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ORIGINAL ARTICLE

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Efficacy of Serratiopeptidase After Impacted Mandibular Third Molar Surgery: A Split-Mouth Randomized Controlled Trial

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ABSTRACT

Background: Surgical extraction of impacted mandibular third molars is frequently associated with postoperative complications such as trismus, facial edema, and pain, primarily due to inflammatory responses. Conventional management using corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) is effective but may cause adverse systemic effects with prolonged use. Serratiopeptidase, a proteolytic enzyme with anti-inflammatory and analgesic potential, has been investigated as a safer adjunctive therapy, though evidence remains limited. This study aimed to evaluate the clinical efficacy of serratiopeptidase in reducing postoperative complications following impacted mandibular third molar surgery.

Methods: A triple-blind, randomized controlled clinical trial using a split-mouth design was conducted in twelve healthy patients requiring bilateral surgical removal of impacted mandibular third molars. Each patient served as their own control, with one extraction site receiving conventional therapy alone (amoxicillin, metronidazole, and diclofenac sodium) and the contralateral site managed with the same regimen supplemented by oral serratiopeptidase. Assessments of trismus, facial edema, and pain were performed preoperatively and on the 2nd , 3rd , and 5th postoperative days. Data were analyzed using repeated-measures analysis of variance (RMANOVA), with significance set at $P < 0.05$.

Results: All 12 participants completed the trial, yielding 24 surgical sites for analysis. Trismus improved significantly over time in both sides ($P < 0.001$), with no significant interaction effect between treatment and time. Facial edema across all types demonstrated significant reduction across time points ($P < 0.001$), but between-group comparisons showed no significant differences. Pain scores were consistently lower in the serratiopeptidase side, with significant main and interaction effects ($P < 0.001$), confirming superior analgesic benefit.

Conclusion: Serratiopeptidase is a valuable adjunct to conventional postoperative therapy in mandibular third molar surgery, particularly for pain reduction. However, its effects on trismus and facial edema are limited, with recovery patterns largely comparable to those observed with standard care. These findings support the use of serratiopeptidase as a safe, effective adjunct to conventional therapy for improving patient comfort.

Keywords: Serratiopeptidase ▪ Mandibular Third Molar ▪ Postoperative pain ▪ Split-mouth randomized controlled trial

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1. Introduction

The surgical extraction of impacted third molars is among the most common procedures performed in oral and maxillofacial surgery. However, it is frequently accompanied by undesirable postoperative complications, including trismus, facial edema, and pain.[1,2] These complications typically result from the body's inflammatory response to surgical trauma.

Traditionally, such complications have been managed through pharmacological interventions, most notably corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).[3] While these medications exhibit strong anti-inflammatory and analgesic effects that effectively alleviate pain and facial edema, their long-term use can lead to adverse effects, such as gastrointestinal bleeding, renal impairment, and hematological disorders, raising safety concerns.[4]

Serratiopeptidase, a proteolytic enzyme of natural origin, demonstrates potential for modulating postsurgical inflammatory responses. Contemporary evidence indicates efficacy in reducing inflammation in peri-implant and periodontal contexts,[5] suggesting possible clinical utility in third molar surgery.[2,7,20]

Although prior trials have investigated serratiopeptidase in third-molar surgery, methodological differences limit comparability and leave uncertainty regarding its adjunctive benefit. Some studies employed randomized or split-mouth designs,[5,6] whereas others did not clearly report blinding or placebo control, which increases the risk of performance and detection bias.[7] Outcome measures were also heterogeneous, ranging from subjective pain scales to varying linear facial measurements or newer image-processing methods.[5–8] Differences in dosing regimens, timing, and concomitant postoperative medications further complicate direct comparison. A systematic review and meta-analysis confirms that serratiopeptidase can reduce postoperative trismus, but the effect on pain and swelling remains inconsistent, and the quality of evidence is limited by study heterogeneity.[9] These gaps underscore the need for a rigorously controlled trial that integrates a split-mouth design, triple-blinding, standardized objective and subjective outcome measures, a uniform postoperative regimen, and an appropriate washout period to minimize carry-over effects.

Addressing these gaps, the present study aimed to evaluate the efficacy of serratiopeptidase in reducing postoperative trismus, facial edema, and pain following impacted mandibular third molar surgery. Specifically, it sought to determine whether the adjunctive use of serratiopeptidase provides superior outcomes compared to conventional therapy alone, thereby offering evidence-based guidance for safer and more effective postoperative management in clinical practice. It hypothesized that serratiopeptidase, as an adjunct to conventional therapy, may provide greater efficacy than conventional drugs alone in reducing postoperative complications (trismus, facial edema, and pain) following impacted mandibular third molar surgery.

2. Methods

2.1. Study design, population and setting

This investigation was designed as a split-mouth triple-blind randomized clinical trial, allowing each patient to act as their own control. Twelve medically healthy individuals, each requiring bilateral extraction of impacted mandibular third molars, were enrolled from the outpatient clinics of the College of Dentistry, University of Science and Technology, Yemen (USTY) in 2024.

In one session, an impacted mandibular third molar was extracted and treated with conventional medications alone, while after a three-week washout period, the contralateral tooth was removed and

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managed with the same regimen supplemented by 10 mg oral serratiopeptidase (Mascot Biotech, Rajasthan, India), given immediately after surgery and then three times daily for five days. Alternatively, the initial extraction could have involved the serratiopeptidase regimen, followed by conventional treatment alone during the second procedure. The standard postoperative regimen included amoxicillin 500 mg twice daily, metronidazole 500 mg three times daily, and diclofenac sodium 50 mg twice daily.[10]

Eligible patients were medically healthy, with two mandibular third molars indicated for surgical extraction, while those with systemic disease, pregnancy, drug allergies, recent or acute infection, and prior maxillofacial irradiation were excluded.

2.2. Sample size calculation

Sample size was estimated based on the effect size reported by Costa et al.,[11] who demonstrated that preemptive administration of etoricoxib reduced the need for rescue analgesics compared with placebo. Using OpenEpi software,[12] with 80% statistical power and a 95% confidence interval, the minimum required number was calculated as 11 surgical sites per group. To account for potential attrition, this was increased to 14 sites per group. Ultimately, 12 patients completed the trial, providing 24 surgical sites for final analysis.

2.3. Randomization and blinding

Randomization in this trial was carried out using the simple randomization method described by Oliveira et al.,[13] ensuring unbiased allocation of surgical conditions. A sequence of sealed opaque envelopes was employed to assign treatment conditions and surgical order. Each envelope contained a designation for whether the surgical site would act as the test (supplemented with oral serratiopeptidase) or control (standard regimen), whether the right or left mandibular third molar would be addressed, and whether the selected tooth would be operated in the first or second session. This stepwise process guaranteed that allocation remained concealed until the moment of surgery, thereby preventing prediction or manipulation.

To preserve trial integrity, blinding was strictly upheld, where patients, the operating surgeon, and the outcome evaluator were all unaware of group assignments throughout the study. Specifically, the procedures were carried out by one operator who was blinded to both the evaluation data and whether the postoperative regimen included serratiopeptidase or conventional therapy at the time of prescribing medications. The evaluator, who had access to patients' symptom responses, remained unaware of which treatment was administered on each side. Likewise, patients were blinded to the treatment or intervention received on each side of their mouth.

2.4. Data collection

Prior to surgery, all impacted mandibular third molars were evaluated radiographically and classified according to Winter's angulation (mesioangular, distoangular, horizontal, vertical)[14] and Pell and Gregory depth and ramus relationship.[15] These parameters were combined to calculate the Pederson Difficulty Index (3–10 points), categorizing surgical difficulty as slight (3–4), moderate (5–7), or very difficult (8–10).[16] This classification ensured balanced distribution of surgical complexity across the Serratiopeptidase and control sides, allowing valid comparison of postoperative outcomes.

Postoperative outcomes were measured consistently across all patients. Trismus was determined by measuring the maximum interincisal distance between the upper and lower central incisors using a calibrated ruler, both before and after surgery, at each designated interval.[17] Facial edema was quantified following the method outlined by Schultze-Mosgau et al,[18] using a flexible measuring scale across five fixed anatomical landmarks (F1: tragus of the ear, F2: angle of the mandible, F3: soft

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tissue pogonion, F4: corner of the mouth, and F5: lateral canthus of the eye) and three standardized reference lines [S1: from tragus of the ear to corner of the mouth (Tr-Com), S2: from tragus of the ear to soft tissue pogonion (Tr-Pgo), and S3: from lateral canthus of the eye to angle of the mandible (Lc-Gn)] to capture linear facial dimensions over time. Pain intensity was evaluated using a 10-cm visual analogue scale (VAS), with scores ranging from 0 (no pain) to 10 (worst possible pain), as described by Sirintawat et al.[19] Patients indicated their pain level at each assessment point, and these values were recorded systematically for analysis.

All postoperative outcomes were assessed at baseline, immediately postoperatively, and on the 2nd, 3rd, and 5th postoperative days, applying identical methods throughout to maintain consistency and reliability.

2.5. Surgical procedures

To minimize variability and potential bias, all extractions of impacted mandibular third molars were performed by a single oral surgeon following a standardized surgical protocol.[20] Local anesthesia was administered through inferior alveolar, lingual, and long buccal nerve blocks. Access was obtained using a Modified Ward's incision (sulcular incision around the second molar with a short vertical releasing incision), and a full-thickness mucoperiosteal flap was elevated. Bone removal and, when required, tooth sectioning were performed under continuous sterile saline irrigation. The alveolar socket was curetted and irrigated, then closed with 4–0 absorbable sutures. This consistent technique was applied to all patients in both the serratiopeptidase and control sides to ensure uniformity of surgical intervention.

2.6. Postoperative management

Following surgery, participants received their allocated postoperative regimen, serratiopeptidase and standard management in the intervention side and standard management alone in the control side, along with written instructions regarding diet, oral hygiene, and postoperative care. All patients were also advised on potential complications and instructed to report any symptoms during follow-up.

2.7. Data analysis

Data were analyzed using IBM SPSS Statistics, version 28 (IBM Corp., Armonk, NY, USA) and Jeffreys's Amazing Statistics Program (JASP), version 0.18.3 (University of Amsterdam, Amsterdam, The Netherlands). Comparisons between the serratiopeptidase and control sides were conducted using Repeated-measures analysis of variance (RMANOVA), to evaluate the outcome changes across postoperative days. A *P*-value <0.05 was considered statistically significant.

3. Results

3.1. Participant demographics and molar characteristics

Table 1 summarizes the demographic characteristics, impacted mandibular third molar features, and Pederson Difficulty Index for the study participants. All participants were under 30 years of age, with the majority being female (66.7%). The right and left sides were nearly equally represented. Radiographic evaluation revealed that all teeth were deeply impacted (Pell & Gregory Level C), with the majority being mesioangular (Control: 75%; Test: 66.7%), followed by vertical and horizontal angulations, and no distoangular cases. Most teeth were positioned within Ramus Class II, with only two test teeth classified as Class III. Based on these parameters, the Pederson Difficulty Index indicated that most extractions were moderately difficult (Control: 10/12; Test: 9/12), with a few classified as very difficult (Control: 2/12; Test: 3/12), and none as slightly difficult. This distribution demonstrates that surgical difficulty was largely comparable between the test and control sides, support-

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ing balanced comparison of postoperative outcomes such as trismus, facial edema, and pain.

Table 1: Demographic, impacted mandibular third molar characteristics, and Pederson difficulty of test and control groups

Variable	Test group (N=12)	Control group (N=12)
	n (%)	
Age (<30 years)	12 (**100.0**)	12 (**100.0**)
Gender		
Male	4 (**33.3**)	4 (**33.3**)
Female	8 (**66.7**)	8 (**66.7**)
Side		
Right	7 (**58.3**)	5 (**41.7**)
Left	5 (**41.7**)	7 (**58.3**)
Depth (C)	12 (**100.0**)	12 (**100.0**)
Angulation		
Horizontal	1 (**8.3**)	1 (**8.3**)
Mesioangular	9 (**75.0**)	8 (**66.7**)
Vertical	2 (**16.7**)	3 (**25.0**)
Class		
II	12 (**100.0**)	10 (**83.3**)
III	0 (**0.0**)	2 (**16.7**)
Difficulty		
Moderately difficult (5–7)	10 (**83.3**)	9 (**75.0**)
Very difficult (8–10)	2 (**16.7**)	3 (**25.0**)

3.2. Surgical parameters

Surgical parameters demonstrated procedural uniformity. All patients received 2–3 cartridges of local anesthetic, and the majority of procedures (83.3%) lasted between 30–60 minutes during the first visit, whereas a greater proportion (66.7%) of procedures were completed in under 30 minutes during the second visit. Bone removal was required for all patients (100%) across both visits, and tooth sectioning was performed in 5 patients (41.7%) at each session (Table 2).

Table 2: Surgical parameters for serratiopeptidase (*N* = 12)

Variable	First visit (N=12)	Second visit (N=12)
	n (%)	
Number of surgical cartridges (2-3)	12 (**100.0**)	12 (**100.0**)
Duration (minutes)		
<30	2 (**16.7**)	8 (**66.7**)
30–60	10 (**83.3**)	4 (**33.3**)
Bone removal	12 (**100.0**)	12 (**100.0**)
Tooth sectioning	5 (**41.7**)	5 (**41.7**)

3.3. Postoperative outcomes

Comparison of postoperative outcomes between the study and control sides is presented in Table 3.

3.3.1. Postoperative trismus

Table 3 shows that the test side consistently exhibited higher mean trismus values, indicating less restriction, compared with the control side. On day 2, the test side recorded 35.67 ± 3.89 compared to 27.17 ± 6.39 in the control side. By day 5, trismus improved to 41.00 ± 4.00 in the test side and 33.75 ± 5.19 in the control side. Trismus increased significantly over time (within-subjects effect: $F = 35.715$, $P < 0.001$, $\eta^2 = 0.619$). The interaction effect between time and treatment was not significant ($F = 0.598$, $P = 0.554$, $\eta^2 = 0.026$), suggesting similar progression trends in both sides. Although the serratiopeptidase side showed higher interincisal distances across all timepoints (between-subjects effect: $F = 20.918$, $P < 0.001$, $\eta^2 = 0.487$), the sub-hypothesis that serratiopeptidase would provide superior trismus reduction over time was not supported.

3.3.2. Postoperative facial edema

Across all types (Tr-Com, Tr-Pgo, and Lc-Gn), edema scores showed slight reductions over time in both sides, with minimal differences between the test and control sides. Tr-Com: On day 2, the test side recorded 110.75 ± 7.37 compared to 112.75 ± 5.90 in the control side. By day 5, scores decreased slightly to 109.33 ± 7.28 in the test side and 108.42 ± 6.91 in the control. Edema decreased significantly over time in both sides (within-subjects effect: $F = 57.550$, $P < 0.001$, $\eta^2 = 0.723$). The interaction effect between time and treatment was significant ($F = 12.016$, $P < 0.001$, $\eta^2 = 0.353$), indicating that the pattern of reduction differed between sides at specific timepoints. However, the between-subjects effect was not significant ($F = 0.125$, $P = 0.727$, $\eta^2 = 0.006$), showing that there was no meaningful overall difference in edema

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between the test and control sides. Therefore, the sub-hypothesis that serratiopeptidase would provide superior Tr-Com edema reduction was not supported.

Tr-Pgo: On day 2, the score of the test side was 146.58 ± 9.81 *versus* 149.50 ± 9.64 in the control. By day 5, scores declined to 143.75 ± 8.86 in the test side and 146.58 ± 10.38 in the control side. Edema decreased significantly over time in both sides (within-subjects effect: F = 42.784, *P* <0.001, η^2 = 0.660). However, the interaction effect between time and treatment was non-significant (F = 2.560, *P* = 0.089, η^2 = 0.104), suggesting similar progression trends in both sides. Moreover, the between-subjects effect was not significant (F = 0.776, p = 0.388, η^2 = 0.034), showing no reliable overall difference between sides. Accordingly, the sub-hypothesis that serratiopeptidase would provide superior Tr-Pgo edema reduction was not supported.

Lc-Gn: On day 2, the test side recorded 105.33 ± 5.26 compared to 105.92 ± 3.53 in the control. By day 5, scores slightly decreased to 104.08 ± 4.80 in the test side and 103.92 ± 4.19 in the control. Edema decreased significantly over time in both sides (within-subjects effect: F = 11.630, *P* < 0.001, η^2 = 0.346). The interaction effect between time and treatment was not significant (F = 0.576, *P* = 0.567, η^2 = 0.025), and the between-subjects effect was not significant (F = 0.009, *P* = 0.927, η^2 = 0.000), showing that there was no overall difference in edema between the test and control sides. Accordingly, the sub-hypothesis that serratiopeptidase would provide superior Lc-Gn edema reduction was not supported.

3.3.3. Postoperative pain

Pain scores were consistently lower in the serratiopeptidase side at all time points. On day 2, the mean score of the test side had 2.58 ± 0.52 *versus* 5.58 ± 0.52 in controls. By day 5, pain decreased to 1.00 ± 0.00 in the test side and 2.00 ± 0.43 in the control side. Pain decreased significantly over time in both sides (within-subjects effect: F = 282.871, *P* <0.001, η^2 = 0.928). The interaction effect between time and treatment was significant (F = 52.440, *P* <0.001, η^2 = 0.704), indicating that the pattern of pain reduction differed between sides across postoperative days. The between-subjects effect was also significant (F = 253.441, *P* < 0.001, η^2 = 0.920), demonstrating that the serratiopeptidase side experienced consistently lower pain scores compared with the control side. Accordingly, the sub-hypothesis that serratiopeptidase would provide superior pain reduction was supported.

Table 3: Descriptive and RMANOVA results for postoperative outcomes with serratiopeptidase

Outcome	Group	Timepoint (mean ± SD)			RMANOVA (effect) (F, *P*, η^2)		
		Day 2	Day 3	Day 5	Within-subjects (time)	Time × Group	Between-subjects (group)
Trismus	Test	35.67 ± 3.89	37.25 ± 2.45	41.00 ± 4.00	35.715, <0.001, 0.619	0.598, 0.554, 0.026	20.918, <0.001, 0.487
	Control	27.17 ± 6.39	28.50 ± 5.98	33.75 ± 5.19			
Facial edema – Tr-Com	Test	149.50 ± 9.64	150.75 ± 9.37	146.58 ± 10.38	57.550, <0.001, 0.723	12.016, <0.001, 0.353	0.125, 0.727, 0.006
	Control	112.75 ± 5.90	113.08 ± 6.19	108.42 ± 6.91			
Facial edema – Tr-Pgo	Test	146.58 ± 9.81	146.33 ± 8.76	143.75 ± 8.86	42.784, <0.001, 0.660	2.560, 0.089, 0.104	0.776, 0.388, 0.034
	Control	149.50 ± 9.64	150.75 ± 9.37	146.58 ± 10.38			
Facial edema – Lc-Gn	Test	105.33 ± 5.26	105.25 ± 5.55	104.08 ± 4.80	11.630, <0.001, 0.346	0.576, 0.567, .025	0.009, 0.927, 0.000
	Control	105.92 ± 3.53	105.33 ± 3.50	103.92 ± 4.19			
Pain (VAS)	Test	2.58 ± 0.52	1.75 ± 0.62	1.00 ± 0.00	282.871, <0.001, 0.928	52.440, <0.001, 0.704	253.441, <0.001,0.920
	Control	5.58 ± 0.52	4.67 ± 0.49	2.00 ± 0.43			

SD, standard deviation; VAS, Visual Analogue Scale.

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4. Discussion

This study evaluated the efficacy of serratiopeptidase, as an adjunct to conventional drugs, in reducing postoperative complications following impacted mandibular third molar surgery, including trismus, facial edema, and pain. Overall, the findings indicate that serratiopeptidase provides a significant analgesic effect, while its impact on trismus and facial edema appears limited, with recovery patterns largely similar to conventional therapy.

Postoperative trismus improved significantly over time in both sides, with the serratiopeptidase side showing a trend toward greater mouth opening. However, the lack of a significant interaction between time and treatment suggests that the overall recovery trajectory was comparable across sides. This indicates that while serratiopeptidase may offer some benefit in managing trismus, it does not confer a marked advantage over standard postoperative care. These findings align with prior literature, which reports mixed outcomes; some studies and a meta-analysis suggest modest improvements in trismus with serratiopeptidase,[6,7,9] whereas others show no significant differences compared to placebo or alternative anti-inflammatory treatments.[1, 10, 21–23]

Facial edema also decreased significantly over time at all measured sites. Minor differences between sides were observed, but the between-subjects effects were not significant, indicating similar recovery patterns across the serratiopeptidase and control sides. While an interaction effect was noted at one site, this did not translate into a clinically meaningful benefit. These results suggest that serratiopeptidase does not substantially enhance edema reduction, which is consistent with previous reports showing limited[6,7] or inconsistent effects compared to other anti-inflammatory agents or enzyme combinations.[10,21,22]

In contrast, serratiopeptidase demonstrated a clear analgesic effect, with pain levels being significantly lower in the test side compared to controls over the postoperative period. The significant interaction between time and treatment indicates that pain reduction was more pronounced in patients receiving serratiopeptidase, supporting its role as an effective adjunct for postoperative analgesia. Prior studies show inconsistent results regarding pain relief. Some studies found no significant difference compared to placebo or other treatments,[6,7,10,21] while others observed relatively improved pain control when serratiopeptidase was combined with conventional drugs alone.[24]

The inconsistent findings on the efficacy of serratiopeptidase after impacted mandibular third molar surgery largely stem from methodological weaknesses in the available literature. Variations in study design, including different sample sizes, inconsistent dosing regimens, treatment duration, and poorly defined outcomes, have produced heterogeneous results. Differences in assessment methods for postoperative complications such as trismus, edema, and pain further contribute to these discrepancies. Moreover, most clinical studies are of limited quality and many lack adequate blinding or randomization.[9,25]

The study limitations include the single-center design, the short follow-up period limited to early postoperative outcomes, and the absence of objective biomarkers of inflammation, relying instead on clinical parameters. Future studies with larger multicenter trials, longer follow-up periods, and the inclusion of biochemical or imaging markers to complement clinical findings are recommended to validate and extend these findings. Comparative studies of serratiopeptidase with other anti-inflammatory agents, as well as dose-response analyses, would also provide valuable insights for opti-

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mizing postoperative management after third molar surgery.

5. Conclusion

Serratiopeptidase is beneficial in postoperative pain management following mandibular third molar surgery, but its effects on trismus and facial edema are limited. These findings underscore its value as an adjunct in enhancing patient comfort without substantially altering the recovery trajectory for other postoperative complications.

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Ethical considerations

Ethical approval for this study was granted by the USTY Research Ethics Committee (Approval Reference No. 1445/0012/UREC/UST; dated 30/07/2024). Written informed consent was obtained from each participant, who retained full autonomy to accept or decline participation without any coercion.

Clinical trial registration

The study was registered with ClinicalTrials.gov (Identifier: NCT07304882) on December 26, 2025, and with the International Standard Randomised Controlled Trial Number (ISRCTN) registry (Registration No.: ISRCTN 15432618) on November 11, 2025.

Conflict of interest

The authors declare no conflict of interest associated with this article.

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