 14 and 21 days (P = 0.083) in 0.8% HA group, where the differences were not significant (P>0.05).

The mMSP index, assessing color match, contour, and distortion during the healing phase was significantly different among the three groups (P<0.05). Comparison of color match, contour, and distortion at 3, 7, 14, and 42 days among different groups yielded statistically significant differences (P<0.05). Intergroup comparison of the mMSP index on day 3 showed statistically significant differences between the control group and 0.8% HA group (P=0.001) with a 95% confidence interval of 0.32-1.37, and between the two experimental groups (P=0.001) with a 95% confidence interval of 1.37-0.32, both in favor of 0.8% HA group. At 7 days, statistically significant differences were observed in intergroup comparison between the control group and 0.8% HA group (P=0.006) with a 95% confidence interval of 1.14-0.09, and between the control group and 0.2% HA group (P=0.018) with a 95% confidence interval of 0.01-1.07, favoring the experimental groups over the control group.

On day 14, intergroup comparison of the mMSP index revealed significant differences between the control group and 0.8% HA group (P<0.001) with a 95% confidence interval of 0.37-1.32, and between the control group and 0.2% HA group (P=0.003) with a 95% confidence interval of 1.17 - 0.22, both in favor of the experimental groups. Additionally, on day 42, intergroup comparison of the mMSP index revealed a significant difference between the experimental groups (P=0.015) with a 95% confidence interval of 0.05-0.87, favoring 0.2% HA group.

DISCUSSION

FGG surgery is a frequently employed technique for augmentation of keratinized tissue surrounding teeth and dental implants. The natural healing process of the FGG donor site, primarily through secondary intention, often takes too long, causing discomfort for patients. Thus, it is pivotal to increase patient comfort. Numerous studies have been carried out to explore methods for protection and coverage of FGG donor site with various materials, including periodontal dressings, gelatin sponges, stents, platelet-rich fibrin, and other materials [4, 5, 22, 23].

HA plays a pivotal role in the wound healing process, coordinating various cellular activities essential for tissue healing. In the initial stages of healing, HA facilitates the migration and adhesion of polymorphonuclear leukocytes and macrophages to the inflamed site, aiding in phagocytosis of the invading microorganisms. Concurrently, it promotes cell proliferation and migration into the granulation tissue matrix, thereby contributing to the organization of the granulation tissue. The regulation of the inflammatory response is crucial at different stages of wound healing. HA dynamically modulates this process, initially promoting inflammation to trigger healing cascades while later dampening it to facilitate proliferation and wound closure. By modulating the inflammatory phase at an appropriate time, HA

provides a conducive environment for cell proliferation and eventual wound closure. After the resolution of inflammation, fibroblasts and myofibroblasts emerge as central players of the remodeling phase. Fibroblast migration, guided by an upsurge in cytokine levels, initiates the formation of a framework crucial for extracellular matrix deposition, including collagen. HA has a pivotal role in this process as well, expediting the wound-healing cascade and aiding in the formation of a structural framework. Thus, HA emerges as a key regulator throughout the dynamic process of wound healing, orchestrating cellular activities essential for tissue repair and regeneration. Additionally, research suggests that HA incorporation may improve soft tissue texture, enhancing its therapeutic efficacy [7, 24, 25].

The widespread utilization of HA in various wound dressings, from films to gauze pads and sponges, stems from its versatile properties. These dressings provide numerous benefits, such as maintaining a moist wound environment, stimulating granulation tissue formation, and aiding epithelialization. Film-type drug delivery in oral healthcare has gained popularity due to its ease of application, precise targeting, and adhesiveness, rendering them well-suited for clinical use in the oral environment. Thus, HA mucoadhesives were used in the present study as a viable option to promote oral wound healing [7, 24, 25].

In the present triple-blind randomized controlled clinical trial, the authors aimed to evaluate how two different concentrations of mucoadhesives containing HA influence the healing process at the donor site and alleviate postoperative discomfort of patients following FGG surgery. To achieve this, the authors assessed the efficacy of HA for pain relief, patient's sensitivity to thermal stimuli, appearance of the donor site (including color match, contour, and distortion), and complete epithelialization. These assessments were conducted at 3, 7, 14, 21, and 42 days after FGG surgery.

Analysis of the mMSP index revealed that at 3, 7, and 14 days, 0.8% HA group displayed superior outcomes in terms of color match, contour, and distortion compared to both 0.2% HA and control groups. Furthermore, on day 14, 0.2% HA group demonstrated better results than the control group. These findings underscore the optimal efficacy of HA in expediting the healing process, resulting in improved outcomes concerning color match, contour, and distortion. Additionally, when comparing the mMSP index between the two different concentrations of HA and the control group, it was found that higher concentrations of HA might have a more favorable effect on accelerating the wound healing process. Yildirim et al. [1] noted a noticeable advantage in favor of HA-containing groups concerning color match, a finding that aligns with the outcomes of the current study.

Complete epithelialization, as a crucial phase in secondary intention healing, serves as a valuable metric for assessing the impact of an experimental approach or substance on the wound healing process [26]. To date, numerous techniques have been developed for assessing wound healing in oral soft tissues. One of the initial indices in this regard is the healing index devised by Landry [19] in 1988. This index assesses various factors, including tissue color, presence of granulation tissue, wound appearance, and notably, the characteristics of wound margins. In the current study, we employed the Landry's healing index to evaluate the extent of wound healing and complete epithelization through direct observation and examination. The dimensions and thickness of the remaining soft tissue on the palatal bone following gingival graft harvesting are linked to the duration of the healing process [27]. Consequently, great care was taken during graft harvesting to minimize variations in dimensions among patients, ensuring the reliability of the results. Regarding the Landry's index, a statistically significant difference favoring 0.8% HA group was found compared to the control group after 21 days. Additionally, higher concentration of HA exhibited superior outcomes on 3, 14, 2, and 42 days when compared to the control group. This finding underscores the constructive influence of HA on expediting the wound

healing process and promoting re-epithelialization. In the study by Yildirim et al, [1] complete epithelialization was observed in all participants of the experimental group (HA gel) at 21 days, while it was only evident in a limited number of patients in the control group. These findings are consistent with the results obtained in the present study.

Based on previous research highlighting the favorable impact of HA on expediting the healing process [6, 7, 9, 23, 27], the outcomes of the present study align with the concept of HA's role in acceleration of wound healing. Furthermore, the subtle alterations observed in the wounds provide further affirmation of the HA's positive effects on promoting epithelialization, achieving good color and contour matching, and diminishing distortion at the donor site. Yildirim et al. [1] documented superior complete epithelialization results with 0.2% HA gel at 14 days compared to 0.8% HA gel, which parallels the present findings since the Landry's index was higher in using 0.2% HA mucoadhesive compared to 0.8%. Consequently, there exists a demand for additional research to explore the potentially enhanced efficacy of higher concentrations of HA.

In the current investigation, pain reduction in patients during the healing phase was significant in all groups. However, when comparing the groups, the differences in pain did not reach statistical significance. Nevertheless, it is worth noting that in 0.8% HA group, no statistically significant difference in pain reduction was noted between 3 and 7 days. This slight discrepancy may stem from the relatively lower pain levels reported by patients in 0.8% HA group, suggesting the potential benefit of HA in alleviating discomfort. Conversely, the present results indicated that the control group exhibited inferior pain scores compared to 0.2% HA group but superior pain levels compared to 0.8% HA group. This seemingly contradictory finding warrants further exploration.

Interestingly, the literature presents conflicting findings regarding the impact of HA on pain reduction. While some studies reported significant pain reduction with HA application [8, 23], others failed to establish statistically significant differences [14, 28]. Yildirim et al. [1] reported that at 3 and 7 days, 0.2% and 0.8% HA led to significantly lower pain compared to the control group. It is noteworthy that Yildirim et al, [1] primarily assessed pain as their main outcome, and patients did not use any pain-reducing medication, which could amplify the potential influence of HA on pain score and might have led to a noticeable change in VAS pain scores, resulting in statistical significance. In the present study, the authors adhered to the ethical research protocols and prioritized patient comfort and anxiety reduction. Therefore, pain-reducing medications were prescribed, potentially masking any potential effects of HA on patients' pain score. Additionally, considering the self-reported nature of pain assessment and individual variations in pain perception and thresholds, absence of statistically significant results in the present study can be justified.

In conclusion, while the present findings suggested a trend towards pain reduction with HA, conflicting results in comparison to previous studies highlight the need for further research with larger sample sizes and standardized methodologies to better understand the precise effects of HA on postoperative pain.

Patients' sensitivity to thermal stimuli decreased as they healed, disappearing by day 14 in all groups. When comparing this parameter, there was no statistically significant difference among the three groups. However, at 3 days, 0.8% HA group exhibited a slightly lower response compared to other groups, hinting at the potential influence of HA on reducing the patients' thermal sensitivity. This aligns with the findings of Yildirim et al, [1] where burning sensation at the donor site was diminished by HA gel on day 3 and disappeared by day 14. This consistency with the present results suggests that HA application may offer benefits through its biological effects on speeding up wound healing, and providing a physical barrier that alleviates pain, burning sensation, and thermal sensitivity [29].

The present results regarding complete

epithelization, color match, contour, and distortion at the donor site support earlier conjectures about the positive impact of HA. This includes promoting primary granulation tissue formation, possessing anti-inflammatory properties, and exhibiting angiogenic potential. Additionally, HA-containing mucoadhesives aid in maintaining hydration and lubrication, and potentially serve as structural scaffolds during the wound healing process [30].

It is important to consider the trauma associated with removing and reapplying the periodontal dressing on day 3 and its potential impact on wound healing. Several factors can help justify this approach: First, direct evaluation and observation of the donor site wound were essential because the study's focus was on investigating HA's effects on wound healing, which is consistent with similar previous studies [1, 31, 32]. Second, the palatal dressing material tends to loosen during the initial days post-surgery, which is almost common. To maximize the potential benefits of the periodontal dressing in protecting the wound from mechanical trauma and to ensure consistent HA concentration, changing the dressing material at the donor site was a wise decision. Furthermore, since the periodontal dressing was applied uniformly in all groups, all patients experienced the same level of trauma, ensuring that this factor did not compromise the study results.

While the current study primarily focused on assessing clinical parameters, a multidisciplinary approach could offer valuable insights into changes in wound dimensions (depth or length) and provide a more comprehensive understanding of regional angiogenesis, cellular properties, and activity during the healing process. Incorporating biochemical, histological, and mathematical parameters into the research design could establish standardized and reproducible models. This, in turn, could enhance our understanding of wound healing and contribute to advancements in medical technologies aimed at improving patient comfort. These considerations should be taken into account in future studies [33]. Future research should explore HA's potential in pain reduction and assess the efficacy of higher HA concentrations in wound healing to establish a more precise and quantifiable relationship.

CONCLUSION

Application of mucoadhesives containing HA may offer several advantages, including expediting complete epithelialization at the donor site, ensuring favorable color and contour alignment, minimizing potential distortion during the healing phase, and serving as a promising wound dressing material.

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CONFLICT OF INTEREST STATEMENT

None declared.

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