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Effect of 0.8% High Molecular Weight Hyaluronic Acid on Soft Tissue Healing Following Third Molar Extraction

A Randomized Clinical Trial

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Abstract

To determine the clinical efficacy of intra-socket delivery of 0.8% HMW-hyaluronic acid in accelerating the early stages of mucosal healing after surgically extracting impacted mandibular third molars was the focus of the current study. In this double-blinded randomized clinical trial (RCT), 50 patients with impacted mandibular third molars (Pell & Gregory I-II, A-B) were assigned equally into two groups. The experimental group received 0.8% HA gel (Gengigel forte ™) via a collagen-based sponge, while the control group received a collagen-sponge only. Soft tissue healing was assessed on the seventh postoperative day using the early healing system index (EHS). The HA group yielded an overall median EHS of 7.00 (3.00 - 10.00) compared to 6.00 (2.00-10.00) in the control group. The Wilcoxon rank-sum test indicated no statistically significant difference between groups (P=0.214). Although statistical significance was not achieved, data suggested a clinical advantage of 0.8% HA in optimizing tissue healing scores. Future studies with larger sample sizes and multiple applications are recommended to verify these findings.

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Introduction

A considerable amount of intentional trauma to the hard and soft tissues is required during the routine surgical intervention of extracting impacted mandibular third molars. Complete surgical care goes beyond tooth extraction and requires optimal biological conditions for the regeneration of tissues to reduce the possibility of localized alveolar osteitis, impaired wound closure, and other secondary infections. Hyaluronan, or its salt form sodium hyaluronate (HA), is a glycosaminoglycan of considerable molecular weight, characterized by its structure of repeating disaccharide units [1]. Hyaluronic acid is an essential supporting structure of the extracellular matrix (ECM) that provides the physical support to the cells within the ECM, gives the tissue its shape and function, and is naturally prevalent within the connective, epithelial, and nerve tissues [2]. being able for HA to induce the growth of granulation tissue, modulate inflammation, and hasten angiogenesis and re-epithelization has attracted attention for the treatment of wounds [3,4].

The biological activities of hyaluronic acid and its subsequent therapeutic applications are significantly influenced by its molecular weight. Extracellular HMW HA acts as an anti-angiogenic mediator and regulates the inflammatory responses, restores the damaged tissue, and accelerates the closure of wounds. Under some clinical and environmental conditions, HMW HA can break into smaller pieces, LMW HA, which has a contrary effect. This may potentially promote remodeling of the ECM and the growth of tumors by inducing pro-inflammatory and pro-angiogenic pathways [5]. Considering the potential of exogenous HA as a treatment to optimize the healing phases, the purpose of this prospective, randomized, controlled clinical study was to assess the influence of applying 0.8% high molecular weight hyaluronic acid intra-socket on soft tissue healing after surgically extracting impacted lower 3rd molars.

Material and Methods

Study design and participants

At the department of Oral Surgery/college of dentistry, this prospective randomized clinical investigation carried out from January to July of 2025.A sum of 79 patients were assessed for eligibility in the study at the oral surgery

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department. 16 patients were excluded prior to randomization, consisting of ten individuals who fell outside the inclusion criteria, two declined to participate, and four were rejected due to other reasons. Random assignment of the available 63 patients yielded (30 subjects) in control and (33 subjects) in study groups, and both groups received their designated treatment. Postoperative dropouts accounted for 13 individuals who either missed their recall appointment or failed to adhere to postoperative instructions (control group n=5; HA group n=8). therefore, a final sample size of 50 participants (n=25 per group) successfully completed the trial protocol and were included in the definitive statistical analysis. The CONSORT flow diagram (Figure 1) offers a comprehensive depiction of this stage. This was a two-arm, parallel-group, randomized controlled trial with a 1:1 allocation ratio, designed as superiority trial to determine whether 0.8% of high molecular weight HA gel produces superior soft tissue healing outcomes compared to the control group. No changes were made to the trial protocol or outcome measures after the trial started. Patients and the public were not involved in the design, conduct, or reporting of this study. All surgical procedures were performed by a single operator. As this was a single-site study, there were no separate site eligibility criteria existed. The operator (corresponding author) was a qualified oral and maxillofacial student; no additional eligibility criteria applied to the operator. the study finished at the scheduled time after completion of the period of recruitment and follow-up; the trial was neither discontinued early nor were interim stopping rules applied.

Inclusion criteria were impacted 3rd molar teeth classified as Pell & Gregory class 1 or 2 (Depth) and position A or B (ramus relationship); patients were available for follow-up; and no active systemic conditions impeding healing (e.g uncontrolled diabetes). Exclusion criteria included systemic health issues (bleeding disorders, recent MI, immunosuppression), pregnancy or use of oral contraceptives, severe periodontal disease, pericoronitis, smoking and poor oral hygiene. the flow of participants through the trial is shown in (Figure 1).

Sample size calculation and randomization

Sample size was calculated by G*Power software (v3.0.10) based on 85% power and a significance level (α) of 0.05, using previously published trismus data of Kokash et al. [6], who found statistically significant differences of maximum. Mouth opening at day 7 between the hyaluronic acid (19.22 ± 12.8 mm) group and the control group (32.45 ± 15.3 mm), resulting in Cohen's D=0.938. the minimum required samples according to these calculations was 44. Thus, the 50 cases enrolled in the present study (25 per group) were considered sufficient to achieve the desired statistical power. For sample allocation, Simple randomization was carried out by the researcher using a random number generator (graphpad) among eligible patients only after preoperative eligibility screening, which included Pernambuco index assessment and the omission of high difficulty cases. Since the eligibility requirements themselves reached homogeneity, no stratification by surgical difficulty was used during allocation. The assignments were put into opaque, sealed envelopes. For each eligible participant who provided informed consent, an independent assistant drew one envelope, and was opened before the intervention was performed, thus concealing the allocation until the moment of assignment. This trial was double-blinded where Participants were informed about the different type of treatment but remained blinded to the assignment. Furthermore, the operating surgeon performed the extraction, but the assistant handled the allocation envelope and applied the specific material (HA-enriched sponge or dry sponge) into the socket. The operating surgeon wasn't notified to come back for suturing the wound until the entire material had been saturated with blood-this helped disguise the true material. The intervention and comparator were delivered as intended for all the 50 participants.

Surgical procedure and intervention

Pre-operative radiographs (OPG or CBCT) were taken to assess the difficulties and proximity to the inferior alveolar nerve. To minimize inter-operator variability and standardize the surgical technique, all extractions were executed by the same oral surgeon. Under local anesthesia, a full thickness mucoperiosteal flap was raised. Bone removal and tooth sectioning were performed as required under saline irrigation. Following extraction, sockets were irrigated with saline. The HA-enriched gelatin sponge was then gently inserted into the socket by an independent operator assistant; in the control group, the process was restricted to the placement of a gelatin sponge. To maintain double blinding, the surgeon was only called back for suturing once the material was completely soaked with blood. The intra-socket administration of HA gel is shown in this (Figure 2). In both groups, the same collagen sponge was used as the base carrier; in the experimental group, the sponge was saturated with approximately 1 ml of 0.8% HMW-HA gel prior to insertion.

Group A (Experimental) had a collagen sponge impregnated with 0.8% of HMW-HA gel (Gengigel forte ™, Ricer pharma, Italy) was used to fill the socket (Figure 3).

The socket in Group B (Control) was given a collagen sponge without any medication.

Post-operative management

Amoxicillin-Clavulanate (three times a day for five days), Paracetamol (500mg, tab) was the primary analgesic, while ibuprofen (200mg, tab) was provided as a rescue analgesic. Patients were advised on standard post-post-operative care.

Outcome assessment

In the registered clinical trial, study outcomes included pain, swelling, and trismus that were designated as primary endpoints, while soft tissue wound healing was assessed as a secondary endpoint, to maintain a focused narrative, these postoperative sequelae outcomes will be presented in a separate, later publication. Soft tissue recovery was evaluated using the early healing system (EHS) index on the seventh post-operative day [7]. The (EHS) evaluates three clinical parameters: clinical signs of re-epithelization (CSR), clinical signs of hemostasis (CSH), clinical signs of inflammation (CSI). the overall score of this index ranges between 0 (worst healing) to 10 (ideal healing).

Harms and adverse events assessment

Alveolar osteitis, sever bleeding, and localized infection are examples of the expected outcomes that were predetermined before the begin of trial. At postoperative days 1, 3, and 7, harms were methodically assessed using open-ended patient questions and standardized clinical assessments by the clinician. The case report form contained documentation for every unfavorable incident encountered during the study. No formal statistical comparison was performed for harms because the low event count precluded meaningful testing.

Statistical analysis

SPSS version 21 was used to analyze the data. The Shapiro-Wilk test was used to determined. As the (EHS) represents ordinal non-parametric data, healing scores between groups were compared between groups using the Mann-Whitney U test. The distribution of scores was summed up using descriptive statistics. Statistical significance was defined as a P-value of less than 0.05. No subgroup or sensitivity analyses were pre-specified or conducted for this trial. No interim analyses were planned or conducted. A per-protocol analysis was performed, including only those participants who attended the 7-day follow-up visit. No data were missing for the final 50 subjects who were entered in the final analysis; the 13 participants who were lost to follow-up were removed prior to this process, as described above.

Ethical considerations

Approval for this study's protocol was granted by the Research Ethics Committee of the University of Baghdad. Informed consent to participate in this research was formally obtained and signed by each patient before their inclusion in the study. This study was registered

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with the Thai clinical trials registry (TCTR, www.thaiclinicaltrials.org), Registration ID number: TCTR20260110003; Date of registration: January 10, 2026. registration occurred retrospectively after the start of patient enrollment. The trial protocol and statistical analysis plan are available from the corresponding author on reasonable request. individual participant data supporting this study are available from the corresponding author on reasonable request.

Results

Fifty patients completed the study were divided equally between the HA and control group. Age and gender showed no significant differences between groups according to demographic analysis (Table 1).

Surgical difficulty and duration

The Pernambuco index [8] was used to gauge the surgical complexity prior to surgery and the technique employed during surgery (e.g osteotomy, tooth sectioning) was used to assess the intra-operative difficulty.

With respect to duration of surgery, it was rated as 1 (short; if less than 15 minutes), 2 (normal; if 15-30 minutes), or 3 (long; over 30 minutes). pre-operative difficulty, intra-operative method, and operation length didn't differ significantly between the groups, according to statistical analysis (Table 2), suggesting that these variables did not influence the outcomes.

Soft tissue healing outcome

The HA group demonstrated a mean EHS of 6.24 (Median 7.00), which was descriptively higher than the control group's mean of 5.52 (median 6.00). Nevertheless, this difference was not statistically significant (P=0.214) according to Mann-Whitney U-test (Table 3). According to (Table 4) of EHS score distribution, the most common score was 7, which was found in 48% of the HA group and 28% of the control group.

Postoperative complication

Alveolar osteitis (dry socket) was tracked as the main sign of poor surgical healing in a total of three patients: two individuals within the control group of the study complained of it (Figure 4). In contrast, this complication was encountered in one individual in the HA group. It is noteworthy that the cause of this complication in the HA group participant was identified because of sutures falling out early, leading to the subsequent disruption of the protective blood clot, rather than a failure of the therapeutic agent. No subgroup, sensitivity, or other ancillary analysis beyond the primary between-group comparison were performed.

Discussion

This study utilized the early healing system (EHS) index due to its high reliability both within and between examiners, and its capacity to assess primary healing parameters on its own [7]. According to study findings, the HA group showed higher mean score of (6.24) when compared to control group (5.52), but the difference was not statistically significant. In contrast, several earlier research [9-12] found that using HA significantly improved soft tissue recovery. But it's consistent with other research [13] that revealed no difference.

Limitations of the study

Several factors may explain this lack of statistical significance: first, it's possible that the sample size was insufficient to detect a clinically meaningful effect. Second, the topical presence of high- concentration HA gel might prolong bleeding time by inhibiting platelet aggregation [14], potentially affecting the early homoeostasis scores (CSH) within the EHS. Third, the half-life of HA in the oral environment ranges from 12 hours to 3 days, due to rapid degradation by hyaluronidases and reactive-oxygen species [1,15], since re-epithelization peaks between days 3 and 7, the therapeutic effect of single intra-socket application may have diminished, before the proliferative phase was fully established.

Conclusion

When compared to the control group, intra-socket treatment of 0.8% HMW-HA did not result in a statistically significant improvement in soft tissue repair.

A possible clinical advantage is shown by descriptive data, which shows that the HA group had higher EHS ratings and fewer occurrences of alveolar osteitis.

By day seven, a single application of 0.8% HMW-HA gel doesn't seem to be enough to greatly change the extraction socket healing progress.

Recommendations

1. Conducting a study to evaluate the impact of hyaluronic acid on socket bone healing using CBCT, a larger sample size, and a longer follow-up time.
2. Examine the effects of hyaluronic acid with multiple applications instead of single use, to prolong the therapeutic efficacy.
3. Using the split-mouth study design to reduce the number of variables, individuals with bilateral impactions who require surgery can have the therapeutic effects of hyaluronic acid investigated.

Author Contributions

Concept and design: Dr. Yassir Ryadh Al-Khannaq, Data collection and curation: Dr. Safaa Mohammed Assim, Statistical analysis: Dr. Mohammed Galib, Drafting the manuscript: Dr. Safaa Mohammed Assim, Critical revision of the manuscript: Dr. Yassir Ryadh Al-Khannaq, Final approval of the version to be published: All authors.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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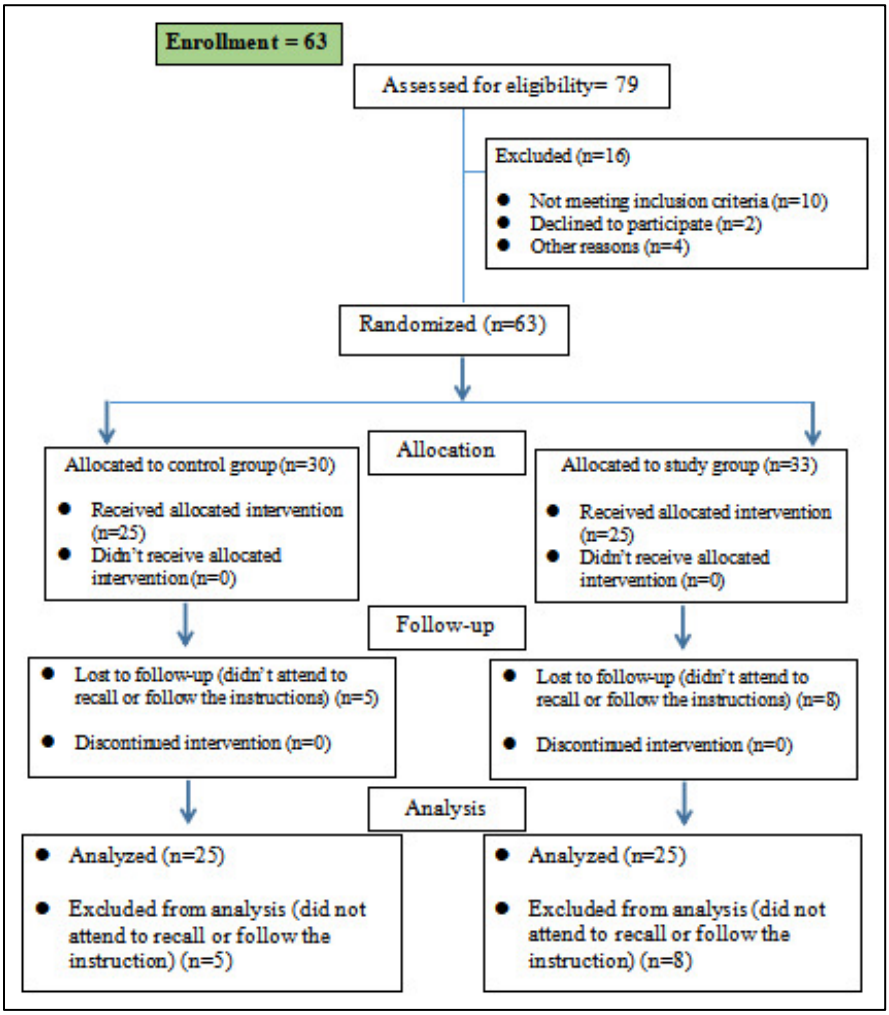

Figure 1. Flow chart diagram of the study.

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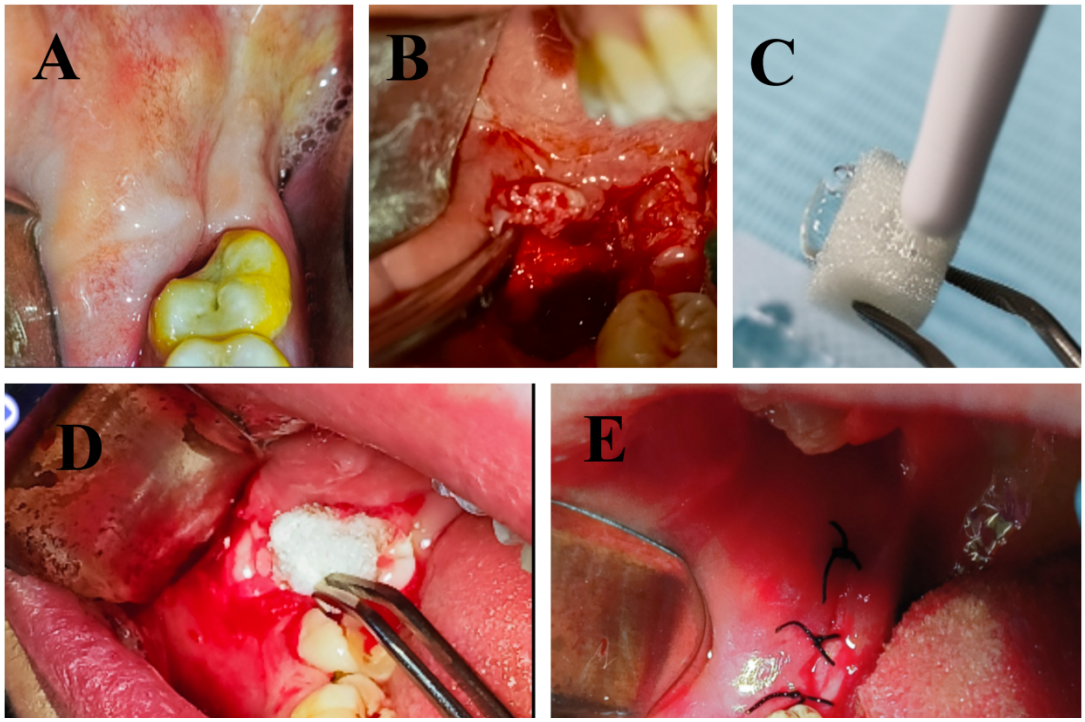

Figure 2. Clinical photograph showing intra-socket application of the study material (H.A): (A) Pre-operative intra-oral view. (B) Empty socket after flap reflection and tooth removal. (C) Applying hyaluronic acid gel 0.8% via a white applicator tip to collagen sponge held with tweezers to avoid washout and ease with delivery of material. (D) clinical photo showing collagen sponge impregnated with H.A gel inside socket. **(E)** Wound closure with 3/0 black silk suture, interrupted suture technique.

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Figure 3. Hyaluronic acid (0.8%) oral gel and gelatin (hemostatic) sponge.

Table 1. Distribution of subjects by age and gender among groups.

		Control		Study		Pearson's chi square	Total	
		N	%	N	%		N	%
Age (years)	<25y	17	68	19	76	0.529	36	72
	>=25y	8	32	6	24		14	28
Gender	Males	10	40	6	24	0.229	16	32
	Females	15	60	19	76		34	68

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Table 2. Distribution of subjects by pre-operative difficulty, intra-operative surgical difficulty, and surgical duration.

		Control		Study		Statistics	Total	
		N	%	N	%		N	%
Pre-operative difficulty	Low	14	56	15	60	0.774	29	58
	Moderate	11	44	10	40		21	42
Surgical technique	Low	5	20	5	20	0.922	10	20
	Moderate	17	68	16	64		33	66
	High	3	12	4	16		7	14
Surgical duration	Low	3	12	3	12	1.0	6	12
	Moderate	10	40	12	48		22	44
	High	12	48	10	40		22	44

Table 3. Descriptive and statistical tests of the Early Healing Score (EHS) index among groups.

	Groups		Wilcoxon statistics	P-value
	Control	Study		
Minimum	2	3	1.243	0.214
Maximum	10	10		
Mean	5.52	6.24		
Median	6	7		
Mean rank	23.02	27.98		

Table 4. Frequency distribution of Early Healing Scores among groups.

		Control		Study		Total	
		N	%	N	%	N	%
Scores	2	3	12	0	0	3	6
	3	3	12	4	16	7	14
	4	3	12	2	8	5	10
	5	1	4	1	4	2	4
	6	5	20	3	12	8	16
	7	7	28	12	48	19	38
	8	1	4	0	0	1	2
	9	1	4	1	4	2	4
	10	1	4	2	8	3	6