Original Article

The Efficacy of Hyaluronic Acid in Postextraction Sockets of Impacted Third Molars: A Pilot Study

N Yilmaz, N Demirtas, HO Kazancioglu, S Bayer, AH Acar, A Mihmanli

Deparment of Oral and Maxillofacial Surgery, Bezmialem Vakif University, Faculty of Dentistry, Istanbul, Turkey

ABSTRACT

Objective: This study aims to evaluate the effectiveness of local hyaluronic acid (HA) administration to surgically remove impacted third molar sockets and measure pain, swelling, and trismus. **Materials and Methods:** The study included a total of 25 healthy patients aged 18-29 years with asymptomatic bilaterally impacted lower third molars. All cases have been performed under local anesthesia. In the study group, 0.8% HA (Gengigel®) was applied in the postextraction sockets of the right third molars and in the control group nothing was applied to the extraction sockets of the left third molars. Postoperative pain, trismus, and swelling were evaluated on the 1st, 3rd, and 7th postoperative days. **Results:** No difference was determined between groups in facial swelling and maximum mouth opening. However, the amount of pain significantly reduced in HA groups according to visual analog scale (P = 0.001). **Conclusion:** The results of this study showed that HA can produce an analgesic action in postextraction sockets after surgical removal of impacted teeth and therefore it has a clinical benefit to reduce usage of nonsteroidal anti-inflammatory drugs after dentoalveolar surgery.

KEYWORDS: *Hyaluronic acid, pain, surgery, third molar*

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INTRODUCTION

The surgical extraction of wisdom teeth is one of the most common procedures in oral surgery. However, numerous complications can develop, such as nerve injury, bone fractures, delayed healing, inflammation, pain, swelling, and trismus.[1] All these conditions have negative effects on quality of life for patients. Many studies were based on reducing the complications after impacted tooth surgery[2,3] For instance, local or systemic steroid, nonsteroidal anti-inflammatory drugs consumption, and antibiotic prophylaxis are common medication methods. Pharmacological therapy, especially corticosteroids, seems an effective method to increase postoperative oral quality of life for surgically extracted impacted third molars.[3] Although, routine prescribtion of these drugs can cause problems due to their potential adverse effects.

Hyaluronic acid (HA) is one of the major linear polysaccharides of the extracellular matrix which can be found in various body tissues especially in connective tissue and synovial fluid. It has a great number of functions, such as elastoviscosity of the synovial fluid in joints, control of tissue hydration, and a mechanism of cell detachment. In addition, HA can be used safely in medicine because it is nonimmunogenic and nontoxic.[4,5] HA has a multifunctional role in the wound healing process. In dentistry, it was first used in the treatment of periodontal disease such as gingivitis. Clinically, good results have been obtained with local application. On the contrary, it has been used in the postoperative phase of knee surgery surgery to reduce orally administered analgesic dose.[6]

The available studies provide insufficient information to assess the efficacy of the usage of HA after dentoalveolar surgery. Hence, the purpose of this clinical trial was to investigate whether there is any beneficial value

***Address for* correspondence:** Dr. Ahmet Mihmanli, Bezmialem Vakif University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery 34093, Fatih, Istanbul, Turkey.
E-mail: dr_amihmanli@mynet.com

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of local administration of 0.8% HA gel formulation (Gengigel®; Farmalink Saglik, Istanbul, Turkey) on the postoperative pain, trismus, and swelling.

Materials and Methods

Study design

This prospective study is performed with 25 healthy patients among 40 patients who applied to the Department of Oral and Maxillofacial Surgery at Bezmialem Vakif University, Istanbul, Turkey between January 2015 and May 2015 for surgical extraction of impacted asymptomatic lower third molars. Initially, pretreatment data were collected. All of the patients had bilaterally impacted lower third molars. A total of 15 patients were excluded from the study because they did not meet the inclusion criteria. The experimental study was conducted in agreement with the Helsinki Declaration and ethical approval was obtained from the local ethic committee (No.2015-4385). All patients were informed about the study and signed consent forms were obtained. Additionally, the including criteria are listed as follows:

1. Age >18
2. To have bilaterally impacted lower third molars with equal surgical difficulty (III B surgical difficulty grade according to Pell–Gregory and Winter scales)
3. To have no systemic disease

Exclusion criteria are listed as follows:

1. Having a history of allergies or adverse effects to antibiotics, analgesics, or local anesthetics, pregnancy, mental disability, or bleeding problems
2. To use contraceptives or corticosteroids which can affect the postsurgical healing phase and amount of swelling on the face
3. To have difficulty with cooperation
4. To have acute infection such as pericoronitis and/or pain on the tooth site before extraction
5. To take antibiotics and analgesics for 15 days before surgery
6. Tobacco use.

All surgical extractions were carried out by the same surgeon (NY) according to standardized surgical technique and equipment. All measurements were administrated objectively by a blinded operator Nihat Demirtas (ND). A total of 25 patients were investigated and their right third molars were included in group 1 (HA group) and left third molars were included in group 2 (control group). Tooth extractions were performed at different times for each patient in order not to affect measurements of mouth openings. The teeth (all of them were totally impacted) were evaluated before surgical procedure according to Pell-Gregory and Winter scales to reduce discrepancies in the degree of surgical difficulty.[7] All patients were advised to avoid analgesics for 12 h before operation time.

Postoperatively, patients underwent antibiotic treatment (oral amoxicillin 1000 mg twice daily for 5 days) and simple analgesic medication (550 mg naproxen sodium) recommended as necessary. In addition, total analgesic dose taken in the postoperative period was recorded. Additionally, oral hygiene instructions were given after the tooth extraction.

Surgical phase

The operation procedure was performed according to conventional surgical impacted third molar extraction. Routine regional anesthesia procedure was applied including inferior alveolar nerve block together with buccal infiltration anesthesia by two 1.8 mL cartridges of 4% articaine hydrochloride solution with 1:100 000 epinephrine (Maxicaine Fort Ampul, VEM Ilac, Istanbul, Turkey). After three-sided incision, mucoperiosteal soft tissue flap was reflected laterally and tooth extraction was performed following adequate bone osteotomy with 40 mL/min saline irrigation. Finally, the extraction socket was irrigated, debrided mechanically, and the flap was repositioned. In group 1, teeth (right side of the patients) 2 mL Gengigel® 8% HA was inserted in the postextraction socket before suture placement and stayed in the socket post operatively. In group 2, teeth (left side of the patients), the flaps were sutured after a blood clot formed at the extraction site. Aseptic, atraumatic, and nonheat-producing techniques were considered to managing both soft and hard tissues. In all cases, firstly right side (HA group) of the patients has been operated. The second operation (left side or control group) was performed at least 4 weeks later to assess objective evaluation.

Postoperative evaluation

Visual analog scale (VAS) which has a 10 units number line marked by degrees was used for detecting the degree of postoperative pain. According to this scale, score of 0 indicated"absence of pain" and score of 10 indicated "excessive pain." The intermediate scores have been indicated "moderate pain." The exact question was "On the scale, how much pain are you having for today?" In addition, it contains facial expression illustrations to direct the patients. Brokelman *et al*.[8] reported that VAS scale is a simple instrument to evaluate the postsurgical pain and satisfaction of a patient with the intraclass coefficient of 0.95. In our study, measuring postoperative pain was recorded by using VAS in the immediate postoperative 1st, 3rd, and 7th days.

Pre- and postoperative amount of mouth openings were used to determine the degree of trismus. Both parameters

were assessed by the measurement of inter incisor distance with calipers.[9]

In this study, assessment of facial swelling was determined by using modification of Gabka and Matsumara method.[10] The measurement points included tragus (T), soft tissue pogonion (P), lateral border of alaeque nasi (AN), lateral corner of the eye (CE), angle of the mandible (AM), and the corner of the mouth (CM). Seven different measurements (D1 to D7) were recorded between each case respectively; D1: T-AN; D2: T-CM; D3 T-P; D4: AM-CE; D5: AM-AN; D6: AM-CM and D7: AM-P. All measurements were taken before surgery and on the 1st, 3rd, and 7th days after surgery from both sides for all cases [Figure 1].

Statistical analysis

The statistical analysis of the study was performed using the SPSS® version 15.0 (SPSS Software, Chicago, IL, USA). Descriptive statistics including mean values and standard deviations were determined for all variables in the study and control groups. Data were initially tested for normally distribution using the Shapiro–Wilk test. Paired sample t-test was used for normally distributed variables (VAS scores and mouth opening). Additionally, Mann-Whitney U test was used to asses statistical differences between groups for non-normally distributed variables (numbers of analgesic doses and swelling). *P* value of less than 0.05 for the 95% confidence interval was accepted as significant.

Results

A total of 25 patients (13 male; 12 female) were included in this study. The age range was 18-29 years; median age was 20 years, and mean age was 21.16 ± 2.97. The degree of surgical difficulty was similar in each group according to Pell-Gregory and Winter scales.[11] Both impacted asymptomatic

Table 1: Mean ± standard deviation, maximum interincisal opening (in cm) for postoperative 1st, 3rd, and 7th days in bilaterally extraction sites of 25 patients (right side = HA group; left side = Control group; n = Number of extracted teeth)

n (extracted teeth)	Preoperative	1 day	3 days	7 days
Control group				
25	47 ± 3.8	36.7 ± 8.8	41.3 ± 6.5	46.8 ± 5.3
Main ± SD				
Median (min;max)	48 (41;55)	38 (20;50)	42 (32;55)	46 (37;55)
HA group				
25	47.4 ± 4.9	41.3 ± 8.3	43.8 ± 6.6	45 ± 4.8
Main ± SD				
Median (min;max)	48 (40;55)	43(25;54)	46 (30;55)	48 (35;55)
P value	0.752	0.065	0.179	0.214

SD=Standard deviation

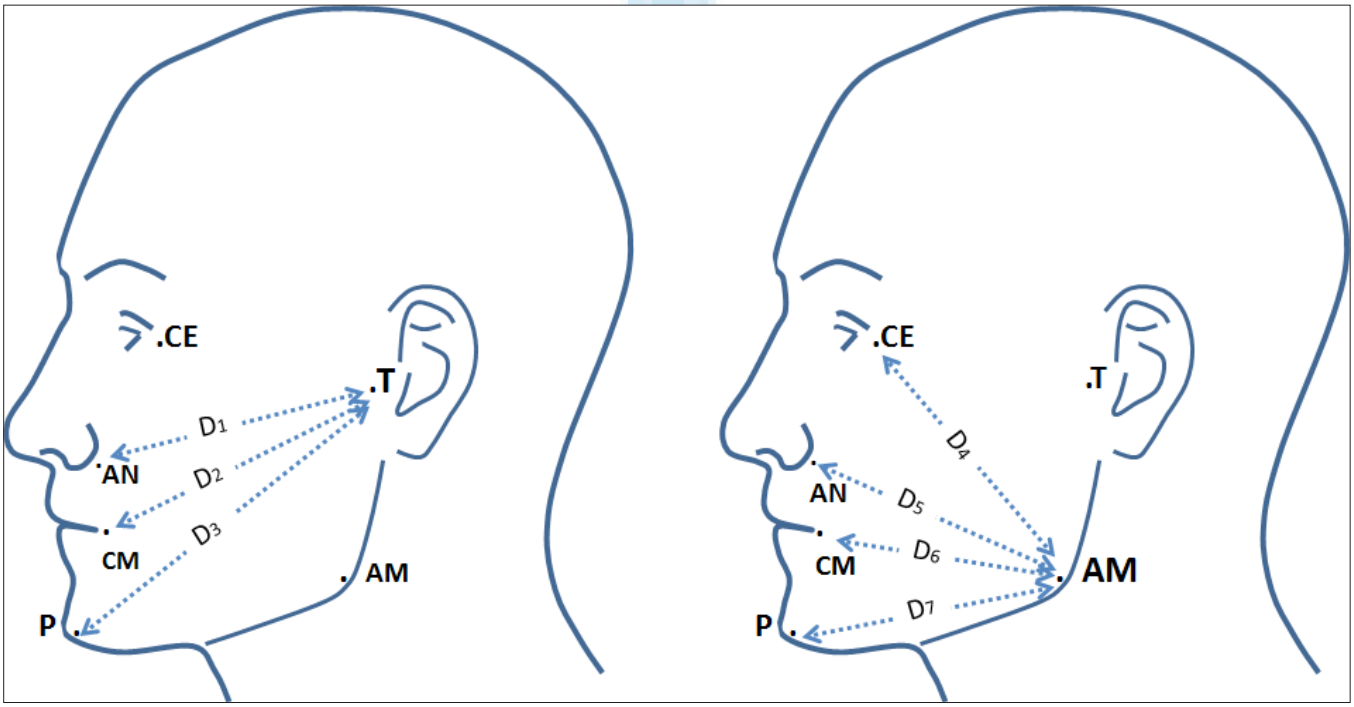

Figure 1 : The measurement points T: Tragus, P: Soft tissue pogonion, AN: Lateral border of alaeque nasi, CE: Lateral corner of the eye, AM: Angle of the mandible, and CM: Corner of the mouth

Table 2: Pain scores on VAS for postoperative 1st, 3rd, and 7th days for 25 patients (right side = HA group; left side = Control group; n = Number of extracted teeth)

n (extracted teeth)	1 Day	3 Days	7 Days
Control group			
25	7.08 ± 1.38	4.68 ± 1.25	1.72 ± 1.14
Main ± SD			
Median (min;max)	8 (4;9)	5 (2;7)	2 (0;4)
HA group			
25	4.92 ± 1.82	3.64 ± 1.70	0.92 ± 0.81
Main ± SD			
Median (min;max)	5(2;8)	4 (1;7)	1 (0;2)
P value	0.001	0.018	0.006

SD=Standard deviation

Table 3: Total numbers of analgesic doses in 7 days (right side = HA group; left side = Control group; n = Number of extracted teeth)

	n (extracted teeth)	Mean ± SD
Control group	25	6.04 ± 1.1
Median (min;max)		6 (5;9)
HA group	25	5.28 ± 1.2
Median (min;max)		5 (3;8)
P value		0.032

SD=Standard deviation

lower third molars were extracted from each patient without any complication. The mean operation time (from the incision till the last suture) was determined as 17.2 ± 6 min for the study group and 18.7 ± 2.5 min for the control group. There was no significant differences in the operation time between the two groups ($P = 0.14$).

Patients were recalled on the postoperative 1st, 3rd, and 7th days to evaluate the trismus, pain, and facial swelling. Maximum mouth opening (interincisal distance) was recorded in every recall appointment. It is clearly shown that the degree of mouth opening significantly decreased in postoperative 1st and 3rd days ($P = 0.001$). There was no significant difference in changes in interincisal opening values between control and HA groups. Pre- and postoperative measurements of the mean interincisal opening are shown in Table 1 for each group.

Pain scores on VAS are shown in Table 2. On the 1st, 3rd, and 7th postoperative days, VAS scores were significantly decreased in the HA group ($P = 0.001$).

The number of analgesic tablets taken was noted and it shows that the HA group took significantly fewer analgesics compared with the control group ($P = 0.032$; Table 3).

On postoperative 1st day, a modest increase was observed in the mean facial swelling scores (D1–D7) of the subjects. On postoperative 7th day, the scores were returned to normal levels. On the 1st, 3rd, and 7th postoperative days; there was no statistically significant

Table 4: Mean ± standard deviation swelling (in cm) measured from seven different drawings and comparisons between groups. (D1: T-AN; D2: T-CM; D3 T-P; D4: AM-CE; D5: AM-AN; D6: AM CM and D7: AM-AP ; right side = HA group; left side = Control group)

		1 Day		3 Days		7 Days	
	Preoperative	Control group	HA group	Control group	HA group	Control group	HA group
D1	11.67 ± 0.69	12.02 ± 0.70	12.04 ± 0.72	11.84 ± 0.74	11.86 ± 0.69	11.7 ± 0.7	11.68 ± 0.72
D2	11.27 ± 0.5	11.59 ± 0.7	11.56 ± 0.6	11.48 ± 0.66	11.34 ± 0.6	11.3 ± 0.6	11.27 ± 62
D3	14.3 ± 0.9	14.74 ± 0.85	14.77 ± 0.98	14.5 ± 0.9	14.6 ± 0.97	14.45 ± 0.95	14.47 ± 0.97
D4	10.56 ± 0.62	10.75 ± 0.6	10.68 ± 0.6	10.61 ± 0.63	10.6 ± 0.61	10.57 ± 0.62	10.58 ± 0.63
D5	11.16 ± 0.84	11.52 ± 0.88	11.55 ± 0.87	11.35 ± 0.86	11.31 ± 0.88	11.16 ± 0.84	11.20 ± 0.84
D6	9.23 ± 0.78	9.6 ± 0.85	9.59 ± 0.8	9.36 ± 0.9	9.4 ± 0.81	9.27 ± 0.7	9.26 ± 0.79
D7	11.25 ± 1.67	11.65 ± 1.68	11.54 ± 1.7	11.53 ± 1.67	11.43 ± 1.69	11.26 ± 1.66	11.23 ± 1.6
	+*P*	*P* > 0.05		*P* > 0.05		*P* > 0.05	

difference between facial swelling in HA and control groups. All of the mean values and comparisons between groups are shown in Table 4.

Discussion

Pain, swelling, and mouth opening limitation caused by the expected acute inflammatory response are still the most common complications after wisdom tooth removal despite all variable methods. Many studies aim to reduce postoperative discomfort in oral and maxillofacial surgery.[1,2,12,13] It is clearly known that postoperative inflammatory reactions reach a maximum level 2 days after surgery and generally wear off in 1 week. Thus, the 1st week after surgery has a strong effect on patients' quality of life, and it is critical to eliminate associated factors affecting the initial phases of wound healing.[14]

The purpose of this current study was to increase postoperative satisfaction of oral surgery patients by alternative antiinflamatuary and analgesic drug options with minimal adverse drug reactions. Our results showed that local administration of HA into the extraction socket may provide a decrease in pain.

Our study included several limitations. First, we had a small sample size. Likewise, there is limited number of clinical studies including HA in oral and maxillofacial surgery. However, further trials should be designed with larger participants to investigate the efficacy of HA.Second, individual variations such as pain threshold and other psychological factors may affect the results of pain scale.

Several studies in the literature reported that HA reduces symptoms especially pain for the patients with osteoarthritis. To illustrate, Xia *et al*.[15] reported its positive effect on reducing pain in patients with Kashin-Beck Disease which is a kind of chronic osteoarthritis. Das *et al*.[16] suggested that HA has a benefit for patients with osteoarthritis knee pain in reducing symptoms as much as oral nonsteroidal anti-inflammatory drugs or steroid injection. Gotoh *et al*.[17] reported that HA has an analgesic effect by covering bradykinin receptors in synovial tissues and support a role in pain medication. In addition, they suggested a correlation between molecular weight of HA and its analgesic effects. According to their study, the analgesic effect of HA exists if its molecular weight is greater than 40 kilodaltons. In the literature, there are so few studies explaining the molecular mechanism of the relationship of HA and other glycosaminoglycans. Nelson *et al*.[18] investigated the efficacy of oral HA administration (Oralvisc®) by spectral analyses of serum and joint fluid in knee osteoarthritis patients. They found a remarkable decrease in the majority of inflammatory cytokines such as interleukin-1α (IL), IL-1β, IL-6, interferon, tumor necrosis factor alpha, and granulocyte macrophage colony stimulating factor, leptin and bradykinin in serum and synovial fluid. Finally, they suggested that HA reduces not only pain but also local and systemic inflammation.

In our study, decreasing the pain in the HA group may be related to the anti-inflammatory contribution of HA. Gocmen *et al*.[19] stated that HA applied after third molar extraction showed less leucocyte infiltration and more angiogenesis. Contrary to our study, they stated that although HA has anti-inflammatory effect, there were no statistically significant differences in pain or trismus between the groups. Koray *et al*.[20] evaluated the efficacy of HA spray after third molar extraction and reported a reduction of trismus and swelling. On the contary, they did not find any statistically significant difference occurring in the pain measured with VAS. They also stated that HA decreases swelling postoperatively and it may lead to less alveolar osteitis. In our study, the degree of mouth opening decreased postoperatively but it was not statistically significant between HA and the control group for swelling and trismus.

There are a few studies in the literature that investigated the effect of HA on wound closure.[21,22] They concluded that HA accelerates wound closure rate and re-epithelization. Juhasz *et al*.[21] stated a reduction in the wound size although there is resolution of pain. Similarly, Onesti *et al*.[22] in addition to wound size reduction, they also declared a decrease in pain by half of the patients and no pain in the majority of the rest.

Several studies reported that bone regeneration is accelerated when HA is used with autologous bone grafts. [23] In addition, 1% HA gel supports new bone formation in the critical size defects on the calvarium of rats and rabbits.[24,25] These results support that HA may have a positive effect for bone healing after wisdom tooth surgery.

Conclusion

It has been observed that the pain occurred after surgery effects the patient's quality of life more than trismus and swelling. Therefore, the potential analgesic effect of HA should be discussed in future studies. Additionally, HA can be a good choice because it has clinical advantages for reducing usage of nonsteroidal anti-inflammatory drugs after third molar surgery.

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Nil

Conflicts of interest

There are no conflicts of interest.

Ethics statement/confirmation of patient permission

The study protocol and experimental design were approved by the local ethic committee of the University. Informed consent form were obtained from all patients.

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