Subject Area:

Evaluation of pain after third molar extraction surgery using hyaluronic acid versus ozone gel as socket preservatives

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Evaluation of Pain After Third Molar Extraction Surgery Using Hyaluronic Acid Versus Ozone Gel as Socket Preservatives

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Abstract

Objectives: This study aimed to evaluate pain following surgical extraction of the impacted mandibular third molar with inward fragmentation technique in combination with the use of ozone gel versus hyaluronic acid (HA) for socket preservation.

Patients and methods: This study involved 45 patients who were randomly divided into three equal groups after extraction of their impacted mandibular third molars, as follows: group I: ozone gel was placed in the socket, group II: HA gel was placed in the socket, while in group III (control group): normal healing was allowed without placing any material in the socket. All patients were assessed clinically on the 2nd and 7th days postoperatively regarding pain (using a modified visual analog scale).

Results: Regarding pain, no statistically significant difference was recorded on the 2nd day among the groups. On the 7th day postoperatively, there was a statistically significant difference between HA and control group (P ≤ 0.001) as well as between ozone gel and HA (P = 0.001), but there was no statistically significant difference between ozone and control group (P = 0.827).

Conclusion: The use of the HA gel after impacted mandibular third molar surgery can yield better results in controlling pain. Ozone gel showed no effect on pain.

Keywords: Hyaluronic acid gel, Mandibular third molar impaction, Ozone gel, Pain

Introduction

Extraction of impacted third molars is one of the most frequent interventions in oral surgery.1,2 Despite being a common procedure, surgical removal of the mandibular third molars can result in a variety of intra- and postoperative complications, ranging from minor swelling and pain to serious bone defects that, in rare situations, could result in fractures of the mandible.3,4

To lessen intra- and postoperative complications, there have been a lot of discussions recently on the use of minimally invasive surgical techniques.3,4 According to reports, the inward fragmentation technique (IFT) using an occlusal approach provides low-traumatic access to partially erupted mandibular third molars.6,7 As a result, for patients who have had surgery on their mandibular third molars, the inward fragmentation technique was suggested due to the simplicity of tooth sectioning, decreased pain and edema, decreased alveolar bone resorption, and absence of lingual nerve sensory impairments.1,8

For preserving extraction sockets, several approaches have been suggested, such as atraumatic tooth extraction, immediate implant placement, grafting materials with or without barrier membrane, and also barrier membrane alone can be used without grafting materials.9,10

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Ozone gas is a triatomic molecule with three oxygen atoms that is thermodynamically highly unstable and decomposes into pure oxygen with a half-life of 40 min at 20 °C. Ozone therapy is regarded as a current, nonmedicated alternative treatment with proven antibacterial and anti-inflammatory effects.\(^{11}\) It can influence both cellular and humoral immunity by activating macrophages and promoting the manufacture of physiologically active compounds that lessen inflammation and enhance wound healing.\(^{12}\)

Ozone is currently available and applied in gaseous, aqueous, or gel forms.\(^{13}\) The ozone gas dissolves in plant oils, such as olive oil, to create ozonized olive oil gel. This gel has antimicrobial properties that improve oral cavity lesion healing.\(^{14}\)

Hyaluronic acid (HA) has been widely utilized in dentistry due to its vital physiological effects on the gingiva, alveolar bone, and periodontal connective tissue.\(^{15,16}\) According to research, HA may help treat edema, trismus,\(^{17}\) and the inflammatory response that follows third molar extraction surgery.\(^{18,19}\) This study aimed to evaluate pain following surgical extraction of impacted mandibular third molars with inward fragmentation technique and applying ozone gel versus HA for socket preservation.

Patients and methods

This study involved 45 patients requiring mandibular third molar extraction. All patients were chosen from the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Mansoura University. This study was conducted after the approval of the Ethical Committee of Dental Research at the Faculty of Dentistry, Mansoura University (code number A18060421). All patients were asked to sign an informed written consent about the procedure steps of the study, and they had the right to quit the study at any time.

Patients' selection was done according to the inclusion criteria: patients aged between 18 and 40 years of any sex with impacted mandibular third molars were classified as vertical or mesial angulations according to Winter's classification.\(^{20}\) Good oral hygiene and good general health without any contraindication for minor oral surgery and/or local anesthesia were included in the study and the exclusion criteria were patients with a history of chronic use of medications such as contraceptives or corticosteroids that can affect the postsurgical healing phase and degree of facial swelling, patients receiving treatment affecting blood coagulation, medically compromised patients with diseases that might affect passively the clinical procedure or result (only ASA-I and ASA-II patients were involved\(^{21}\)), individuals with periodontal disease or active infection, pregnant or lactating women, smoking patients, and uncooperative patients.

First, ozone gel was prepared by extra virgin olive oil that was ozonated by a Matra ozonator and air purifier (MATRA S.P.A via Zuccola, 7141015 NONANTOLA (MO) ITALY). Ozone gel is regarded as a natural material composed of a suspension of medical-grade ozone (a mixture of oxygen and ozone in the ratio of 0.25 % and 99.75 %, respectively) and unoxidized olive oil.\(^{22}\) Second, HA gel (Hyalubrix: FIDIA Farmaceutici S.P.A., Abano Terme, Padova, Italy) was used in the form of a prefilled syringe that contains HA sodium salt 1.5 % (15 mg/ml) solution of nonmodified HA obtained by biofermentation, possessing a molecular weight within the 1.5–2.0-MDa range.\(^{23}\)

All patients' data that were recorded included name, sex, age, phone number and detailed history consisting of chief complaint, and relevant past medical and dental histories. Clinical examination was performed both extraorally and intraorally by inspection and palpation. Panoramic radiography film was performed as a screening tool for the detection of the selected criteria in the region of operation. None of the patients received an antibiotic or an anti-inflammatory medication before surgery. The patients were prepared preoperatively by performing full mouth scaling and root planning whenever required, and were instructed to follow proper oral hygiene measurements.

All surgical procedures were done under local anesthesia by nerve block technique of the inferior alveolar nerve and lingual nerve in addition to long buccal infiltration using 2 % Mepivacaine (Alexandria Co. for Pharmaceuticals and Chemical Industries, Egypt) with 1 : 20 000 levonordrfin. In all patients, a sulcular incision was made from the second molar's mesiobuccal edge to its distal surface. Along the extension of the mandibular third molars, the incision line extended sagittal toward the mandibular ramus. On the lateral and lingual aspects of the site, the periosteum was not reflected. Independent of the tooth's angulation or level of impaction, crestal exposure of the mandibular third molars was only made on the occlusal aspect. To gain access to the pulp, the mandibular third molars were trepanned using Lindemann straight burs. The trepanation was carried out in a transverse orientation to create an internal cavity. To expose the furcation area, a transverse cut was made in the buccal and central portions of the crown, but not in the lingual aspect.
To provide a space for the inward fragmentation of the crown and to gain a general view of the internal morphology of the tooth and the furcation area, the pulp was opened widely using a round bur toward the level of the furcation. To guarantee complete separation of the roots before inward fragmentation and prevent lingual nerve injury, the use of large-diamond round burs in the furcation area was necessary.

The crown was removed by internal fragmentation. The mesial half was luxated, likewise internally, and then removed after the distal crown was removed by inward fracturing with an elevator. Most of the time, the adjacent root and the fragment of the mesial crown can be removed together. By removing the crown fragments, space was provided for viewing the furcation area and remaining roots. The remaining roots were detected when the crown was removed. Elevators were used to extract most of the roots.

In this stage, a single-blinded, randomized clinical trial (RCT) of the 45 patients was done by dividing the patients into three equal groups. Simple randomization was used by employing computer-generated random tables using program version 25 after entering sampling frames of all cases from which the sample was drawn.

Sample size calculation was based on the difference between the groups as regards visual analog scale (VAS) score after treatment retrieved from previous research by Yousef et al. Using G power program version 3.1.9.4 to calculate sample size based on effect size of 0.568, using two-tailed ANOVA test, $\alpha$ error = 0.05, power = 90.0%, and number of groups III, the total calculated sample size was 45.

The total calculated sample size was 15 in each group. In group I, ozone gel was placed in the socket after impacted mandibular third molar extraction (Fig. 1). Concerning group II, HA was placed in the socket after impacted mandibular third molar extraction (Fig. 2). Finally, in group III (control group), normal healing of the socket was allowed after impacted mandibular third molar extraction without placing any material in the socket.

Wound edges were carefully approximated with simple interrupted stitches using 3.0 silk-braided nonabsorbable sutures (Silk, GMS, Alexandria, Egypt).

All patients were asked to bite down gently but firmly on the gauze pack that had been placed over the surgical site, keeping it in place for nearly an hour. Patients were advised to repeat the procedure if bleeding persisted. After extraction, rinsing was not done for 24 h.

To help with swelling reduction, patients were instructed to apply extraoral cold packs for the side of surgery and an antiseptic mouthwash of 0.12% chlorhexidine hydrochloride (Hexitol Manufactured by Arab Drug Company (ADCO), Cairo, Egypt) for gentle rinsing after 24 h. For the first two days, only soft meals were allowed.

All patients got an oral antibiotic (Augmentin Amoxicillin 875 mg + Clavulanic Acid 125 mg; Manufactured by GlaxoSmithKline) twice daily for 4 days in addition to receiving analgesic (Paracetamol 500 mg: Manufactured by GlaxoSmithKline) two times daily for 4 days.

Clinical follow-up visits were scheduled on the second and seventh day after surgery; the sutures were removed on the 7th postoperative day.

A modified VAS with numeric pain ratings was used to measure postoperative pain on the 2nd and 7th days after surgery. The VAS had two extremes: the leftmost end, which represented no pain (score 0), and the rightmost end, which
represented the most severe pain (score 10). Patients graded their degree of pain. The pain rating scale goes from 0 (no pain), 1–3 (mild pain), 4–7 (moderate pain), and 8–10 (severe pain).

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). The normality of data was first tested with the Shapiro test. Qualitative data were described using numbers and percentages. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data and median (min–max) for nonparametric data. Four tests were used. First, Chi-square test was used to compare qualitative variables. Second, Fisher exact test was employed to compare qualitative variables when the expected count is less than 5. Third, Independent t-test was used to compare two quantitative variables (parametric). Fourth, Mann–Whitney test was employed to compare two quantitative variables (nonparametric). For all the mentioned statistical tests done, the threshold of significance was fixed at a 5 % level. The result was considered significant when $P \leq 0.05$. The smaller the $P$-value obtained, the more significant the result was.

Results

This study included 45 patients, 32 females and 13 males, having impacted mandibular third molars selected from the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Mansoura University. The patients' ages ranged from 18 to 45 years with a mean of 24.11 ± 4.51. No statistically significant difference was recorded among the study groups regarding age and sex as shown in Table 1. They were divided into three groups: group I: ozone gel ($n = 15$), group II: HA gel ($n = 15$), and group III: control ($n = 15$). There was no statistically significant difference regarding the side of the surgery among the same group as shown in Table 2.

The surgery was done on patients with impacted mandibular third molars classified as vertical or mesial angulations according to Winter's classification. There was no statistically significant difference regarding classification among the same group as shown in Table 2.

Pain assessment using VAS on the 2nd day: the means of VAS were 5.53 ± 1.35, 5.00 ± 1.06, and 6.00 ± 2.03 in ozone gel, HA, and control groups, respectively. There was no statistically significant difference between ozone gel and control ($P = 0.466$), HA gel and control ($P = 0.103$), as well as ozone gel and HA ($P = 0.242$).

As regards the 7th day, the means of swelling ratio were 2.43 ± 1.39, 0.80 ± 0.86, and 2.53 ± 1.06 in ozone gel, HA, and control groups, respectively. There was no statistically significant difference between ozone gel and control ($P = 0.827$), on the other side, there

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Ozone gel ($n = 15$)</th>
<th>Hyaluronic acid gel ($n = 15$)</th>
<th>Control ($n = 15$)</th>
<th>Test of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>24.87 ± 4.54</td>
<td>22.33 ± 2.82</td>
<td>25.13 ± 5.51</td>
<td>$t = 0.144$</td>
</tr>
<tr>
<td>Min–max</td>
<td>20–37</td>
<td>19–28</td>
<td>17–40</td>
<td>$t = 1.75$</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>$t = 1.83$</td>
</tr>
<tr>
<td>Male</td>
<td>5 (33.3 %)</td>
<td>5 (33.3 %)</td>
<td>3 (20.0 %)</td>
<td>FET</td>
</tr>
<tr>
<td>Female</td>
<td>10 (66.7 %)</td>
<td>10 (66.7 %)</td>
<td>12 (80.0 %)</td>
<td>FET</td>
</tr>
</tbody>
</table>

*Significant $P \leq 0.05$, P1: ozone gel versus control, P2: hyaluronic acid gel versus control, P3: ozone gel versus hyaluronic acid gel. FET, Fisher exact test; t, Independent t-test.

<table>
<thead>
<tr>
<th>Side</th>
<th>Ozone gel ($n = 15$)</th>
<th>Hyaluronic acid gel ($n = 15$)</th>
<th>Control ($n = 15$)</th>
<th>Test of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>9 (60.0 %)</td>
<td>5 (33.3 %)</td>
<td>8 (53.3 %)</td>
<td>$\chi^2 = 0.136$</td>
</tr>
<tr>
<td>Left</td>
<td>6 (40.0 %)</td>
<td>10 (66.7 %)</td>
<td>7 (46.7 %)</td>
<td>$\chi^2 = 1.22$</td>
</tr>
</tbody>
</table>

*Significant $P \leq 0.05$, P1: ozone gel versus control, P2: i-Hyaluronic acid gel versus control, P3: ozone gel versus hyaluronic acid gel. $\chi^2$, Chi-square test.
was a statistically significant difference between HA gel and control (P ≤ 0.001*), as well as ozone gel and HA (P = 0.001*) as shown in Table 3.

4. Discussion

Manipulation of both soft and hard tissues is required for the surgical removal of an impacted mandibular third molar, which results in postoperative complications. Careful preoperative planning and the integration of the surgical technique and surgical principles are necessary to reduce the risk of complications that could arise during surgery or later on during the healing process.

This study was designed to evaluate the effect of ozone gel versus HA on pain after impacted mandibular third molar extraction surgery using the inward fragmentation technique.

In this study, to reduce participant bias and factors, only patients who had vertical or mesial angulations, according to Winter's classification, were chosen for the study. To prevent discrepancies in the surgical techniques of various surgeons, which can affect the outcomes, the preoperative assessment and the surgical procedure were performed by the same operator. The participant age distributions were the same across all groups as well.

In this study, a technique, known as the IFT, has been developed in the management of all patients with third molar impactions for decreasing postoperative morbidity. Rajashri et al. noted fewer postoperative complications and improved quality of life when using IFT compared with conventional rotary instruments, as it decreased pain, edema, and alveolar bone height loss.

Additionally, Engelke et al. conducted a study of impacted mandibular third molar surgery and concluded that IFT reduced the incidence of major bone defects and allowed the preservation of greater than 90% of the buccal bone height adjacent to mandibular third molars. Furthermore, it might reduce postoperative morbidity without raising the risk of inferior alveolar nerve lesions.

In this study, both ozone and HA were used in a gel form that coincides with the studies conducted by Gupta et al. and Sechi et al. They reported that once the gel form is applied inside the surgical cavity, it becomes stable for a long time with sustained release of the active ingredient to be clinically effective. VAS was chosen for pain assessment in this study because it is simple and applicable with confirmed reliability and sensitivity following oral surgical procedures.

This study showed that there was a considerable decrease in pain in the HA group on the seventh postoperative day. These findings are in line with those of Bayoum et al. in their split-mouth study that included 14 patients, who experienced much less pain in the HA group than the control group on the 7th day after surgery. According to Deleme et al., the topical HA gel was just as effective as diclofenac tablets at reducing pain and swelling after the surgical removal of the impacted wisdom teeth. They suggested using HA instead of nonsteroidal anti-inflammatory drugs for patients with compromised health.

The analgesic effect of HA can be linked to its ability to block bradykinin receptors. In addition, it is claimed that there is a connection between the molecular weight of HA and its analgesic effects. Furthermore, HA reduces postoperative pain because it has an anti-inflammatory effect. In other words, HA inhibits tissue breakdown, blocks inflammatory cell-derived serine proteinases, and promotes healing by scavenging reactive oxygen species such as superoxide radicals (O$_2^-$) and hydroxyl radicals (OH$^-$).

Contrary to our study, Koray et al. who evaluated the efficacy of HA spray after third molar extraction, did not find any statistically significant difference in pain measured with VAS. This finding may be explained by the application of HA in a different form (0.2% HA spray).

In this study, the mean value of the VAS scale in the ozone group was less than that of the control group. The reason can be related to the possibility that the protective layer of ozone gel over the surgical site avoids wound contamination and covers

### Table 3. Visual Analog Scale among the studied groups.

<table>
<thead>
<tr>
<th>Visual Analog Scale</th>
<th>Ozone gel (n = 15)</th>
<th>Hyaluronic acid gel (n = 15)</th>
<th>Control (n = 15)</th>
<th>Test of significance ≤ ≤</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd day</td>
<td>5.53 ± 1.35</td>
<td>5.00 ± 1.06</td>
<td>6.00 ± 2.03</td>
<td>t = 0.739</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t = 1.68</td>
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<td></td>
<td></td>
<td></td>
<td>P = 0.466</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.242</td>
</tr>
<tr>
<td>7th day</td>
<td>2.43 ± 1.39</td>
<td>0.80 ± 0.86</td>
<td>2.53 ± 1.06</td>
<td>t = 0.221</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t = 4.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.827</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P ≤ 0.001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.001*</td>
</tr>
</tbody>
</table>

*Significant P ≤ 0.05, P1: ozone gel versus control, P2: t-Hyaluronic acid gel versus control, P3: ozone gel versus hyaluronic acid gel.

*Independent t-test.
the exposed nerve endings in the immediate post-operative period. Hence, it lowers pain when compared with the control groups. However, this finding did not record a statistically significant difference value in our study due to the limited sample size and the single application of the gel.

In contrast to our study, Yousef et al., 11 who observed the effectiveness of ozone gel following impacted mandibular third molar surgery on 12 patients, realized a statistically significant difference in pain. This outcome could be the result of using the ozone gel three times a day for three days.

The limitations of this study included a small sample size and a short-term follow-up, in addition to the relatively high viscosity of the ozone gel, which compromised its effectiveness.

Conclusion

The use of HA after impacted mandibular third molar surgery could yield better results in controlling pain. Ozone did not affect pain.

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Data availability

Data are available upon reasonable request from the corresponding author.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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