

## Research Article

### The Effects of Serratiopeptidase Enzyme in Reducing Pain and Edema Post-surgical Removal of Impacted Mandibular Third Molar Teeth

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#### Abstract

**Aims:** The present study aimed to find the effect of using a Serratiopeptidase capsule on reducing pain and edema in patients undergoing surgical removal of impacted mandibular third molars.

**Materials and Methods:** Ten healthy men with bilateral partially impacted lower wisdom teeth were selected to enroll in this study ages ranged between 18 to 35 years. They underwent surgical removal of impacted mandibular third molars under local anesthesia with standard technique, manipulation, and instructions. The oral cavity of these patients was divided into two sides: the right side is regarded as group I, which received Serratiopeptidase capsule 40.000 IU for 5 days after surgery. and the second group's left side (group II), received a Dexamethasone tablet 0.5 mg for 5 days after surgery. The following parameters were assessed: Pain and edema on the first, third, and seventh postoperative days.

**Results:** There is no statistically significant differences were recognized for pain and swelling values between the two treatment groups on the 1st, 3rd, and 7th day after surgery.

**Conclusion:** The use of the Serratiopeptidase capsule has nearly the same effectiveness compared with the Dexamethasone tablet in reducing post-operative pain and swelling. So, it can be used as an alternative therapy to reduce side effects in certain cases.

**Keywords:** Edema, Pain, Mandibular, Molar, Serratiopeptidase

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## INTRODUCTION

One of the most prevalent irregularities in tooth position is tooth impaction. An impacted tooth is fully developed but fails to erupt properly into the dental arch due to lack of space or obstruction by other teeth. This condition is outside the normal physiological eruption stage and is often covered partially or entirely by hard and soft tissues (1). The teeth most frequently impacted, especially in the lower jaw, are the third molars. Mandibular third molar impaction happens when there is insufficient distance between the mandible's anterior border and the second molar's distal surface and ascending ramus (2).

In oral and maxillofacial surgery, surgical extraction of the impacted mandibular third molar is a common procedure that is usually linked to postoperative problems including pain, dry socket, swelling, and trismus (3). Pain is a physiological response of the body, serving as a defense mechanism against potentially damaging stimuli. It is not a direct complication of surgery but rather a natural response to tissue injury. (4). Inflammation is the primary cause of postsurgical dental pain, especially when prostaglandins are produced by the cyclooxygenase system. (5). Therefore, localized pharmacologic approaches to reduce the clinical signs of surgical injury aim to prevent the production of or reduce the actions of acute inflammatory mediators (6). When third-molar surgery is performed, corticosteroids are frequently used to manage post-operative inflammation.

Large doses of external cortisone or artificial steroids seem to inhibit all stages of the inflammatory process, whereas natural cortisone from the cortex of the adrenals does not seem to significantly modify the inflammatory process. (7,8). Because of their safety and effectiveness, enzymes are becoming more and more used in medicine. They are incredibly powerful chemicals. Plants (papain and bromelain), animals (chymotrypsin and trypsin), bacteria (streptokinase, streptodornase, and Serratia peptidase), and fungi are the sources of enzymes. (9). The proteolytic enzyme Serratia peptidase is generated by the *Enterobacterium Serratia* spp. E-15, which is currently recognized as *Serratia marcescens* ATCC 21074. This microbe was first discovered in

the intestines of silkworms in the late 1960s. One modulator of inflammation is serrati peptidase. It lessens viscosity, makes drainage easier, and lessens discomfort by preventing the production of bradykinin, an amine that causes pain. (10-12).

The present study aimed to find the effect of using a Serratiopeptidase capsule on reducing pain and edema in patients undergoing surgical removal of impacted mandibular third molars.

## MATERIALS AND METHODS

### Ethical approving

This trial, which was planned and completed at the Dentistry Department of Oral and Maxillofacial Surgery, University of Mosul. A split-mouth design (13) was used in this investigation. On June 12, 2023, the scientific committee registered the study. Before initiating the investigation, ethical authorization had been given by the research ethics board as well as the local scientific committee (**UoM.Dent. 24/1004 on 2/1/2024**). **Informed consent** was obtained from all participants. The participants in the current study gave their verbal and written agreement. The research goal was explained to the participants, and they were assured of the privacy and confidentiality of their data.

Ten male patients, ages 18 to 35, who required the surgical extraction of impacted wisdom teeth on both sides of the mouth made up the sample.

Excluded patients: medically compromised patients, patients who have an allergy to Amoxicillin, local pathological lesions associated with IMTM, heavy smokers, pregnant and lactating women, and those taking contraceptive pills, who are already on antibiotic medication, the patient cannot attend follow-up visits.

The categorization of the bony type of impaction and level (Class I or II, level A or B), and moderate difficulties as per Pell and Gregory, and information regarding the kind of angulation given by the Winter's classification. The patients were split into two groups, each consisting of ten instances. Serrati peptidase group (group I): the patient received a Serrati peptidase capsule 40.000 IU (ELLEZEN PHARMA, CANADA) (14),

(production date 10/2023 and expiration date 9/2024), used for reducing edema, anti-inflammatory, and anti-biofilm.

Every 8 hours for 5 days after surgery. Dexamethasone group (group II): The patient received a dexamethasone tablet 0.5 mg (DEXON, Samarra Drug Industry, Samarra, Iraq) (15) every 8 hours for 5 days after surgery. The difference in drug form (capsule vs. tablet) and dosage (40,000 IU for Serrati peptidase vs. 0.5 mg for dexamethasone) is due to their different pharmacological properties and mechanisms of action. Serrati peptidase, an enzyme, is measured in International Units (IU), reflecting its activity level, whereas dexamethasone, a corticosteroid, is measured in milligrams (mg) based on its mass.

Using the parameters of Pain Assessment: The operator ensured that all patients received a self-assessment pain questionnaire, in the form of a numeric rating scale (NRS) (16) for pain designed in a colored horizontal ascending graph segmented into a single 11-point numeric scale (0-10 integers). The patients were educated to select the number that reflects the intensity of their pain, where 0 represents no pain, while the number 10 represents the worst possible pain. Measured and recorded on the days following surgery, at the first, third, and seventh intervals.

To assess facial edema using a flexible measuring tape, three measurements of the face were taken to the nearest millimeter to establish baseline data for recording facial edema (17). Pre-operatively and on the operating days, the first, third, and seventh. The following are included in facial measurements: The tragus is a small pointed eminence on the external ear. The lateral canthus is the outer corner of the eye where the upper and lower eyelids meet. The gonion is the most posterior, inferior, and lateral point on the angle of the mandible (jawbone) (18).

### **Statistical Analysis**

Version 22 of the Statistical Program for Social Science was used to record and evaluate the collected data. The independent sample T-test was utilized to analyze the data. Every research variable underwent descriptive data analysis and interpretation. The threshold for significance was p-value <0.05.

## RESULTS

Twenty cases of ten patients enrolled and completed the questionnaire measurements and follow-up appointments. The cases' average age was 26.5 years. All the participants were male patients incorporated into the research. The average time spent performing the surgery was 19.3 minutes, and the average space between teeth (interincisal distance) was 42.8 mm.

**Pain measurements within the group (I):** Pain was high on day one and decreased gradually by day seven. Pain among the 3 days (day 1, day 3, day 7) in group I (Serratiopeptidase group) shows high significance with the Friedman test appears  $P=0.000$ , except on day 1 vs. day 3, which shows non-significant results, as shown in (Figure 1).

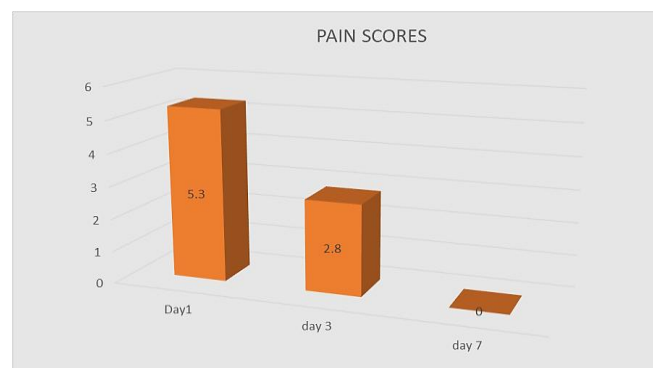


Figure (1): Pain profile differences within group I.

**Pain measurements within group (II):** Pain scores (by NRS) in group II (Dexamethasone group) peaked on day one of the mean measurement (5.2) and gradually decreased until reaching (0.0) on day seven. The Friedman test revealed that pain throughout the three days (days 1, 3, and 7) was very significant, with  $p=0.000$  in all-day intervals, as shown in Figure 2.

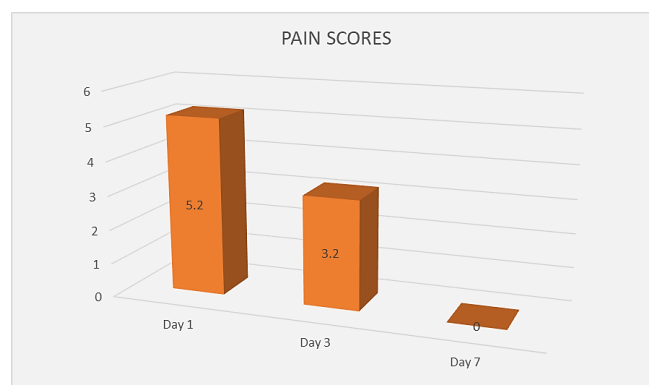


Figure (2): Profile differences in pain within Group II

**Edema measurements within the group (I):** Edema peaked on the first postoperative day and gradually decreased over the following assessment readings to nearly reach the pre-operative reading on the seventh day. Edema across the periods (pre, Day1, Day3, Day7) in the control group; one-way ANOVA shows non-significant P values except for (pre-measurement vs day1) and (day7 vs day1, day3), which were statistically significant using a paired sample t-test, as shown in (Figure 3).

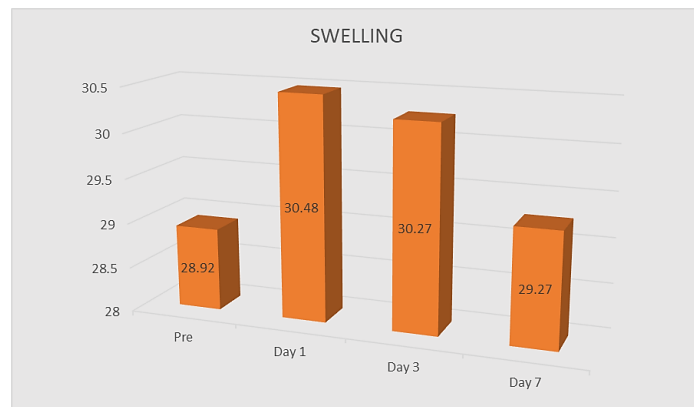


Figure (3): Swelling profile differences within group I.

**Edema measurements within group (II):** Edema in group II showed that the P value was non-significant, as shown in (Figure 4).

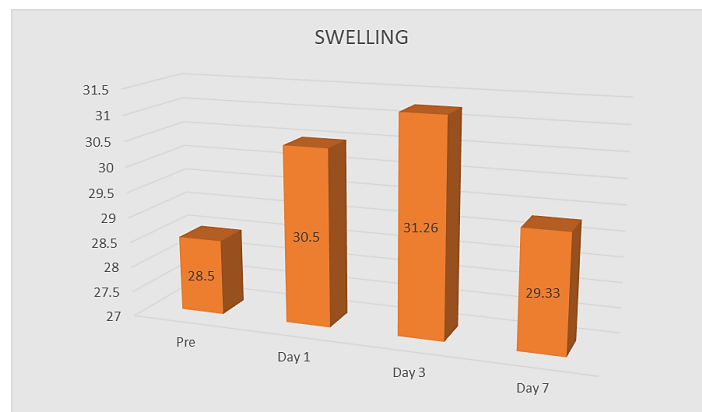


Figure (4): Swelling profile differences within group II.

Also, the results show (Tables 1 and 2) the descriptive analysis among group I and group II for pain and swelling parameters, in which pain with the highest level on day 1 disappeared at day 7 and to a lesser extent in group II.

Table (1) Swelling, pain analysis among participants within group I.

| Study group | Swelling |      |      |      | Pain |      |      |
|-------------|----------|------|------|------|------|------|------|
|             | Pre      | D1   | D3   | D7   | D1   | D3   | D7   |
| Mean        | 28.5     | 30.5 | 31.2 | 29.3 | 5.20 | 3.20 | 0.00 |
| SD*         | 1.68     | 0.52 | 1.15 | 0.90 | 1.22 | 0.78 | 0.00 |
| SE*         | 0.53     | 0.16 | 0.36 | 0.28 | 0.38 | 0.24 | 0.00 |
| Median      | 28.8     | 30.3 | 30.5 | 29.3 | 5.00 | 3.00 | 0.00 |
| IQR***      | 2.39     | 1.04 | 2.83 | 2.67 | 2.25 | 1.25 | 0.00 |

Table (2) Swelling and pain analysis among participants within group II.

| Study group | Swelling |      |      |      | Pain |      |      |
|-------------|----------|------|------|------|------|------|------|
|             | Pre      | D1   | D3   | D7   | D1   | D3   | D7   |
| Mean        | 28.9     | 30.4 | 30.2 | 29.2 | 5.30 | 2.80 | 0.30 |
| SD*         | 1.91     | 1.92 | 1.64 | 1.89 | 1.56 | 2.20 | 0.94 |
| SE*         | 0.60     | 0.60 | 0.51 | 0.60 | 0.49 | 0.69 | 0.30 |
| Median      | 30.0     | 31.1 | 30.6 | 30.0 | 5.50 | 3.50 | 0.00 |
| IQR***      | 3.68     | 2.41 | 1.77 | 3.58 | 3.25 | 4.25 | 0.00 |

**Pain profile between groups:** results of pain as a mean of the days between the groups show the analgesic effect of Serratiopeptidase in comparison to Dexamethasone. As shown in Figure 5.

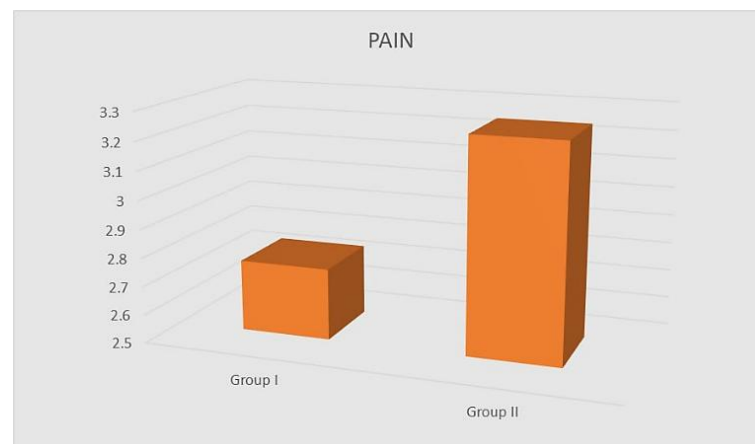


Figure (5): Pain profile differences between groups

**Swelling profile differences between groups:** the mean swelling across days between the groups shows the anti-edema effect of Serratiopeptidase compared with Dexamethasone. As shown in Figure 6.

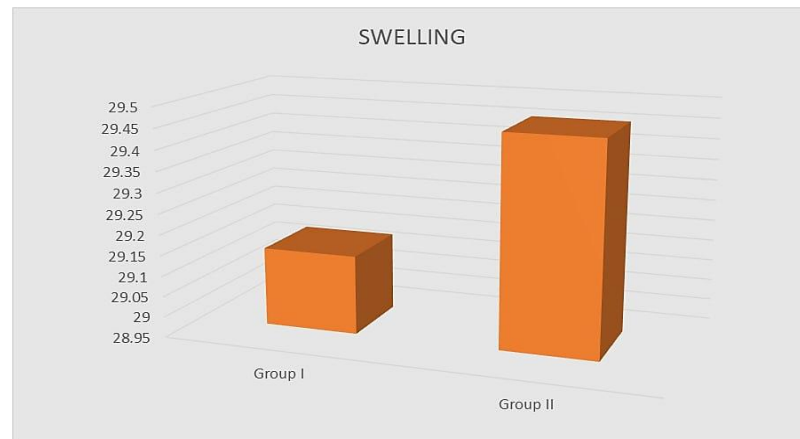


Figure (6): Swelling profile differences between groups.

The aforementioned results (Table 3) explain the time comparison that showed significant results for edema on days 1 and 3 from baseline and significant pain data for all days' comparison. As seen in Table 3.

Table (3): Comparisons of Edema and Pain, Between groups in days' interval

| Variable                           | Group I (study) | Group II (control) | p- value |
|------------------------------------|-----------------|--------------------|----------|
| <b>Edema</b>                       |                 |                    |          |
| <b>(Independent sample T-Test)</b> |                 |                    |          |
| Pre X Day 1                        | 4.121           | 4.158              | 0.003*   |
| Pre X Day 3                        | 3.196-          | 6.004              | 0.011*   |
| Pre X Day 7                        | 1.756           | 2.109              | 0.113    |
| Day 1 X Day 3                      | 1.909           | 0.334              | 0.743    |
| Day 1 X Day 7                      | 1.424           | 3.520              | 0.172    |
| Day 3 X Day 7                      | 1.198           | 1.005              | 0.247    |
| <b>Pain</b>                        |                 |                    |          |
| <b>(Mann – Whitney U test)</b>     |                 |                    |          |
| Day 1 X Day 3                      | 18.500          | 8.000              | 0.016*   |
| Day 1 X Day 7                      | 1.000           | 0.000              | 0.000*   |
| Day 3 X Day 7                      | 18.000          | 0.000              | 0.006*   |

## DISCUSSION

If a lower wisdom tooth is surgically extracted, it could lead to evident anxiety, edema, and malfunction. Healing necessitates the inflammatory process, but inflammation can have unintended consequences like pain and swelling (18, 19). Usually, two to three days following the surgical treatment, swelling peaks. Although careful surgical methods may lessen the aftereffects of inflammation but cannot entirely block it; the vasoactive amines produce vasodilatation, increasing blood flow to the inflamed area (20).

Enzymes play a major role in the cellular matrix's proteolytic modification of various physiological functions, including tissue formation and tissue healing, angiogenesis, and tissue modulation. This reduces bruising, edema, discomfort, and healing time. Enzymes used in oral enzyme treatment are ingested and absorbed in the intestine and have systemic effects. Enzymes that are absorbed systemically promote and maintain natural enzymes that control oxidative stress, cell signaling, immune response, and circulation. (21).

Serratio peptidase is regarded as a miracle enzyme that can substitute NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) (22). A class of steroids known as glucocorticoids has anti-inflammatory qualities. Corticosteroids reduce or obstruct capillary expansion, edema formation, fibrin deposition, leucocyte migration, and digestion, which could avoid inflammation. This is perhaps one of their most significant activities. The mechanism of action of glucocorticoids is attributed to their impact on leukocyte activity and mobility suppression, macrophage aggregation at the inflammatory location, and inhibition of the arachidonic acid cascade, which prevents prostaglandin formation. Steroids create the endogenous protein lipocortin. It prevents phospholipase A2 from functioning, which in turn prevents arachidonic acid from being released from cell membranes and the production of prostaglandins, leukotrienes, and thromboxane. (23).

The capacity of Serratia peptidase, a proteolytic enzyme with an anti-inflammatory impact, and dexamethasone, a long-acting corticosteroid with an intense anti-inflammatory effect, to reduce postoperative edema was evaluated and compared. According to this study, dexamethasone and serratiopeptidase were equally useful in reducing edema; however, dexamethasone was marginally more helpful than serratiopeptidase in this regard.

The effectiveness of Serratiopeptidase in its analgesic activity was examined in this study; it is linked to the inhibition of bradykinin and other amines that cause pain and inflammation, and the regulation of inflammatory cytokines (24).

## CONCLUSIONS

Within the limitations of this study:

The application of the Serratiopeptidase capsule has nearly the same effectiveness compared with the Dexamethasone tablet in reducing post-operative pain and swelling. No side effects or problems, such as dry sockets or wound infections, were noted in any of the patients, demonstrating that Serratiopeptidase and Dexamethasone are both safe for controlling postoperative sequelae.

## Acknowledgment

The faculty and staff of the University of Mosul/ College of Dentistry have been tremendously helpful throughout this process, and we are very grateful to them.

## Authors' Contribution

The authors, Naqi Sh designed the study, and Deleme Z supervised the work. Naqi Sh conducted the experiments, collected data, performed the data analysis, and wrote the manuscript. Deleme Z contributed by providing scientific information and assisting in the study.

## Ethical statement:

The scientific committee registered the study. Ethical authorization had been given by the research ethics board as well as the local scientific committee (UoM.Dent. 24/1004 on 2/1/2024). Informed consent was obtained from all participants. The participants in the current study gave their verbal and written agreement. The research goal was explained to the participants, and they were assured of the privacy and confidentiality of their data.

## Conflict of interest

The author declares that there are no conflicts of interest regarding the publication of this manuscript.

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article and its supplementary information files.

## Declaration of Generative AI and AI-assisted technologies

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this manuscript. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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### تأثير إنزيم سيراتيوببتيداز في تخفيف الألم والتورم بعد الجراحة لإزالة ضرس العقل السفلي المظموور

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#### الملخص

**الأهداف:** تهدف الدراسة الى معرفة تأثير استخدام كبسولة سيراتيوببتيداز على تقليل الألم والوذمة لدى المرضى الذين يخضعون لعملية الاستئصال الجراحي للأضراس الثالثة الفك المنظرة. **المواد وطرائق العمل:** تم اختيار عشرة رجال أصحاء لديهم ضروس عقل سفلية منظرة جزئياً في الجانبين، وتراوح أعمارهم بين 18 و35 عاماً، وكانوا يحتاجون إلى الاستئصال الجراحي للأضراس الثالثة المنظرة في الفك السفلي تحت التخدير الموضعي باستخدام التقنية القياسية. والتعليمات. تم تقسيم أفواه هؤلاء المرضى إلى جانبين: الجانب الأيمن ينتمي إلى المجموعة الأولى التي تلقت كبسولة سيراتيوببتيداز بجرعة 40,000 وحدة دولية كل 8 ساعات لمدة 5 أيام بعد الجراحة والمجموعة الثانية في الجانب الأيسر (المجموعة الثانية) تلقت قرص ديكساميثازون 0.5 ملغ لمدة 5 أيام بعد الجراحة. تم تقييم المعلمات التالية: الألم والوذمة في فترات الأيام الأول والثالث والسابع بعد العملية الجراحية. **النتائج:** بشكل عام لم يتم التعرف على فروق ذات دلالة إحصائية لقيم الألم والتورم بين مجموعتي العلاج في اليوم الأول والثالث والسابع بعد العمل الجراحي. **الاستنتاجات:** إن استخدام كبسولة Serratiopeptidase له نفس الفعالية تقريباً مقارنة بقرص الديكساميثازون في تقليل الألم والتورم بعد العملية الجراحية لذلك ينصح باستخدامه كدواء بديل للحالات المطلوبة.

**الكلمات المفتاحية:** وذمة، ألم، الفك السفلي، ضرس، سيراتيوببتيداز.