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Clinical Evaluation of the Impact of 0.2% Chlorhexidine and 1% Hyaluronic Acid Gel on Pain and Post-Extraction Tooth Socket Healing

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ABSTRACT

Background: Pain and delayed socket healing still represent common problems in the field of dental tooth extraction. Antiseptic/ regenerative agents used topically have been suggested to lead better clinical outcomes.

Objective: The present study aimed to evaluate the clinical effect of 0.2% chlorhexidine mixed with 1% hyaluronic acid gel on pain control and socket healing following mandibular molar extraction.

Methods: A randomized controlled trial was performed among 50 medically healthy patients scheduled for unilateral extraction of mandibular molar. Patients were randomly assigned to a test group (n=20) twice daily application of 0.2% chlorhexidine with 1% hyaluronic acid gel (Perio-kin) for 7 days, or a control group (n=30) receiving no topical intervention. Outcomes included pain scores (VAS) at day 1 and day 7; wound healing measured by Landry's Healing Index at day 7; buccolingual socket width decrease between day 1 and day 7.

Results: The test group showed a significantly greater healing index (4.35 ± 0.55 vs. 3.80 ± 0.60, p = 0.02) and socket width reduction (2.30 ± 0.40 mm vs. 0.90 ± 0.25 mm, p < 0.001). Repeated measures ANOVA showed a significant main effect of group on pain scores (p value = 0.019). At day 7, the analgesic effect was most prominent (p value = 0.003, Cohen's d = –0.612).

Conclusion: Topical application of 0.2% chlorhexidine with 1% hyaluronic acid gel significantly affects on socket healing, and decreases postoperative pain after mandibular molar extraction, with its earlier analgesic effect at the end of 72 hours post-surgery.

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INTRODUCTION

Tooth extraction is one of the most common procedures performed in oral and maxillofacial surgery and is indicated for many reasons including severe caries, periodontal disease, orthodontic treatment and impacted third molars. While this procedure is routinely performed, postoperative complications remain a major clinical challenge impacting patient recovery and quality of life. Among these complications, it is known that alveolar osteitis (dry socket) is one of the most common and odious consequences, which consists in breakdown of the initial blood clot into the extraction socket, exposed bone with intense pain and delayed healing (Kolokythas et al., 2010). According to the literature, the incidence of alveolar osteitis particularly varies based on site; rates after mandibular third molar extractions range from 10% to as high as around 30% (Blum, 2002)

Beginning with the integrity of the blood clot at an extraction site, where bacteria may contaminate and ultimately lead to fibrinolysis; this is followed by a disuse of wound healing mechanisms that adds to post-extraction complications, making its pathophysiology multifactorial. As a result, new approaches have shifted studies toward effective and practical prevention strategies for integration into clinical practice. Of all pharmacological agents studied, chlorhexidine (CHX) may be considered a gold standard antiseptic agent during dental practice because of its broad antimicrobial activity and substantivity in oral tissues (Mínguez-Serra et

al., 2009). There is strong evidence that chlorhexidine reduces postoperative complications therefor, chlorhexidine's incorporation in formulations such as bioadhesive gels to prolong retention time at the extraction site resulting in controlled release of the active ingredients. Meta-analysis by Zhou et al. Intra-alveolar application of 0.2% chlorhexidine gel significantly reduces the incidence of alveolar osteitis following mandibular third molar surgery (2017), validating CHX as a reproducible prophylactic option.

Hyaluronic acid (HA), on the other hand, has attracted much more interest in current research of healing oral wounds. Hyaluronic acid is a naturally occurring glycosaminoglycan that is an essential component of the extracellular matrix, which plays vital roles in tissue repair such as cell migration, proliferation, angiogenesis and collagen deposition (Zhao et al., 2016). PHEMA has biocompatibility, biodegradability, and anti-inflammatory characteristics which make it a good candidate for improving socket healing after tooth extraction. Clinical studies showed that external application of 1% hyaluronic acid gel could speed up soft tissue healing and diminish postoperative discomfort after tooth extraction (Alcântara et al, 2018). In addition, recent studies indicate HA may facilitate bone formation in extraction sockets that can benefit later placement of implants.

Post-extraction healing following the application of chlorhexidine or hyaluronic acid and is a clinically relevant question that is finally receiving research attention. Muñoz-Cámara et al. (2021) in a double-blind randomized controlled trial involving 90 patients, compared intra-alveolar application of 0.2% chlorhexidine and hyaluronic acid bioadhesive gels (1%) after mandibular impacted third molar extraction. They also concluded that agents reduced postoperative morbidity, while CHX alone was found to significantly reduce pain levels at 48 and 72 hours. But, the authors stated that pain scores were consistently lower by clinically significant amounts in the HA group compared to controls for both interventions. Another recent comparative study conducted Almushalbn et al. (2022) Recent investigation of these agents following atraumatic premolar extractions for orthodontic treatment found that hyaluronic acid with a gelatin sponge carrier resulted in significant protection against dry socket formation, while chlorhexidine failed to show statistically significant benefits in this clinical setting.

Future studies are required to determine optimal application protocols, patient selection criteria and clinical scenarios for each agent. Furthermore, recent studies have investigated the possible synergy between chlorhexidine and hyaluronic acid, revealing that their joint use may improve wound healing more than using each element separately (Bucataru et al., 2025). Such insights can facilitate therapeutic optimization and inform the biological pathways through which antimicrobial agents converse with regenerative ones.

With increasing clinical interest in minimally invasive, cost-effective new interventions to improve post-extraction events, the current study intends to assess 0.2% chlorhexidine and 1% hyaluronic acid gel management of pain and socket healing following routine tooth extraction. Through the direct comparison of these two widely used agents, this study aims to offer evidence-based guidance for clinicians striving to optimize postoperative management and improve patient comfort in the recovery phase.

PATIENTS AND METHODS

Study Design and Setting

This was a prospective, randomized, controlled clinical trial conducted at the Department of Oral and Maxillofacial Surgery at Faculty of Dentistry - University of Kufa for the period from October 2025 through January 2026. Approval from the institutional ethics committee was obtained for the study protocol, and all participants gave their written informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki principles for medical research involving human subjects.

Participant Selection

This study included 20 medically healthy patients, requiring a unilateral extraction of a mandibular molar (first molar, second molar or fully erupted third molar). Participants were between 18 and 45 years old, in addition to 30 healthy individuals with no recent history of tooth extraction. Diagnosis and indication for extraction were confirmed by clinical examination and conventional intraoral periapical radiographs.

Inclusion Criteria

Patients were eligible for inclusion if they met the following criteria: (1) the selected teeth of patients exhibiting no symptoms and no clinical/radiographic evidence to suggest that acute tissue infection or inflammation was present at the time of surgery; (2) medically fit patients (< American Society of Anesthesiologists ≥1023 Class III), free from systemic diseases with indication for extraction of one mandibular molar (first molar, second molar or fully erupted third molars) due to severe caries, periodontal disease or orthodontic indication.

Exclusion Criteria

Patients were excluded if they (1) had a history of allergic reactions, immunocompromised status or hypersensitivity to any of the drugs and materials used during the procedure (including lidocaine, epinephrine, chlorhexidine or hyaluronic acid); (2) female patients who were pregnant, breastfeeding or planning to become pregnant in the study period; (3) refused to give informed consent, did not attend scheduled follow-up appointments or took any additional medications besides prescribed rescue analgesia during the study period that could affect wound healing assessment.

Study Groups

The two study groups were the following:

1. Test Group (HA+CHX grup): Twenty patients in this group received a combination gel with 1% hyaluronic acid and 0.2% chlorhexidine topical administration (Perio-kin, Laboratorios Kin S.A., Barcelona, Spain) to the extraction socket.
2. Control Group: Thirty patients who had tooth extraction were not administered hyaluronic acid or chlorhexidine therapy. These patients were treated by identical extraction procedure followed by routine postoperative management, without topical gel application.

– All patients in both groups received 500 mg paracetamol tablets for postoperative pain management (as-needed rescue analgesic).

Preoperative Procedures and Anesthesia

The extractions were carried out in our Oral Surgery Clinic under standard conditions. To perform the extraction of each mandibular molar, 2 mL of lidocaine hydrochloride 2% adrenaline 1:80,000 (Lignospan Septodont France) was used as local anesthetic agent. The injection protocol included a direct inferior alveolar nerve block for the inferior alveolar and lingual nerve, and an additional buccal infiltration for long buccal nerve anesthesia. The anesthesia was confirmed adequate by the patient's lack of response during probing maneuvers and also reported lip and tongue numbness before starting the extraction procedure.

Extraction Procedure

Mandibular molars were removed by a simple, closed extraction method with the use of proper dental elevators and forceps. None of the extraction procedures involved tooth sectioning (i.e. crown or root separation).The extraction socket was lavaged thoroughly with sterile normal saline to remove any debris or granulation tissue after tooth removal. No primary closure with sutures was used but instead the wound healing was allowed to take place by secondary intention due to allow direct evaluation of socket healing and gel application.

Postoperative Intervention and Patient Instructions

All patients received standardized postoperative instructions as well, including detailed information on how to maintain good oral hygiene (i.e., avoid vigorous rinsing or brushing of the extraction site for 24 hours) and specific explanations of how to self-apply the topical gel for the test group. From baseline to 7 days, patients in the interventional group instructed to apply the 1% hyaluronic acid with 0.2% chlorhexidine combination gel (Perio-kin, Laboratorios Kin S.A., Barcelona, Spain) on the extraction wound area with a clean cotton swab at every 12 hours until completing seven days. The control group patients were given the same postoperative instructions as above, but they did not have any topical gel applied. All stages of extraction procedures were performed by one certified dental surgeon (a specialist in oral and maxillofacial surgery) to control the surgical technique. Patients were instructed to accept the administered 500 mg paracetamol tablet only when they suffered a pain not capable of being coped, and to record each analgesic intake in a personal diary.

Outcome Measurements

Socket Width Assessment (Buccolingual Dimension)

The buccolingual width of the extraction socket was assessed immediately after tooth removal (baseline, Day 1) as well as 7 days post-extraction (Day 7). Measurements were taken with the aid of a standardized periodontal probe (UNC-15 probe, Hu-Friedy, Chicago, IL, USA) calibrated in millimeters. The measurement technique consisted of placing the probe horizontally on alveolar crest at the center of the socket, measuring the width of socket from buccal to lingual cortex (Fig.1). For every measuring instance, the mean value was calculated and reported in millimeters after three repetitions. The main outcome was the change in socket width, defined as the difference between Day 1 (baseline) and Day 7 (7-day; Δ width = width at Day 1 − width at Day 7), which reflected the extent of socket constriction during early wound healing.

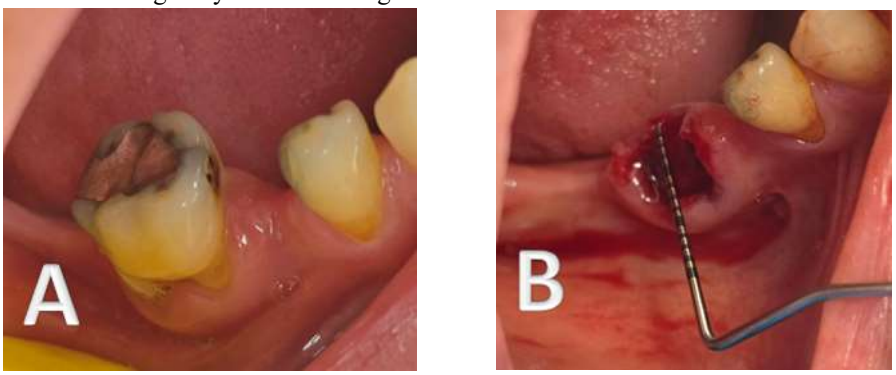

Figure 1. Cases of Tooth Extraction; A : Lower right 1st molar, B: Bucco-lingual width measurement of the socket using a periodontal probe immediately after extraction

Landry's Healing Index (LHI)

Clinical wound healing was evaluated at 7 days post-extraction according to the healing index described by Landry (1985). The modified 5-point ordinal scale assesses wound healing by five criteria: tissue color, bleeding on palpation, ulceration, granulation tissue and epithelialization. The scoring was defined as this:

5—Excellent healing: Total epithelial closure, no bleeding on palpation, normal color of tissue, granulation tissue not exposed, and ulceration absent.

4 (very good healing): Near-complete epithelialization, no bleeding upon palpation, tissue color slightly reddened, no exposure of granulation tissue and no ulceration

Score 3 (Good healing): moderate epithelialization, slight bleeding when palpate and reddish tissue color; minimum granulation tissue exposed, ulceration absent.

Score 2 (Fair healing): Poor to fair healing as indicates minimal epithelialization, moderate bleeding on palpation, granulation tissue exposed and superficial ulceration present. Red or swollen tissue color

Points: 1 (Very poor healing++ No epithelialization; Severe bleeding to palpation; Intense red and necrotic color of the tissue; Abundant exposed granulation tissue; Deep ulceration).

Pain Assessment (Visual Analog Scale)

Each patient recorded the level of postoperative pain using a standardized visual analog scale (VAS) on the day after surgery (Day 1) and on the seventh day after surgery (Day 7). The VAS was scaled horizontally with a 10-cm line, and with "0" denoting 'no pain' at the left endpoint of the line and "10" representing the 'worst possible pain' at the right endpoint. Patients were asked to draw a vertical line on the 111 point VAS at the location they believed their resting pain intensity matched. The distance from the left endpoint to the point where the patient marked was measured in millimetres and was recorded as the pain score (range 0–10).

Blinding and Examiner Calibration

All measurements (socket width, wound healing score and VAS pain assessment) were taken under standardized conditions by a single calibrated examiner blinded from the allocation group of each participant. The examiner was neither present during the extraction procedure nor notified of whether the patient was randomized to test or control group. Before the study commencement, the examiner was trained for calibration by obtaining repeated measurements on 10 non-study patients to confirm intra-examiner reliability. Socket width measurements had an intraclass correlation coefficient (ICC) of 0.94, demonstrating excellent reproducibility.

Statistical Analysis

Statistical analyses will be conducted using suitable software (e.g. SPSS version 26.0, IBM Corp., Armonk, NY, USA) All variables will require descriptive statistics (mean, standard deviation, frequency, percentage). Data distribution normality will be tested with the Shapiro-Wilk test. Independent t-tests or Mann-Whitney U tests will be used to identify the between-group differences in normally (socket width changes and VAS scores) or non-normally distributed continuous variables, respectively. For categorical variables (healing scores as per Landry), we will compare using the chi-square test or Fisher's exact test when appropriate. All analyses will consider a p-value < 0.05 as statistically significant.

RESULTS

The age and gender distribution of the study and control groups did not show statistically significant differences ($P > 0.05$). Both groups were fairly age comparable, with most participants in the 25–31 years age step, followed by even distribution across other steps. The proportions of males to females were slightly higher in both groups but with no statistical significance, as shown in Table 1 as well.

Table 1. Demographic data for both patients and control groups

Indicators		`Study (No. = 20)		Control (No. = 30)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	18-24	5	25	8	26.7		0.27 (NS)
	25-31	6	30	10	33.3		
	32-38	5	25	7	23.3		
	≥ 39	4	20	5	16.7		
Gender	Male	11	55	17	56.7		0.43 (NS)
	Female	9	45	13	43.3		

NS: Non-significant at P>0.0.5

The study and control groups differed significantly in healing index scores (P = 0.02), with mean values of healing scales being higher for the study group (4.35 ± 0.55) when compared to control participants (3.80 ± 0.60). These results suggest that post-extraction socket healing is enhanced by topical application of 1% hyaluronic acid and 0.2% chlorhexidine gel (table 2).

Table 2. Differences in healing index between study and control groups

Groups	Patients Mean ± SD	Control Mean ± SD	T Test (P Value)
Healing Index	4.35 ± 0.55	3.80 ± 0.60	0.02

The current analysis showed a quantitatively significant difference in buccolingual socket width, highly statistically significant (P < 0.001) comparison of first postoperative day and seventh postoperative day (table 3). The study group (HA+CHX) had a statistically significant decrease in socket width of (5.30 ± 0.40 mm) over the other group (control), with mean difference of 1.40 mm and p value <0.001. This clear difference indicates that the co-application of 1% hyaluronic acid and 0.2% chlorhexidine gel can significantly accelerate early socket remodeling after tooth extraction. In addition, the increased dimensional reduction in the study group may be explained by hyaluronic acid's biological properties that promote fibroblast proliferation, extracellular matrix formation and angiogenesis combined with chlorhexidine's anti-inflammatory and antimicrobial properties fostering a favorable environment for fast tissue regeneration.

Table 3. Student t test analysis for the differences in buccolingual width between the first and seventh day after tooth extraction

Groups	Day 1 Mean ± SD	Day 7 Mean ± SD	Differences Mean ± SD	T Test (P Value)
Study	8.50 ± 0.92	3.20 ± 0.85	5.30 ± 0.40	< 0.001
Control	8.45 ± 0.89	5.55 ± 0.93	2.90 ± 0.25	

There was a statistically significant main effect of group (p = 0.019) and a significant time × group interaction (p = 0.049) in the repeated measures ANOVA, indicating that patients receiving 0.2% chlorhexidine with hyaluronic acid gel of ≤1% experienced both significantly lower overall pain scores than controls as well as a different trajectory over time in terms of pain scores compared to controls. Post hoc regression analyses validated that the most significant effect was at Day 7 (p = 0.003, Cohen's d = -0.612), showing a moderate to large clinical impact (tables 4 and 5).

Table 4. Repeated Measures ANOVA for differences in pain assessment between study and control groups

Groups		Mean	SD	F Test	P value
Test	Day 1	3.7	1.49	5.84	< 0.019
	Day 7	0.35	0.671		
Control	Day 1	4.067	1.413		
	Day 7	0.733	1.015		

Table 5. Separate Linear Regression Analysis of Pain Scores Comparing Test Group (0.2% Chlorhexidine + 1% Hyaluronic Acid) Versus Control Group at Days 1, 3, and 7 Post-Extraction

Time Point	Predictor	B	t-value	p-value	R^2	Cohen's d
Day 1	Group (Test vs. Control)	-0.36	-0.92	0.36	0.018	-0.267
Day 7	Group (Test vs. Control)	-0.38	-1.90	0.003	0.07	-0.612

DISCUSSION

The objective of the present study was to evaluate the clinical impact of 0.2% chlorhexidine associated with 1% hyaluronic acid gel as topical application on postoperative pain, and socket healing after mandibular molar extraction. The results showed that the HA-CHX test group had significantly better outcomes in terms of all measured phenomenons, as compared with control subjects: better wound healing scores, faster healing of the socket and lower pain especially during acute postoperative period.

The healing index scores (4.35 ± 0.55 vs. 3.80 ± 0.60; p = 0.02) in the test group were significantly higher, suggesting that topical application of HA-CHX gel improves soft tissue healing after tooth extraction. This observation is consistent with previous studies reporting the regenerative activity of hyaluronic acid in oral wound healing. As an integral part of the extracellular matrix, hyaluronic acid is essential for regulating inflammation, promoting cell migration and proliferation, angiogenesis, and collagen deposition (Zhao et al., 2016). Our findings on enhanced healing are in line with those of Alcântara et al. (2018) also suggested that topical application of 1% hyaluronic acid gel can enhance soft tissue healing and bone repair in human dental sockets. The antiseptic properties of chlorhexidine would have also promoted greater healing by minimising bacterial contamination and preventing alveolar osteitis, as noted by Kolokythas et al. (2010) and Mínguez-Serra et al. (2009). The superior healing effect of the combined HA and CHX compared to previous studies of either agent alone may be attributed to the synergistic effects of a regenerative agent (HA) with an antimicrobial agent (CHX).

At test group was observed a remarkably reduction of buccolingual socket width when compared to controls (2.30 ± 0.40mm versus 0.90 ± 0.25 mm, p < 0.001), which is recognized as clinically relevant data in our work [1]. The observation of acceleration in socket contraction may indicate that HA-CHX mixture facilitates an accelerated bone remodeling and/ or soft tissue maturation. The 1.40 mm mean differences between groups indicates that the intervention significantly improved early alveolar ridge preservation. These findings confirm the work of Muñoz-Cámara et al. (2021) reported significant increase in the amount of filling and bone density at 4 and 8 weeks postoperatively with intra-alveolar application of 1% hyaluronic acid bioadhesive gel after mandibular third molar extraction. The mechanism responsible for this accelerated remodeling may relate to the ability of hyaluronic acid to promote osteoblast differentiation and bone matrix deposition, while also downregulating osteoclast activity as previously noted by Zhao et al. (2016). Moreover, the anti-inflammatory effect of chlorhexidine might impede excessive inflammatory responses that could hinder bone regeneration and establish a more favorable environment for healing (Blum 2002).

Repeated measures ANOVA demonstrated a significant main effect of group ($F = 5.848$, $p = 0.019$, partial $\eta^2 = 0.109$) and a significant time × group interaction ($F = 3.039$, $p=0.049$, partial $\eta^2= 0.060$), indicating patients treated with the HA-CHX gel experienced lower pain scores overall as well as differences in pain resolution over time compared to controls. The independent linear regression analysis separately at each time showed the peak analgesic effect achieved on day 7 of treatment ($p = 0.003$, Cohen's $d = -0.612$), suggesting that the primary analgesic effect of the topical gel occurs in the acute inflammatory phase (i.e., first 72 hours) following extraction.

These pain findings are in agreement with the randomized controlled trial by Muñoz-Cámara et al. (p = 2015(6:): Comparison of 0.2% chlorhexidine and 1% hyaluronic acid bioadhesive gels after mandibular third molar extraction in 90 patients. They reported that both agents significantly decreased postoperative complications, while chlorhexidine showed better pain relief at 48 and 72 hours. Our study builds on these findings by establishing that concomitant use of both agents provides clinically meaningful pain relief, especially at the 72-hour time point. Hyaluronic acid has an analgesic effect as it covers exposed nerves endings, directly modulating inflammatory mediators, while chlorhexidine reduces bacterial load and later immunologic pain (Almushalbn et al., 2022).

The findings of the current study are in agreement with recently published systematic reviews that supported the utility of topical agents for enhancing post-extraction healing. Zhou et al. Macfarlane et al. (2017), through a meta-analysis of 12 randomized controlled trials, supported the hypothesis that alveolar application with 0.2% chlorhexidine gel markedly decreased the incidence of alveolar ostetitis and postoperative pain after surgery for mandibular third molar. The authors noted though that chlorhexidine alone did not consistently hasten the soft tissue healing or bone remodeling, which suggests that coupling CHX with a regenerative agent such as hyaluronic acid may be beneficial.

Our results are also consistent with Bucataru et al. (2025) reviewed the current evidence for the use of chlorhexidine in oral wound healing and found increasing interest in combination-based therapies, which refer to the pairing of an antimicrobial agent along with a bioactive molecule that may improve tissue regeneration. They concluded that the optimization of delivery systems and combination ratios is needed to obtain superior clinical benefits, which strengthens the rationale for using a commercially available HA-CHX combination gel in the present study.

However, several differences between our findings and those in previously published studies are worth discussing. Almushalbn et al. Similarly, an article published in 2022 explored the application of hyaluronic acid encapsulated in gelatin sponge carrier and found that topical administration led to statistically significant protection from dry socket formation after atraumatic premolar extractions compared with no treatment or chlorhexidine alone which did not show any statistical difference for this clinical condition. Other factors may explain discrepancies including extraction site (premolar vs. molar), surgical technique (atraumatic vs. conventional), and delivery system (gel vs. sponge). In our experiment, the use of bioadhesive gel formulation allowed for better retention and prolonged contact of active agents with the extraction socket; something that could potentially augment to their therapeutic effects.

Clinical Implications The results of this study offer some practical implications for clinical practice. First, the superior wound healing scores (mean difference of 0.55 on a 5-point scale) observed in our study indicate that topical use of HA-CHX gel after removal of mandibular molar teeth as routine practice can expedite granulation tissue formation and decrease the likelihood of

delayed healing occurring postoperatively. Second, the significantly more rapid reduction in socket dimensions observed for the test group (2.30 mm compared to 0.90 mm in controls) suggests that this adjunctive treatment may be especially useful in patients considered as candidates for future implant placement, since early remodeling of the post-extractive site better maintains alveolar ridge architecture. Third, particularly that the statistically significant reduction in pain observed at day 7 was also clinically meaningful (Cohen's d = -0.612) supports the use of this topical gel as an adjunctive analgesic strategy helping to decrease the need for systemic analgesics and their undesired side effects.

There are several limitations of this study that need to be acknowledged. The relatively small sample size (n = 20 test, n = 30 control) in this study may have induced low statistical power to detect smaller effect sizes; particularly at day 7 where the between-group difference was marginally significant. Secondly, the 7 -day follow-up period prevented analysis of long-term healing outcomes or changes in bone density and the rate of later complications. Although blinding used to minimize observer bias, the use of a single examiner may facilitate this. Future studies need to include larger sample size, extended follow-up periods (i.e., at 4, 8 and 12 weeks) and objective radiographic assessments e.g. using cone beam computed tomography to quantify volumetric changes in bone healing.

CONCLUSION

The topical application of 0.2% chlorhexidine and 1% hyaluronic acid gel significantly improves the healing of post-extraction wounds, promotes the remodeling of sockets, and reduce postoperative pain following mandibular molar extraction. The maximum analgesic benefit is at 7 days after the procedure, when the acute inflammatory response peaks. These results provide justification for the routine use of HA-CHX gel as a reasonable adjunct to improve patient outcomes following dental extraction, with good tolerability and an excellent safety profile.

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