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Efficacy of Submucosal Hyaluronidase Injection Following Surgical Removal of Impacted Mandibular Third Molars: A Randomized Controlled Trial

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Abstract

Background: Surgical removal of impacted mandibular third molars is frequently associated with postoperative pain, oedema, and trismus. Hyaluronidase, by enhancing tissue permeability and fluid diffusion, may reduce these postoperative complications; however, clinical evidence remains limited.

Objective: To evaluate the efficacy of submucosal hyaluronidase injection in reducing postoperative pain, edema, trismus, and improving patient-centered outcomes following impacted mandibular third molar surgery.

Materials and Methods: A prospective, double-blind, randomized controlled trial was conducted on 60 patients undergoing surgical removal of impacted mandibular

third molars. Participants were randomly allocated into two groups (n = 30 each). The intervention group received a submucosal injection of hyaluronidase (1500 IU), while the control group received normal saline. Postoperative pain (Visual Analog Scale), edema, trismus (maximum interincisal opening), and Patient-Centered Outcome Questionnaire (PCOQ) scores were assessed preoperatively and on postoperative days 1, 3, and 7.

Results: The hyaluronidase group demonstrated significantly lower postoperative pain and improved mouth opening compared with the control group at all postoperative intervals ($p < 0.05$). Patient-centered outcome scores were also significantly better in the intervention group. Although postoperative edema decreased over time in both groups, no statistically significant difference was observed between the groups.

Conclusion: Submucosal hyaluronidase is a safe and effective adjunct following mandibular third molar surgery, significantly reducing postoperative pain and trismus while improving patient-reported outcomes. However, it does not significantly reduce postoperative edema.

Keywords: Hyaluronidase; Impacted mandibular third molar; Third molar surgery; Postoperative pain; Trismus; Edema; Patient-reported outcomes; Randomized controlled trial.

Introduction

Surgical removal of impacted mandibular third molars is one of the most common procedures in oral and maxillofacial surgery. Despite being a routine intervention, it invariably causes tissue trauma due to flap elevation, bone removal, and tooth sectioning, resulting in postoperative pain, facial edema, and trismus. These inflammatory sequelae can impair mastication, speech, oral hygiene, and overall quality of life during the early postoperative period.[1,2]

Various pharmacological agents, including non-steroidal anti-inflammatory drugs and corticosteroids, are routinely used to reduce postoperative morbidity. However, their systemic adverse effects and contraindications have prompted the search for safe and effective local adjunctive therapies.[2]

Hyaluronidase is an enzyme that hydrolyzes hyaluronic acid in the extracellular matrix, reducing tissue viscosity and increasing tissue permeability. This enhances the diffusion of local anesthetic agents, promotes lymphatic drainage, and may reduce inflammatory edema. Owing to these properties, hyaluronidase has been widely used in ophthalmology, plastic surgery, and dermatology, with increasing interest in its application following oral surgical procedures.[3-6]

Although hyaluronic acid has been extensively investigated in third molar surgery, evidence regarding the effectiveness of submucosal hyaluronidase remains limited, with inconsistent findings on postoperative pain, edema, and trismus. Furthermore, randomized controlled trials evaluating patient-centred outcomes are scarce.[7]

Therefore, this randomized controlled trial was conducted to evaluate the efficacy of submucosal hyaluronidase following impacted mandibular third molar surgery. Postoperative pain, facial edema, trismus, and patient-centred outcomes were compared between patients receiving hyaluronidase and those receiving normal saline to determine its effectiveness in improving postoperative recovery.

Aims and Objectives

Aim

To evaluate the efficacy of submucosal injection of hyaluronidase in reducing postoperative pain, edema, trismus, and improving patient-centred outcomes following surgical removal of impacted mandibular third molars.

Objectives

1. To compare postoperative pain between the hyaluronidase and normal saline groups using the Visual Analog Scale (VAS).
2. To evaluate postoperative facial edema following submucosal administration of hyaluronidase.
3. To assess postoperative trismus by measuring maximum interincisal mouth opening.
4. To compare patient-centred postoperative recovery using the Patient-Centered Outcome Questionnaire (PCOQ).

Materials and Methods

Study Design and Setting

A prospective, double-blind, randomized controlled trial was conducted in the Department of Oral and Maxillofacial Surgery, Chhattisgarh Dental College and Research Institute, Rajnandgaon, Chhattisgarh, India, between May 2024 and April 2026. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants before enrolment.

Study Population

Sixty patients aged 18–50 years requiring surgical removal of impacted mandibular third molars under local anaesthesia were recruited. Participants were selected using a convenience sampling technique and randomly allocated into two equal groups (n = 30 each).

Inclusion Criteria

- Age between 18 and 50 years.
- American Society of Anesthesiologists (ASA) Physical Status I.
- Impacted mandibular third molars indicated for surgical extraction.
- Pederson's difficulty index score of 5–6 (moderately difficult impactions).
- Willingness to participate and provide informed consent.

Exclusion Criteria

- Impacted third molars associated with pathology or acute infection.
- Tobacco users or smokers.
- Medically compromised patients.
- Known allergy to local anesthetic agents.
- Pregnant or lactating women and patients receiving oral contraceptives.

Randomization and Blinding

Participants were randomised to the intervention and control groups using a coin toss. A double-blind design was maintained throughout the study, whereby neither the participants nor the investigator responsible for postoperative assessment was aware of the allocated intervention until completion of the trial.

Surgical Procedure

All procedures were performed under local anesthesia using 2% lignocaine hydrochloride with 1:80,000 adrenaline. Following a standard Ward's or Modified Ward's incision, a buccal mucoperiosteal flap was elevated, and surgical extraction of the impacted mandibular third molar was completed with ostectomy and odontotomy whenever required.

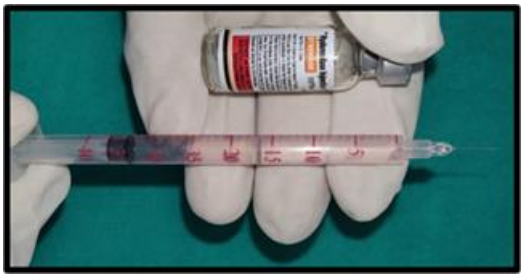

Fig. 1: 1ml Inj. Hyaluronidase(1500IU)

In the intervention group, 1 mL of hyaluronidase (1500 IU) was administered submucosally immediately after extraction, with 0.5 mL injected along the mesial flap margin and 0.5 mL along the distal flap margin before

wound closure. The control group received an identical volume (1 mL) of normal saline using the same injection technique. Flaps were repositioned and secured with interrupted silk sutures. All participants received identical postoperative antibiotic coverage for three days.

Fig. 2: Administration of injection hyaluronidase submucosally

Outcome Measures

Participants were evaluated preoperatively and on postoperative days 1, 3, and 7.

- **Pain:** Assessed using a 10-point Visual Analog Scale (VAS), where 0 indicated no pain and 10 indicated the worst imaginable pain.
- **Facial Edema:** Evaluated using three linear facial measurements (tragus–oral commissure, tragus–pogonion, and lateral canthus–gonion). The sum of these measurements represented facial swelling.
- **Trismus:** Assessed by measuring the maximum interincisal mouth opening using a Vernier caliper.
- **Patient-Centered Outcome:** Assessed using a pilot-tested Patient-Centered Outcome Questionnaire (PCOQ) comprising 13 items adapted from the Oral Health Impact Profile (OHIP).

Statistical Analysis

Data were analyzed using Microsoft Excel, OpenEpi version 3.0, and Epi Info version 7.2.2.2. Continuous variables were summarized descriptively and compared using the Mann–Whitney U test (between groups) and paired *t*-test (within groups). Categorical variables were analyzed using the chi-square test. A p-value ≤ 0.05 was considered statistically significant.

Results

A total of 60 patients who fulfilled the eligibility criteria were enrolled and randomly allocated into two groups: the hyaluronidase (HUD) group (n = 30) and the normal saline (NS) group (n = 30). All participants completed the scheduled follow-up evaluations on postoperative days 1, 3, and 7, and were included in the final analysis.

Table 1: Study and Control Group

S.no.	Groups	Type of Injection used	No. of patients
1.	Study Group	Hyaluronidase 1500 IU	30
2.	Control Group	Normal saline solution	30

Table 2: Age Distribution (N=60)

Age Group (In Years)	Inj. HUD N (%)	Inj. NSM N (%)
18-27	15 (50.0)	18 (60.0)
28-37	13 (43.3)	09 (30.0)
38-47	02 (6.7)	03 (10.0)
Total	30 (100.0)	30 (100.0)

Group with Inj. HUD Mean(±SD) is 29.0 (±5.3)

Group with Inj. NS – Mean (±SD) is 27.6 (±6.8)

Table 3: Sex Distribution (N=60)

Sex	Inj. HUD N (%)	Inj. NS N (%)
Male	19 (63.3)	16 (53.3)
Female	11 (36.7)	14 (46.7)
Total	30 (100.0)	30 (100.0)

Table 4: Involved Tooth Number (N=60)

Tooth Number	Inj. HUD N (%)	Inj. NS N (%)
38	16 (53.3)	19 (63.3)
48	14 (46.7)	11 (36.7)
Total	30 (100.0)	30 (100.0)

Table 5: Type of Impaction (N=60)

Type of Impaction	Inj. HUD N (%)	Inj. NS N (%)
D	8 (26.7)	4 (13.3)
H	10 (33.3)	3 (10.0)
M	10 (33.3)	20 (66.7)
V	2 (6.7)	3 (10.0)
Total	30 (100.0)	30 (100.0)

Table 6: Assessment of Pain (VAS Score) pre and post-op among both groups (N=60)

Operative Day	Mean	Standard Deviation	Chi Square Value	P Value*
Injection HUD Group				
Pre-op (Baseline)	2.8	1.79	NA	NA
P1 (Post-op Day 1)	2.5	1.43	0.75	0.458
P3 (Post-op Day 3)	1.3	1.06	3.53	0.001
P7 (Post-op Day 7)	0.3	0.7	7.05	<0.0001
Injection NS Group				
Pre-op (Baseline)	2.30	1.78	NA	NA
P1 (Post-op Day 1)	4.73	2.16	4.80	<0.0001
P3 (Post-op Day 3)	3.2	1.65	1.87	0.072
P7 (Post-op Day 7)	1.27	1.08	2.77	0.010

Paired T Test

Table 6 compares the changes in VAS pain scores within the Injection HUD and Injection NS groups. The Injection HUD group showed a significant reduction in pain by postoperative days 3 and 7, whereas the Injection NS group experienced a significant increase in pain on day 1, with significant improvement only by day 7. Overall, the HUD group demonstrated earlier and greater postoperative pain reduction than the NS group.

Table 7: Assessment of Mouth Opening pre and post-op among both groups (N=60)

Operative Day	Mean	Standard Deviation	Chi Square Value	P Value*
Injection HUD Group				
Pre-op (Baseline)	45.90	5.08	NA	NA
MO1 (Post-op Day 1)	39.23	6.87	6.51	<0.0001
MO3 (Post-op Day 3)	42.47	4.9	5.11	<0.0001
MO7 (Post-op Day 7)	46.33	4.3	-0.76	0.45
Injection NS Group				
Pre-op (Baseline)	46.33	4.70	NA	NA
MO1 (Post-op Day 1)	32.73	5.49	10.56	<0.0001
MO3 (Post-op Day 3)	37.73	3.67	10.52	<0.0001
MO7 (Post-op Day 7)	43.37	4.46	5.27	<0.0001

*Paired T Test

Table 7 shows that mouth opening decreased significantly in both groups on postoperative days 1 and 3 ($p < 0.0001$). By day 7, the Injection HUD group recovered to baseline levels ($p = 0.45$), whereas the Injection NS group continued to show significantly reduced mouth opening ($p < 0.0001$), indicating faster recovery from trismus with hyaluronidase.

Table 8: Assessment of Swelling pre and post-op among both groups (N=60)

Operative Day	Mean	Standard Deviation	Chi Square Value	P Value*
Injection HUD Group				
Pre-op (Baseline)	85.0	9.21	NA	NA
S1 (Post-op Day 1)	90.3	9.07	11.77	<0.0001
S3 (Post-op Day 3)	87.5	9.36	7.2	<0.0001
S7 (Post-op Day 7)	83.1	9.67	1.4	0.170
Injection NS Group				
Pre-op (Baseline)	84.43	9.67	NA	NA
S1 (Post-op Day 1)	89.17	10.01	7.37	<0.0001
S3 (Post-op Day 3)	87.30	9.93	7.37	<0.0001
S7 (Post-op Day 7)	85.83	9.82	1.34	0.190

*Paired T Test

Table 8 shows that postoperative swelling increased significantly in both the Injection HUD and Injection NS groups on postoperative days 1 and 3 ($p < 0.0001$). By day 7, swelling had returned to near baseline in both groups, with no statistically significant difference from preoperative values (HUD: $p = 0.170$; NS: $p = 0.190$), indicating recovery.

Table 9: Assessment of PCOQ post-operatively among both groups (N=60)

Operative Day	PCOQ Values Mean (±SD)	F	P Value*
PCOQ1 (Post-op Day 1)	49.40 (±6.55)	424.74	<0.0001
PCOQ3 (Post-op Day 3)	33.88 (±5.39)		
PCOQ7 (Post-op Day 7)	21.88 (±2.94)		

*ANOVA Test

Table 9 shows the postoperative changes in PCOQ scores among the study participants (N = 60). The mean score decreased significantly from 49.40 ± 6.55 on postoperative day 1 to 33.88 ± 5.39 on day 3 and 21.88 ± 2.94 on day 7, indicating progressive improvement in patient-reported postoperative recovery. The difference across all time points was highly significant (ANOVA: $F = 424.74$, $p < 0.0001$).

Discussion

Impacted mandibular third molars are commonly removed because of their high prevalence and associated complications. This randomized controlled trial demonstrated that submucosal hyaluronidase significantly reduced postoperative pain and trismus while improving patient-centred outcomes compared with normal saline, although no significant reduction in facial edema was observed.[1,2,10]

The analgesic and functional benefits observed are consistent with previous studies reporting enhanced postoperative recovery following hyaluronidase or hyaluronic acid administration.[7] Improved mouth opening may be attributed to enhanced tissue permeability, reduced inflammatory exudate, and faster resolution of inflammation. In contrast, the lack of a significant effect on swelling agrees with studies suggesting that postoperative edema is multifactorial and influenced by surgical trauma and individual inflammatory responses.[7,11-13]

The study's strengths include its randomized double-blind design, standardized surgical protocol, and assessment of both clinical and patient-reported outcomes. Limitations include the single-centre design, modest sample size, and short follow-up period. Overall, submucosal hyaluronidase appears to be a safe and effective adjunct for improving early postoperative recovery after mandibular third molar surgery.

Conclusion

Submucosal hyaluronidase is a safe and effective adjunct following impacted mandibular third molar surgery, significantly reducing postoperative pain and trismus while improving patient-reported recovery. However, it showed no significant effect on postoperative facial edema. These findings support its potential clinical use to enhance early postoperative recovery, although larger multicenter studies are needed to confirm its efficacy and establish standardized treatment protocols

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