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# Effects of Local Application of Hyaluronic Acid on Postoperative Sequelae after Surgical Removal of Impacted Lower Third Molars

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**الخلاصة**

**الأهداف**: تهدف الدراسة الحالية الى تقيم فعالية التطبيق الموضعي لمادة حامض الهيالورونيك على الالم وتورم الوجه والتشنج العضلي بعد قلع ضرس العقل للفك السفلي. **مواد وطرق البحث**: تم إجراء البحث على ٤٤ مريضا بعد التأكد من عدم معاناتهم من اية أمراض مزمنة. تراوحت أعمار المرضى بين ١٨-٢٩ عاما. لم يكن لدى المرضى أعراض إلتهاب في ضرس العقل وفي الأنسجة التي حوله عند اجراء القلع الجراحي. تم تقسيم المرضى بصورة عشوائية الى مجموعتين. المجموعة الأولى وشملت ٢٢ مريضا استخدم حامض الهيالورونيك بتركيز٠.٨ لكل مل وتم وضعه في حفرة ضرس العقل للفك السفلي بعد القلع الجراحي، أما المجموعة الثانية (المجموعة الضابطة) من المرضى فلم تتم إضافة أي شيء في حفرة ضرس العقل للفك السفلي وعدد المرضى ٢٢ مريض أيضا. تم قياس تورم الوجه والتشنج العضلي والالم للمرضى في الأيام الأولى، الثالثة، والسابعة لما بعد الجراحة. تقييم مستوى الألم تم بإستخدام مقياس التصنيف الرقمي(NRS) . **النتائج**: كان مقياس كل من الألم وتورم الوجه والتشنج العضلي عالي في اليوم الأول بعد الجراحة ثم إنخفض تدريجيا في كل من المجموعة الضابطة ومجموعة حامض هيالورونيك في اليوم الثالث والسابع لما بعد الجراحة. كما أثبتت نتائج الدراسة أن هناك فروقات ذات دلالة احصائية في درجات الألم بين المجموعة الضابطة ومجموعة حامض الهيالورونيك في اليوم الأول، الثالث، والسابع لما بعد الجراحة. بالنسبة لتورم الوجه كانت هناك فروقات ذات دلالة احصائية بين المجموعتين في اليوم الأول والثالث فقط لما بعد الجراحة. لم تكن هناك فروقات ذات دلالة احصائية بين المجموعتين فيما يتعلق بالتشنج العضلي خلال أيام مابعد الجراحة. **الإستنتاجات**: أظهرت نتائج هذه الدراسة انه بعد القلع الجراحي لسن العقل فإن حامض الهيالورونيك له تأثير مسكن للألم وبالتالي قد يكون له فائدة سريرية في تقليل كل من الألم وتورم الوجه لأيام ما بعد الجراحة.

## ABSTRACT

**Aims**: The aims of the current research is to estimate the effectiveness local application of hyaluronic acid (HA) gel on pain, facial swelling, and trismus after extraction of impacted mandibular third molars. **Materials and Methods**: The research included a total of 44 healthy patients between the ages of 18-29 years with asymptomatic impacted lower third molars at time of extraction. Patients were randomly divided into two groups; 0.8% HA was applied to the HA group (n=22) while nothing was applied in the control group (n=22). Patients' pain levels were assessed at the first, third and seventh postoperative days and the pain scored on a numerical rating scale (NRS). **Results**: Pain score, facial swelling and trismus were highest on the first postoperative day and decreased gradually in both Control and HA group on the 3rd and 7th postoperative days. There were statistically significant differences in Pain scores between Control and HA groups on the three postoperative days. However, for swelling the difference between the two groups was significant just on the 1st and 3rd postoperative days. There were no significant differences between the two groups regarding trismus over the days of review. **Conclusions**: The results of this study showed that after surgical removal of impacted teeth HA can produce an analgesic effect and therefore it may have a clinical benefit in reducing postoperative pain and facial swelling.

Keywords: hyaluronic acid, pain, trismus, swelling, third molar impaction.

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## INTRODUCTION

Impaction of third molar is a prevalent state associated with different degrees of difficulties of removal operation and danger of complications that affects postoperative wellness of patients in the first few days following surgical removal [1]. The major complications that occur after surgical removal of mandibular third molars are delayed wound healing, inflammation, facial swelling, discomfort, and trismus [2]. Several studies were focused on reducing the complications after third molar surgery [3, 4]. Some of these studies focused on use of medical drugs. For example researches have manifested on a useful influence of the use of nonsteroidal and steroidal anti-inflammatory drugs after operation in minimizing oedema and trismus manifestations [4, 5]. Nevertheless, these medicines can cause considerable side effects systematically and are contraindicated in some patients due to their potential side effects such as adrenal gland dysfunction, retarded healing of wound and increased susceptibility to infection [6, 7]. Such concerns inspired researchers to investigate or research the use of other biomaterials such as hyaluronic acid (HA). Hyaluronic acid or hyaluronan is a glycosaminoglygan of high molecular weight (50-8000 kilodalton). Its chemical architecture consists of repeated non-sulfated of N- acetylglucosamine and D-glucuronic acid disaccharide units [8, 9]. It's one of components of extracellular matrix of synovial fluid, connective tissue, embryonic mesenchyme, skin, vitreous humor, and mineralized hard tissue like cementum and bone. It has diverse physiological and structural functions, including cellular and extracellular interactions, interactions with growth factors, in addition to tissue lubrication and homeostasis control,[10]. It has a key role in the procedure of morphogenesis and cure of wounds [11, 12]. It's thought to stimulate cell migration, adhesion, reproduction and differentiation leading to tissue reconstruction, reepithelialization of epidermis, and bone formation [13-16] . Hyaluronic acid is safe to use in medicine, because it is biocompatible and non-toxic [17, 18].

Hyaluronic acid used widely in the field of orthopedics, dermatology, and pharmacology for the treatment of inflammatory process of osteoarthritis [19], rheumatoid arthritis [20], and radio-epithelitis [21]. Rabasseda [22] reviewed the use of HA for the treatment of inflammatory conditions of the knee and temporomandibular joint, which has led to study and for the first time in field of dentistry of its topical application in the treatment of periodontal diseases. Hyaluronic acid has shown anti-inflammatory, anti-edematous and antibacterial effects [23].

The available studies provide insufficient information to assess the efficacy of the usage of HA after dental surgeries. Hence, the goal

of this clinical experiment was to investigate whether there is any beneficial value of local application of 0.8% hyaluronic acid gel (Gengigel ® Prof Syringes, Ricerfarma, Italy) on the postoperative swelling, pain, and trismus.

## MATERIALS AND METHODS

**Patient selection:**

The research is a randomized, controlled, prospective study conducted in dental hospital at Erbil, Iraq. Forty-four patients who aged between 18-29 years old were enrolled in the study and provided a signed statement of informed consent. The patients had either (vertical, mesioangular, distoangular, and horizontal) type of impaction according to Winters classification, with class II level B according to Bell and Gregory classification of impaction with partial or total bone cover. Patients with no systemic disease or allergy, or bleeding problems were included in the study.

The following patients were excluded from the study: those with acute infection such as pericoronitis and/or pain on the tooth site before extraction, those who were taking drugs such as corticosteroids and contraceptives that affect the postsurgical amount of swelling on the face and healing process, those who had undergone antibiotic or steroidal /non-steroidal analgesics during the preceding 15 days before surgery, those who were pregnant or nursing a baby, and operations which take time more than one hour.

**Study design:**

In order to minimize differences, all patients were operated by the same oral surgeon with standardized surgical technique and equipment. Patients were divided randomly into 2 groups: study group (22 patients) hyaluronic acid gel locally applied into the socket; control group (22 patients) nothing was applied into the socket.

**Statistical analysis:**

The statistical analysis was carried out using Social Sciences Statistics System version 26 (SPSS). Descriptive statistics including mean values and standard deviations were determined for all variables in the HA and Control groups. Data were initially tested for normally distribution using the Shapiro–Wilk test. The kruskal Wallis test and Friedman test were used for the comparison of mean pain scores. Additionally, Mann-Whitney U test and repeated measures test were used to assess statistical differences between groups for non-normally distributed variables (swelling and trismus). For all tests, a probability of less than 0.05 for the 95% confidence level was selected as the level of significance.

**Surgical procedure:**

Routine regional anesthesia procedure was applied including inferior alveolar nerve block together with buccal infiltration anesthesia by two cartridges of lidocaine hydrochloride 2% solution with 1:80.000 epinephrine (septodont−France) . After incision, mucoperiosteal soft tissue flap was reflected laterally and bone osteotomy with straight handpiece bur coupled with copious saline irrigation was done, Sometimes according to type of tooth angulation sectioning and separation of tooth crown was done. After tooth extraction sharp edges were smoothed with bone file, then socket was irrigated and debrided mechanically. In the study group 1 ml of 0.8% hyaluronic acid gel (Gengigel ® Prof Syringes, Ricerfarma) was applied in the postextraction socket, on contrary nothing was applied in the control group. At last steps the flap was repositioned and sutured with silk 3/0. A compressing pack of gauze was applied to the operation site to aid in hemostasis. All patients were instructed to eat soft and cold diet for the first 24 hour after operation with no ice pack application and instructed not to gargle for the first postoperative day. All patients prescribed Amoclan 1 gm twice daily for 5 days and paracetamol 3 times daily for 2 postoperative days.

**Postoperative evaluation:**

Postoperative assessment of facial swelling was taken with a measuring tape before surgery as a base line and at 1st, 3rd, and 7th postoperative days. Linear measurements were made between anatomical angle of mandible (AAM) to: 1-Tragus (T), 2-Lateral canthus of eye (CE), 3-Lateral border of ala of nose (AN), 4-Corner of mouth (CM), and 5-Soft tissue pogonion (P). Five different measurements were recorded [24]. All measurements were taken before surgery and on the 1st, 3rd, and 7th days following operation (Figure 1).

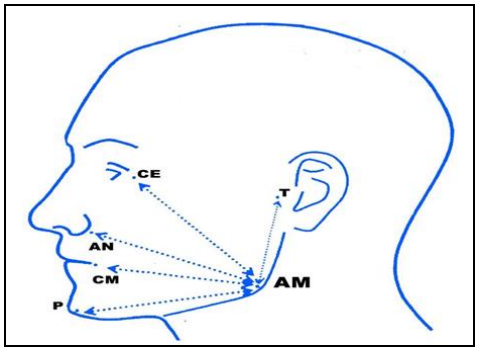


Figure (1): The measurement points AAM: anatomical angle of mandible, T: Tragus, CE: Lateral corner of the eye, AN: Lateral border of ala of nasi, CM: Corner of the mouth, P: Soft tissue pogonion.

Measuring postoperative pain was recorded using numerical rating scale (NRS) which has 10 units' number line marked by degrees. Score of 0 indicated "absence of pain" and score of 10 indicated "excessive pain". The intermediate scores have been indicated "moderate pain". The patients educated about the meaning of scores at beginning then they asked to express their intensity of pain by placing a mark on the scale. Pain measurement was done on 1st, 3rd, and 7th postoperative days. Pre and postoperative degree of mouth openings were used to determine the degree of trismus. Maximal interincisal mouth opening was measured using electronic digital caliper. Postoperative measurement was done on 1st, 3rd, and 7th days.

## RESULTS

A total of 44 patients (16 males: 28 females) were included in this study. The age range was 18-29 years; median age was 25 years, and mean ± SD age was 24.7±2.9. Patients distributed equally and without bias into two groups: Control and HA. Patients were recalled on the postoperative 1st, 3rd, and 7th days after surgical extraction of impacted lower third molar to evaluate the pain, facial swelling and trismus. Pain scores on NRS are shown in Table (1).

**Table (1):** Pain scores on NRS for postoperative 1st, 3rd, and 7th days for in Control and HA groups

| Group | Postoperative pain score | | | Friedman test |
|---|---|---|---|---|
| | 1st Day Mean ± SD | 3rd Day Mean ± SD | 7th Day Mean ± SD | |
| Control | 6.95±2.68 | 3.68±2.42 | 1.68±2.30 | Chi-Square= 24.072 p= 0.000* |
| HA | 3.14±1.83 | 1.73±1.67 | 0.55±1.26 | Chi-Square= 37.507 p= 0.000* |
| Kruskal-Wallis test (H) | H= 20.852 p= 0.000* | H= 7.552 p= 0.006* | H= 4.074 p= 0.044* | |

*Statistically significant at confidence level 95%

On the 1st, 3rd, and 7th postoperative days, NRS scores were significantly decreased in both groups over postoperative days with p value (P = 0.000). However, the HA group showed statistically significantly less pain compared to control group on the first, third and seventh days with p values equal to (0.000, 0.006 and 0.044) respectively. Assessment of facial swelling for each patient on each postoperative day was determined by finding the mean differences between postoperative and preoperative measurements. The results are presented in Table (2).

**Table (2):** Facial swelling on postoperative 1st, 3rd, and 7th days in Control and HA groups

| Group | Facial swelling (postoperative-preoperative) in mm | | | Repeated Measures test |
|---|---|---|---|---|
| | 1st Day Mean ± SD | 3rd Day Mean ± SD | 7th Day Mean ± SD | |
| Control | 5.85±1.38 | 3.58±1.25 | 0.73±0.61 | F= 170.514 p= 0.000* |
| HA | 4.52±1.86 | 2.33±1.06 | 0.50±0.71 | F= 117.983 p= 0.000* |
| Mann Whitney test (U) | U= 118.0 p= 0.004* | U= 108.0 p= 0.002* | U= 171.5 p= 0.089 | |

*Statistically significant at confidence level 95%

The maximum swelling in control and HA groups were found in the 1st postoperative day with mean swelling equal to 5.85 and 4.52 respectively, however, the level of swelling was significantly decreasing over the days of review with (p= 0.00), and on the 7th postoperative day, the swelling was returned approximately to normal levels with values less than 1mm. On the other hand, the HA patients showed a significantly less facial swelling than control group on the 1st and 3rd postoperative days with p values equal to (0.004 and 0.002) respectively. Maximum mouth opening (interincisal distance) was recorded in every recall appointment. For each patient, the interincisal opening on each postoperative day was found by calculating the difference between preoperative and postoperative measurements of the interincisal opening. Table (3) displays the outcomes in each group, it is clearly shown that the degree of mouth opening in both control and HA groups were significantly decreased over the postoperative days (1st, 3rd and 7th) with (P= 0.000). However, there were no significant differences in changes in interincisal opening values between control and HA groups with p values equal to (0.27, 0.139, and 0.577) for the first, third and seventh postoperative days respectively.

**Table (3):** Trismus on postoperative 1st, 3rd, and 7th days in Control and HA groups

| Group | Trismus (Preoperative-Postoperative) in mm | | | Repeated Measures test |
|---|---|---|---|---|
| | 1st Day Mean ± SD | 3rd Day Mean ± SD | 7th Day Mean ± SD | |
| Control | 12.55±7.05 | 9.00±6.46 | 3.20±5.22 | F= 24.666 p= 0.000* |
| HA | 10.19±5.95 | 6.5±5.69 | 1.89±2.23 | F= 41.501 p= 0.000* |
| Mann Whitney test (U) | U= 195 p= 0.27 | U= 179 p= 0.139 | U= 218.5 p= 0.577 | |

*Statistically significant at confidence level 95%

## DISCUSSION

Acute inflammatory reactions after surgical extraction of mandibular third molar that lead to common complications including pain, swelling, and trismus remain until today the most prevalent event in oral and maxillofacial surgery. It's clearly known that postoperative inflammation reaches its maximum at 1-2 days after surgical procedure; it begins to subside on the 3rd or 4th day and completely resolved by the end of first week[25], therefore many efforts try to minimize these complications which affects fineness of patients for the first few days after extraction [2, 3, 26, 27]. It is vital to eliminate related factors affecting the preliminary phases of wound recovery [28].

Many studies in the literature reported that HA reduces symptoms of pain for the patients with osteoarthritis. Das et al.[29] Suggested that HA has a benefit for patients with osteoarthritis knee pain in reducing symptoms as much as oral nonsteroidal anti-inflammatory drugs or topical injection of steroid. Gotoh et al.[30] reported that high molecular weight HA has an analgesic effect by covering bradykinin receptors in synovial tissue. Lee et al[31] claimed that HA gel applied topically on oral ulcers improved in subjective and objective ways the ulcers numerically, time of healing, and pain VAS score.

On the contrary, Yilmaz et al.[32]showed that local administration of HA into the extraction socket may provide a decrease in pain which is not significant. This result may be attributed into several limitations including individual variation in pain threshold and small sample size pilot study conducted among 25 patients. In supporting to this study, Koray et al. [33] confirmed that HA spray decreased facial swelling on the 2nd postoperative day after third molar removal without affecting scores of VAS for pain. However, the operator and patients were blinded to the distribution of the HA spray in their report, but the follow up reviewer was not. Besides that, the treatment procedure was different because the percentage of HA was lower and investigators utilized the HA spray on the wound superficially.

There are studies reporting that postoperative swelling levels differ depending on the age and gender of the patients, and on the operating time and surgical difficulty of the impacted teeth[34, 35]. In this study HA significantly reduced facial swelling.

Longinitti et al.[36] observed that the anti-edematous effects of HA could be related to its osmotic buffering ability. Deleme and Hammed [37] reported that HA (kin care) gel was efficient as diclofenac sodium tablet 50 mg (voltaren) in reducing pain and swelling. However, HA gel can be used as an adjuvant therapy in medically compromised patients for reducing post-surgical discomforts. Nelson et al.[38] suggested that HA reduces not only pain

but also inflammation, he examined the effectiveness of oral HA administration through spectral serum and joint fluid examination in patients with knee osteoarthritis, and noticed significant decreases in proinflammatory cytokines including tumor necrosis factor alpha, IL-1β, IL-1α, IL-6, interferon, macrophage colony stimulating factor, leptin and bradykinin. Gocmen et al.[39]stated that 0.8% HA showed anti-inflammatory effect following surgery.

In comparison, Gokhan et al.[40]mentioned that gel of HA extended time of bleeding and increased early postoperative odema between periods of (2-3 days) after removal of vertical half impacted lower third molars. This is may be due to HA at high concentration inhibits platelet aggregation and adhesion.

In this study, trismus decreased postoperatively but it was not statistically significant between the HA group and the control group. Bayoumi et al.[41]demonstrated that occurring of trismus did not influenced by cross linked HA gel on the second and fourth days after operation. However, it resulted in a return to baseline on the seventh day after operation in the study group but not the control group.

## CONCLUSIONS

HA can be a good choice for decreasing pain and swelling caused by acute inflammation after surgical extraction of mandibular third molar and can be recommended for the patients postoperative comfort.

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