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Effect of 1% Hyaluronic Acid and 0.20% Chlorhexidine Combination on Post Extraction Soft Tissue Healing: A Randomized Controlled Study

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ABSTRACT

Introduction: Hyaluronic acid has become a common studied biomaterial for tissue engineering. Chlorhexidine is commonly used due to its bactericidal effect at 0.20% concentration inside the oral cavity. There is no previous study showing the combination action of hyaluronic acid and chlorhexidine in acceleration of post extraction tissue healing.

Materials and methods: This multi-center, randomized, controlled (split mouth) study was conducted during 6 months' period (1st of April to 30th of September 2021) in Baghdad. It included a convenient sample underwent bilateral extraction of premolars. Sockets were randomly divided into study sockets filled with periokin (0.20% chlorohexidie+HA1%) and control sockets filled with blood clot. The patients were examined after 3 and 7 days for wound closure rate and wound healing scale.

Results: This study included 21 (16 females) patients with an age range of 14 years-19 years old. Wound healing scale was significantly better at the study side at 3 days (P=0.000) and 7 days (P=0.009) follow up. No significant result observed regarding wound closure rate during the same time period.

Conclusion: Periokin improved wound healing in the first week after application. Further studies at more appropriate times are necessary in order to present reliable outcomes.

Key words: Perioskin, Hyaluronic acid, Chlorhexidine, Baghdad, Premolars

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HIGHLIGHTS

- Bioadhesive periokin gel filled the dental socket and not easily dislodged from it.
- Bioadhesive periokin gel allowed the wound to close in a manner greatly similar to the normal blood clot.
- Bioadhesive periokin gel significantly decreased the signs of tissue inflammation in a relatively short period.

INTRODUCTION

Hyaluronic Acid (HA) is a high molecular weight glycosaminoglycan that has become widely used in dentistry due to its biocompatible properties with involvement in biological processes related to tissue healing [1]. In recent years, HA has been used as bioadhesive intra alveolar gel applied inside the socket to reduce the postoperative sequel after Mandibular Impacted Third Molars (MITM) extraction [2,3]. This is due to HA effective adjuvant role as anti-edematous, anti-inflammatory, antioxidant, bacteriostatic and healing or regenerative biological properties [4].

Chlorhexidine (CHX) is biguanide derived and is used on a wide basis as topical antiseptic in dentistry. CHX has a significant antimicrobial action due to its strong dicationic and molecular structure which allows it to interact with the anions [5]. It exhibits broad antibacterial against gram + and gram-bacteria, antifungal activity, some viruses and dermatophytes, due to its capability to damage their internal cytoplasmic layer. It exhibits bacteriostatic action, at low concentrations and bactericidal action at high concentrations [6].

Recently, the most widely used formulation is a 0.2% intra alveolar CHX gel at bactericidal concentration for reducing postoperative complications, such as alveolar osteitis.

There is no previous study showing the action and post extraction squeal and healing by using the combination of hyaluronic acid and chlorhexidine bioadhesive gel.

The study aims to compare the wound closure rate and wound healing scale between the study group (applying bioadhesive gel of 1% HA+0.20% chlorhexidene combination) and control group (placebo) through a randomized controlled trial.

MATERIALS AND METHODS

This superiority, parallel, prospective, randomized (random digit table), controlled (split mouth) and triple blinded clinical trial study was done in the two departments of oral and maxillofacial surgery (multi-center study) at the college of dentistry/Baghdad University (in the center of Baghdad) and Al-Sader dental specialist center (Eastern of Baghdad) from 1st of April to 30th of September 2021.

A convenient sample size was selected from the patients attending the two selected dental specialist centers who indicated for bilateral premolars extraction (14,24,34,44,35,45 teeth) due to orthodontic purpose.

Bilateral extraction of premolars for each patient was made under local anesthesia (lidocaine with adrenaline 1:80000, Huons Co. Ltd., Korea). The sockets were divided randomly into study sockets completely filled with Periokin (0.20% chlorohexidie+HA1%) Kin company and provided by Kin Company Delegate/ Baghdad/Iraq) and control sockets normally filled with blood clot. Using two labeled, opaque sealed envelopes, randomization was performed by an operator that was not directly involved in the outcomes assessment. Twenty one cards labeled either right or left were sealed in the #1 envelope and another twenty one cards labeled with the groups (group A or group B) were sealed at the #2 envelope. The same operator informed the surgeon's assistant which side was chosen to receive Perio kin (0.20% chlorohexidie+HA1%) Kin Company. Application of the gel was made by using a sterile disposable syringe (10 ml). The syringe was hold on the sockets for 30 seconds in each side, but the 0.5 ml of periokin gel was placed only in the socket that was selected to be receive periokin as a treatment. This trick was performed in order to make the patient blinded about the socket that received the treatment.

The study included individuals presenting with teeth indicated for non-traumatic bilateral premolar extraction for orthodontic purpose, individuals with no signs or symptoms of any systemic disease or allergy or bleeding problem. The study excluded patients with per apical abscess, traumatic extraction, patients habituated to the use of tobacco and/or alcohol, drug abuse, pregnancy or lactation.

Before starting the application of this study, a special training has been made for the operator in order to inject the perio kin gel and to assess the wound healing rate according to a modified Wound Healing Scale (WHS) which was developed by Vandana Shenoy, et al. [7].

All the required information's about the patient medical and dental history and other individual data were taken from each patient by a direct interview. Full examination of head and neck in addition to comprehensive intraoral examination was done in order to select eligible patients for the study.

Armamentarium/instrument and materials (Appendix I)

- **Instruments:** Probe, mirror, tweezers (Aesculap/ Germany), dental syringe (Aesculap/Germany), dental needle (C-K Ject disposable anesthetic needles 27G), premolar dental extraction upper forceps SSI786-105. (English Pattern/medical expo company), premolar dental extraction lower forceps SSI786-105. (English Pattern/medical expo company), periodontal probe (Aesculap/Germany), disposable syringes (10 ml), occlusal mirror, check retractor and tongue retractor.
- **Material:** Perio kin (0.20% chlorohexidie+HA1%) Kin company, cotton.
- **General equipment and devices:** Autoclave (Melag, Germany) and sterilization pouch (ADS, Australia), canon camera 90D, intraoral scanner Medit i700 with laptop, Medit compare 1.1.1.61, Exocad, SPSS.
- **Medications:** Local Anesthesia (LA); Lidocaine hydrochloride 2% with Adrenaline 1: 80,000, paracetamol tablet 500 mg.

The patients included in the study were examined after 3 and 7 days and followed up by two methods:

- **Wound Closure Rate (WCR):** By the use of inter oral scanner, immediately post extraction, 3 and 7 days post extraction alongside with using Medit compare 1.1.1.61 software in order to made the measurement at the same cross section (the selected points on the same line).
- **Wound Healing Scale (WHS):** According to criteria done by Vandana Shenoy, et al. with the aid of periodontal probe.

Wound healing scale was categorized into: Poor (sign of inflammation of surrounding soft tissue is moderate or severe, exposing bone surface and insufficient granulation tissue amount), moderate (sign soft tissue inflammation is moderate, moderate epithelium amount, granulation tissue filled half to about two thirds of the socket), good (sign of inflammation of surrounding soft tissue is absent or mild, good epithelium amount, granulation tissue completely filled the socket), excellent (signs of surrounding tissue inflammation is absent, good epithelium amount, granulation tissue completely filled the socket. The Statistical Package of Social Sciences (SPSS) version 21 was used to perform statistical analysis using Man-Whitney and *Chi-square* tests because the data was not normally distributed.

Baghdad university research ethics committee approved this study, (protocol/2020) with a unique registration number and followed declaration of Helsinki instructions. A statement of informed consent was a signed for each patient prior to involvement in the study. Parents/caregivers signed the informed consent statement of for patients that were under 18 years old.

RESULTS

A total of 21 patients who met the inclusion criteria were enrolled in this study, all patients attend the recall visit after 3 and 7 days.

Results demonstrate that the 21 subjects who participated in this study were with age range between (14-19) years old with a mean age of 16.86 ± 2.637. Females were more than males in this study (16 versus 5). This is all shown in Table 1.

Table 1: Distribution of the participants according to the age and gender, Baghdad, 2021.

Variable		Frequency n=21	Percent %
Age	14	2	9.5
	15	3	14.3
	16	7	33.3
	17	2	9.5
	18	6	28.6
	19	1	4.8
Gender	Male	5	23.8
	Female	16	76.2

Regarding the extracted teeth, upper first premolar was the most common (71.4%), followed by lower first premolar (23.8%) as shown in Figure 1.

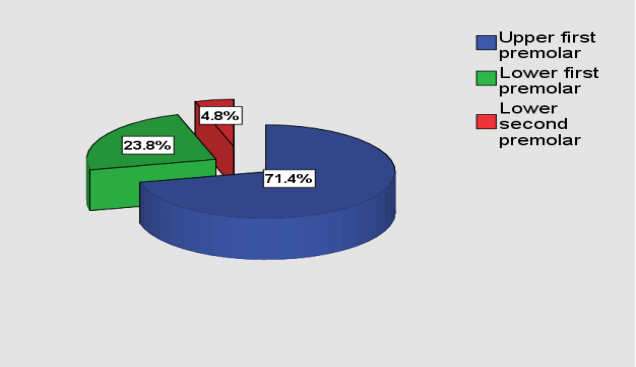

Figure 1: Distribution of the participants according to the extracted teeth, Baghdad, 2021.

Regarding the comparison of wound closure rate between study and control groups, by using the mean of buccopalatal distances and mesiodistal distances in both groups after 3 and 7 days, the statistical difference was not significant between two group at the time points after tooth extraction which mentioned previously at (P>0.05) as illustrated in Table 2.

Table 2: Comparison between the study and the control groups at 3 and 7 days follow up, Baghdad, 2021.

Variable	Wound Closure Rate (WCR)		P value
	Study % (Mean ± SD)	Control % (Mean ± SD)	
3 days B-P	60.03 ± 10.28	60.63 ± 11.29	0.753
3 days M-D	51.66 ± 13.61	54.39 ± 13.54	0.428
7 days B-P	46.23 ± 9.38	41.85 ± 10.24	0.11
7 days M-D	38.33 ± 11.67	40.37± 13.22	0.678

Regarding comparison of the wound healing between study and control groups at 3 and 7 days after teeth extraction, the result showed statistically significant difference in the study group when compared with the control group (P=0.000 and 0.009) respectively as illustrated in Table 3.

Table 3: Distribution of the participants according to the WHS at 7 and 14 days follow up, Baghdad, 2021.

WHS	Excellent n (%)	Good n (%)	Moderate n (%)	Poor N (%)	P value
3 days					
Study	0 (0)	16 (76.2)	5 (23.8)	0 (0)	0.000*
Control	0 (0)	3 (14.3)	17 (81.0)	1 (4.8)	
7 days					
Study	0 (0)	20 (95.2)	1 (4.8)	0 (0)	0.009*
Control	0 (0)	13 (61.9)	8 (38.1)	0 (0)	

*Significant result

No harms or side effects were reported in the study and control groups.

DISCUSSION

To the best of our knowledge, this is the first controlled randomized trial that aims to assess the effect of periokine gel on soft tissue healing after tooth extraction. 1% HA gel was used in one previous study to achieve the desired healing acceleration and prevent post extraction complication associated with blood clot loss [8]. CHX in the formulation of gels and mouthwashes are the most requested for use by both patients and dentists. They are used before or after oral or periodontal surgery to decrease the load of microbes in the oral cavity as shown in many studies [9-11]. Gel form of chlorhexidine allows it to be laid in the socket, to provide a long term and direct action in comparison with superficially applied CHX mouthwash. Other studies assessed the intra alveolar CHX gel application intra operatively following lower third molars extraction, which seemed to decrease the alveolitis incidence, even in patient suffering from coagulation disorders [12-14].

It is noteworthy that the experimental current model implemented; split mouth enables every participant to act as her/his own control, in order to minimize Individual factors which in turn might interfere with the study results.

In current study, the age of the patients attending orthodontic department was ranging from 14 years-19 years old and this coincides with other studies regarding the age of patient seeking orthodontic treatment [15-17]. The majority of the patients (76.2%) were females, since female gender is more concerned about their aesthetic appearance than doe's male gender and this result agreed with many studies done in different cities in Iraq [18-20].

The majority of extracted teeth (71.4%) were upper first premolars, followed by lower first premolars (23.8%) and the least common were lower second premolars (<5 percent). This is may be related to the fact that Angle's class I malocclusion with crowding was the most prevalent, followed by class II malocclusion while the least predominant was class III malocclusion [21].

In the present study, we use premolars' fresh sockets of orthodontic's indicated extraction to show the effect of combination of HA and CHX on wound closure rate and wound healing scale under non-traumatic and healthy circumstances. So selection of such teeth was practical, because these teeth are sound, single rooted, with no inflammatory signs and are commonly extracted for orthodontic purposes. This was in agreement with Aclantara, et al. study [22].

In this study, the researcher used one type of intraoral Medit i700 scanner, the latest intraoral scanner from Medit, in which the Medit company improved most of the features presented by Medit i500 and the data acquisition is based on the principle of 3D in motion video technology/3D full color streaming capture [23].

All measurements have been taken by using intraoral scanner due to its ability to capture precisely the soft tissue and this was in agreement with Kattadiyil, et al. who fabricated a partially removable denture framework successfully using the intraoral scanner [24].

The present study did not show significant difference regarding the wound closure rate between the study and control groups (P>0.05) at 3 and 7 days after tooth extraction. It is noteworthy to mention that there are no other studies that demonstrate the effect of 1% hyaluronic acid and 0.20% chlorhexidine in combination as bioadhesive gel but our result in somehow came in agreement with Mostafa, et al. study in his pilot study [25].

Regarding WHS, a significant result obtained in favor of the study group (P<0.05). The anti-inflammatory effect of hyaluronic acid shown by Gontiya and Galgali and Sahayata, et al. as they observed the locally applied 0.2% HA gel effect on the inflamed gingiva achieved a significant improvement on the gingival and bleeding indexes in comparison of the control placebo group (scaling+placebo gel) and the negative control group (only scaling) [26-27].

LIMITATIONS

The first limitation of the current study was that the assessment of wound healing is considered a challenge for many reasons; lack of a standard accurate criteria for socket healing description and the absence of a method

approved for measuring and wound healing evaluating. However, measuring wound borders alone according to Mokhtari, et al. study is considered sufficient for wound healing reporting, despite neglecting the wound depth [28]. Another limitation was the difficulty in selecting larger sample size due to the effect of COVID-19 pandemic.

CONCLUSION

This first randomized controlled trail; to the best of our knowledge, that aims to assess the effect of periokine gel on soft tissue healing after tooth extraction showed that the study group (with bioadhesive gel) had better WHS than did the control group. On the other hand, no significant difference obtained between both groups regarding wound closure rate. Further repeated studies examining parameters at more appropriate times are necessary in order to present more useful and reliable outcomes.

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CONFLICT OF INTEREST

No supporting source involved in the current study.

AUTHOR CONTRIBUTION STATEMENT

The author is responsible for what is included in this manuscript.

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