Hyaluronic acid addition to collagen reduces the trismus and swelling after surgical extraction of impacted lower third molars: A Split-Mouth, randomized controlled study

Moemeneh Kokash
Damascus University

Khaldoon Darwich
Damascus University

Jawdat Ataya (dr.jawdat.ataya@gmail.com)
Damascus University

Research Article

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Abstract

Background: Removal of impacted third molars is associated with postoperative complications such as pain, swelling, ecchymosis, trismus, infection, and hematoma. Thus, contemporary surgery aims to reduce complications by applying collagen or hyaluronic acid in the socket after extracting the impacted mandibular third molars.

This study aimed to study the efficacy of Hyaluronic Acid (HA) addition to collagen, compared to collagen application alone, on the magnitude of swelling and trismus following impacted mandibular third molar surgery.

Methods: About 20 patients underwent impacted bilateral lower third molars surgery (n = 40). Opaque envelopes carried out randomization; two materials were applied topically in the socket collagen alone or with hyaluronic. The post-operative mouth-opening limitation and swelling rate were assessed on the third and seventh days after the extraction.

Results: The mean age was 22.7 ± 3.079 years (75% female, 25% male). A statistically significant difference was detected for the trismus between the two treatment groups on the seventh (p= 0.005) but the difference between the groups was not statistically significant on the third day (p= 0.061). The swelling scores of the hyaluronic acid addition group were significantly lesser than those of the collagen alone group on the third and the seventh days (p<0.05) except for lateral canthus to angulus mandibulae on the third day (p= 0.133).

Conclusion: Adding hyaluronic acid to collagen could effectively reduce the severity of facial swelling and trismus following surgical extraction of impacted lower third molars.

Trial registration: The trial was registered in the Isrctn.com database (06/07/2021, ISRCTN16820104).

Background

Mandibular third molars are the most common impaction teeth, which is extracted for several indications like unrestorable caries, pulpal and periapical pathology, fracture of the tooth and cyst development (1).

Removal of impacted third molars is associated with postoperative complications such as pain, swelling, ecchymosis, trismus, infection, and hematoma (2). Thus, contemporary surgery aims to reduce complications by applying collagen or hyaluronic acid in the socket after extracting the impacted mandibular third molars (2).

Collagen favours the migration of osteoblasts, stabilizing blood clots, hemostasis, and aids in wound protection and bone reconstruction because it acts as an extracellular matrix (3). This absorbable material has the chemotactic ability to attract fibroblasts, therefore enhancing primary wound coverage and augmenting flap thickness by providing a collagenous scaffold (4). This abovesaid benefits of collagen increase revascularization and fibroplastic activity that promotes wound healing (5).
Glycosaminoglycans (GAGs) are the main components of the extracellular matrix (ECM), Hyaluronic acid (HA) is a member of these large family (6).

HA is also called hyaluronan or hyaluronate, which is naturally found in many tissues such as skin, synovial fluid, cartilage, tendons, eyes, and most body fluids (7, 8).

Hyaluronic acid (HA) facilitates wound healing by inducing beneficial early granulation tissue formation, inhibiting destructive inflammation during the healing phase, and promoting re-epithelialization and angiogenesis (9). HA can be safely used as an anti-inflammatory agent (10). This biocompatible molecular appears to benefit from managing swelling and trismus and the inflammatory reaction following third molar extraction surgery (11). This study aimed to study the efficacy of HA addition to collagen, compared to collagen application alone, on the magnitude of swelling and trismus following impacted mandibular third molar surgery.

Methods

Study Design

A single-blind, single-centre, randomized clinical trial using a split-mouth design was conducted on patients who presented at the Department of Oral and Maxillofacial Surgery at Damascus University between February 2020 and March 2022. Split-mouth design was chosen to reduce bias coming from any single patient that may have affected the reliability of the study. The study followed the Declaration of Helsinki for ethical principles for medical research (12). The research protocol was reviewed, and ethical approval was obtained by the Research Ethics Committee of Damascus University (Registration No. 2020-711). The trial was registered in the Isrctn.com database (06/07/2021, ISRCTN16820104).

Participants

The inclusion criteria were healthy patients (American Society of Anesthesiologists [ASA] classifications I or II) between (18-25 years) of both genders, bilateral impacted mandibular third molars having the same Winter classification (impacted angulation).

Patients with a pathological condition in the region of surgery, pregnant, lactating women, smokers, allergic reaction to drug prescription or substances of study and patients who had a more-than-10-minute difference between the first and second surgical times were excluded.

Sample Size Calculation

The sample size was calculated according to the program (G Power 3.1.7V.), considering that the significance level was 5%, the study power was 90%, the effect size 0.6. Twenty teeth in each group were deemed sufficient, and the total sample size was 40.
Randomization and Interventions

After obtaining written informed consent, an opaque envelop randomization method was employed to assign the hyaluronic acid addition to collagen as the case side or collagen alone as a control side when applied topically on the trismus and swelling after mandibular third molar surgery. The patients and the statistician were blinded to the type of applied material.

Under local anaesthesia, the same surgeon performed surgical extraction at separate appointments, 14 days (± three days) apart, and a standardized technique was used. The same patient was randomly assigned to two groups: the CO (Collagen group, 900 mg), involving the application of collagen alone in the socket before suture; the CO and HA (Collagen 900 mg and hyaluronic acid 2% group, 1 ml), involving HA addition to collagen. Each of the two study groups included 20 molars. All patients in the two study groups were prescribed antibiotics (Augmentin Tab, 1000 mg, twice/day), oral analgesic (paracetamol 500 mg, as needed) and mouthwash (0.12% chlorhexidine solution, twice/day) for seven days after surgery.

Study Procedures

The initial preoperative parameter of maximum mouth opening (distance between the upper right and lower right central incisors) was recorded using a Vernier calliper (Rolson 50919 150mm Vernier Caliper), and linear distances between facial landmarks (lateral canthus to gonion; tragus to labial commissure; tragus to pogonion) were measured using a flexible tape-measure graduated in millimetres, which was placed in contact with the skin. Postoperative data were collected from all patients after 3 and 7 days. Facial swelling and trismus were measured twice, and the two measurements were averaged to calculate the final value. The clinical evaluations on the third and seventh days were carried out by a researcher who did not perform the surgical procedure. The clinical evaluation on the third and seventh days of the patients was carried out by another blinded researcher who had not performed the surgical procedure.

Statistical Analysis

The normality of the distributions were tested using the Shapiro-Wilk test. The independent T-test was used to test the difference between the two groups if the variables were distributed normally. When the hypothesis of the normal distribution of the variable was rejected, the Mann-Whitney test was used to study the difference between the two groups, as it was used to test the difference in variables with ordinal type. The significance level was set as α=0.05, and the power was 0.90.

Results

Twenty patients were included in this prospective study after screening 22 patients. Most participants were females (n = 15, 75%), with age ranging from 18 to 25 years (mean: 22.7 ± 3.079). A flowchart of the
progress through enrollment, allocation, follow-up and data analysis phases is shown in (Fig. 1).

The study participants’ demographic information and surgical characteristics were summarized in table (1).

<p>| Table (1): Comparison of patient and surgical characteristics between 2 groups |
|-----------------------------------------------|-------------------|-------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Collagen and hyaluronic acid group</th>
<th>collagen group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 20</strong></td>
<td><strong>n = 20</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td>22.7 (3.079)</td>
<td>22.7 (3.079)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td><strong>Surgical side</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Left</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td><strong>Winter classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mesioangular</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Horizontal</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Extraction technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevator alone</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Osteotomy</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Osteotomy + Tooth sectioning</td>
<td></td>
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</tr>
</tbody>
</table>

\(^a\) Test used: Student’s t-test

\(^b\) Test used: Chi-square

The rate of trismus was calculated by dividing the preoperative and postoperative difference by the preoperative value and multiplying that by 100. The rate of facial swelling was calculated by the same method of trismus for each line.

Mouth opening showed a statistically significant difference between the groups on day seventh (p = 0.005). Although the trismus score on the third day was generally slightly better in the collagen and hyaluronic acid group, the differences between groups were not statistically significant (p = 0.061).
Table (2) shows comparison of mouth opening and Surgery time between two groups (Collagen group, Collagen and hyaluronic acid group)

<table>
<thead>
<tr>
<th></th>
<th>Collagen and hyaluronic acid group</th>
<th>collagen group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (STD)</td>
<td>Mean (STD)</td>
<td></td>
</tr>
<tr>
<td>Mouth opening1 (%)</td>
<td>44.03 (12.852)</td>
<td>52.14 (13.748)</td>
<td>0.061</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth opening1 (%)</td>
<td>19.22 (12.896)</td>
<td>32.45 (15.307)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery time2 (min)</td>
<td>21.75 (7.993)</td>
<td>23.1 (8.188)</td>
<td>0.558</td>
</tr>
</tbody>
</table>

1 Mouth opening was measured by taking the maximum distance between the maxillary and mandibular central incisors using a Vernier caliper. Mouth opening was considered as the percentage difference between the two measurements.

2 Time of surgery was recorded in minutes, from the time of initial incision to the time of final suture.

*: Significant, p < 0.05

The test used: Mann-Whitney

On the third day, the swelling values were the highest in all groups, showing a gradual decrease to the seventh day. On the third day, all oedema measurements (TPO, TCO, and ACA) showed significant differences between groups except lateral canthus to gonion. Table (3) shows comparison of facial swelling between two groups (Collagen group, Collagen and hyaluronic acid group)
Table (3) Comparison of facial swelling (%).

<table>
<thead>
<tr>
<th>Objective Measurements¹</th>
<th>Collagen and hyaluronic acid group</th>
<th>collagen group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (STD)</td>
<td>Mean (STD)</td>
<td></td>
</tr>
<tr>
<td>lateral canthus to angulus mandibulae (%) ACA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>4.17(2.831)</td>
<td>5.75(3.737)</td>
<td>0.133</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.085(1.309)</td>
<td>2.49(2.097)</td>
<td>0.012*</td>
</tr>
<tr>
<td>tragus to labial commissure (%) TCO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>5.665(3.221)</td>
<td>8.725(4.717)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.42(1.959)</td>
<td>4.265(4.283)</td>
<td>0.001*</td>
</tr>
<tr>
<td>tragus to pogonion (%) TPO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>3.41(2.45)</td>
<td>6.75(4.86)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Day 7</td>
<td>0.665(0.842)</td>
<td>2.975(3.86)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

¹ On the third and seventh days, distances between facial landmarks (lateral canthus to gonion; tragus to labial commissure; tragus to pogonion) were measured twice using a flexible tape-measure graduated in millimetres, which was placed in contact with the skin. The rate of facial swelling for each line was calculated by dividing the preoperative and postoperative difference by the preoperative value and multiplying that by 100.

*: Significant, p < 0.05

The test used: Mann-Whitney

Discussion

Mandibular third molars are the most prevalent impacted teeth, so their surgical extraction is one of the most common procedures in oral and maxillofacial surgery (13, 14).

However, the surgeon must understand that surgical extraction of the third molar can lead to complications such as alveolar osteitis, paraesthesia of the inferior alveolar or lingual nerves, trismus, pain and swelling (15). All these complications affect the patients’ quality of life (14).

Evaluating the efficacy of any additional or different procedure on morbidity after the surgery of the impacted 3M, swelling and trismus with the presence of complications have been measured. The present study aimed to reveal the effects of HA addition to collagen in terms of these variables.

Inflammatory exudate within facial tissues, hematoma collection, or both may cause facial swelling (16, 17). However, an increased swelling after the third day may be related to infection rather than
postsurgical swelling (18). Surgical extraction of the mandibular third molar is like any traumatic surgery followed by a normal physiological process of facial swelling, which starts immediately after removing the third molar; it reaches a peak value of two to three days postoperatively and resolves by seven days (19, 20).

The literature offers several studies on hyaluronic acid's remarkable attributes in terms of biocompatibility, biodegradability, and low cost (21); however, no study assesses these effects when combined with another material after surgical extractions.

This study shows lower values of swelling rates in all lines on the third and seventh days in the hyaluronic acid addition group than the application of collagen alone except lateral canthus to angulus mandibulae on the third day; the difference was not significant. These three lines in our research are the most commonly reported method in the literature measurement for facial swelling measure techniques (19).

Nariman et al. concluded that 0.8% HA application in the post-extraction sockets of third molars appears to reduce swelling scores which were evaluated daily in the first week by a visual analogue scale (VAS) with a statistically significant difference on day one, day three and day four but in the other days, the scores were less in HA group, but the differences were not significant (21).

In contrast with the present study results, HA usage was associated with more swelling (22). Gocmen et al. observed that the third-day outcomes of orotragus and mentotragus measurements showed more swelling in the HA group (p < 0.05). However, the swelling was not significantly different at 1 hour and the seventh day (22). Gocmen et al. stated that the HA group showed less leucocyte infiltration and more angiogenesis than the control group at one week, and their results confirm the hypothesis that the HA has an anti-inflammatory effect following M3 extraction (23).

Afat et al. used the same three lines in the present study to measure postoperative oedema, but in their study, they compared three groups: the control group, Leukocyte- and platelet-rich fibrin (L-PRF) group and L-PRF–plus–HA group were evaluated on the second and seventh day after surgery. Their results imply that L-PRF, particularly when combined with HA, can be used to minimize postoperative oedema after mandibular third molar surgery. Their results showed significant differences between groups in all measurements except tragus to labial commissure on the seventh day (10).

There were no significant differences on the third postoperative day in the amount of mouth opening restriction, which is a trismus indicator, while significant differences were observed on the seventh postoperative day.

These results are similar to Muñoz-Cámara et al., who conducted a double-blind, randomized controlled clinical trial of 90 patients with one asymptomatic MITM, applying a bioadhesive gel of 0.2% CHL or 1% HA at 60 MITM sites equally, leaving the other 30 as control sites. These authors recorded that the most frequent complication observed in their trial was postoperative trismus, with more cases in the control
group (6.67%) than in the test groups (0.2% CHL and 1% HA: 0%) on the seventh day, although statistically significant differences were not found (24).

In Guazzo et al. study, patients’ mouth opening measurements had returned to presurgery level by the 14th day with no significant differences between the two groups (control, amino acid and sodium hyaluronate) (25).

Gocmen et al. reported that there was no statistically significant between local injection of HA at 0.8% after third molar extraction on mouth opening limited when compared to pre-op, 1 hour, the third day and seventh day (22). Their results are similar to Afat et al., who evaluated the effects of leukocyte- and platelet-rich fibrin (L-PRF) alone and combined with a hyaluronic acid (HA) sponge; there was no significant difference among groups in trismus (10).

Collagen has been widely used in oral and maxillofacial surgery because it has various benefits, including clot stabilization, wound stabilization, and hemostasis. In addition, it has a chemotactic ability to attract fibroblasts, providing a collagenous scaffold for augmenting flap thickness (3).

Tsai et al. observed a significantly lower frequency of mouth-opening limitation at the follow-up week 1 in patients in the collagen group (45%) than in patients in the control group (90%, P = 0.007) (26).

In Kilinc et al. study, they compared secondary closure, primary closure and collagen membrane-based primary closure. In terms of trismus, they found a statistically significant difference between the three groups on the third day (16). On day two, the collagen membrane group had a lower statistically significant mouth opening rate than secondary closure (p = 0.029) and primary closure (p = 0.000). In terms of facial swelling measured in the subjective and objective method, Kilinc et al. found a statistically significant difference between the three groups on the second and seventh days (p < 0.05). However, the maximum swelling record was in the collagen membrane-based primary closure group compared to secondary and primary closure groups (16).

Kim et al. compared the effectiveness of absorbable collagen sponge insertion in tooth extraction sites for socket healing of the impacted mandibular third molar. However, the facial swelling ratio on the collagen sponge insertion side was lower at one and two weeks, but the difference between the two groups was not significant. In addition, mouth maximum opening showed a decrease in the first week, then gradually increased until 14-weeks recovering to opening close to that to pre-operative (3).

The limitations of the study are no laboratory or histological examinations.

**Conclusion**

Adding hyaluronic acid to collagen could effectively reduce the severity of facial swelling and trismus following surgical extraction of impacted lower third molars.
Abbreviations
Hyaluronic acid (HA), Leukocyte- and Platelet-Rich Fibrin (L-PRF)

Declarations

Ethics approval and consent to participate
The Ethical Committee approved this study in the Faculty of Dentistry at Damascus University, Syria (Registration No. 2020-711). All our methods were carried out in accordance with relevant guidelines and regulations.

Consent to Publish
The informed consent to participate and the consent to publish was obtained.

Availability of Data and Materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
Not applicable

Funding
There has been no funding for this study. However, this study supported by Damascus University.

Authors' contributions
MK and KD contributed to conception and design of the study, collecting and data analysis and Interpretation. MK and JA contributed to writing and drafting the manuscript and revision the final draft. All authors read and approved the final manuscript.

Acknowledgements
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References


Figures
Figure 1
Flow diagram of stages of the split-mouth, randomized, clinical study.