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Evaluation of the efficacy of salmon calcitonin nasal spray on bone healing following surgical removal of impacted third molar: a randomized controlled study

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Abstract (J Korean Assoc Oral Maxillofac Surg 2026;52:73-79)

Objectives: To assess the efficacy of salmon calcitonin spray on postoperative pain, serum calcitonin levels, and bone healing after surgical removal of impacted mandibular third molar.

Materials and Methods: This prospective study included 100 patients who required surgical removal of impacted mandibular third molars under local anesthesia. Group I included 50 patients who received intranasal serum calcitonin spray, and Group II included 50 patients who did not receive serum calcitonin spray. The postoperative pain was evaluated on the 1st, 3rd and 7th days. The serum osteocalcin levels were assessed at 1 month, and bone density was evaluated at the 3rd month postoperatively.

Results: The severity of pain was less in Group I on days 3, and 7 postoperatively compared to Group II (P<0.05). The postoperative serum calcitonin level was higher in Group I compared to Group II (P<0.05), and the bone density was greater in Group I when compared to Group II evaluated at the 3rd month postoperatively (P<0.05).

Conclusion: The results of our study delineate that Group I patients had better efficacy in controlling pain and improved bone healing with calcitonin nasal spray when compared to Group II patients.

Key words: Impacted tooth, Calcitonin, Nasal spray, Pain, Osteocalcin

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I. Introduction

The primary objective of a clinician after third molar removal was to regain the patient's masticatory function and restore aesthetics. Numerous drawbacks have been advocated post-surgery, including pain, paresthesia, edema, and delayed wound healing. The severity of postoperative sequel can be effectively assessed using inflammatory biomarkers, such as, blood counts, C-reactive protein (CRP) and erythrocyte sedimentation rate[1,2]. Whilst neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) accurately predict the systemic and chronic inflammatory conditions[1]. The postoperative bone healing was influenced by various local[3] and systemic factors[4], and habits such as smoking[5] and alcoholism[6] complicate wound healing. Various methods have been employed such as the utilization of bone grafting techniques which acts as an osteoinductive material helps in preservation of the alveolar bone and enhances bone formation, nutritional supplementations includes proteins, minerals and vitamins[7], platelet-rich fibrin[8], bone morphogenic proteins, stem cells[3] and medications[9] have highly favored patient compliance postoperatively.

Calcitonin is a calciotropic hormone, used in the management of osteoporosis, Paget's disease, and hypercalcemia[10]. Calcitonin has been widely used by orthopedic surgeons as an adjunct modality and as a therapeutic agent in the management of fractures and bone-related disorders[11]. Clinically, cal-

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citonin is known for its effectiveness in reducing postoperative pain and decreasing the excretion of hydroxyproline and resultant bone loss[12]. However, only a few animal studies[13,14] have been assessed on the alveolar bone healing using calcitonin spray.

Gabopoulou et al.[15] compared the analgesic effects of opioids combined with salmon calcitonin in patients with complete hip arthroplasty under epidural anesthesia. The authors found that salmon calcitonin, when combined with local anesthesia, produced analgesic effects; hence, calcitonin administration remains an alternative for the control of acute postoperative pain. Lucchesi and Kwok[16] presented a case of chronic osteomyelitis and subsequent mandibular fracture. The patient was subcutaneously administered 50 units of salmon calcitonin daily, which eventually relieved bone pain and improved bone healing. Moreover, no studies have analyzed the utility of salmon calcitonin through the nasal route.

The present study was aimed to focus on the effect of salmon calcitonin spray on bone healing following surgical removal of an impacted mandibular third molar.

II. Materials and Methods

1. Study design

This present study was conducted on 100 patients who reported to the Department of Oral and Maxillofacial Surgery, Madha Dental College and Hospital, Chennai, for the surgical extraction of impacted mandibular third molars. Ethical clearance for the present study was obtained from the Institutional Ethical Review Board of Madha Dental College and Hospital (MDCH/IEC/2022/07) and registered with the Clinical Trial Registry of India (CTRI/2025/09/094339). The nature of the study was explained in detail to all the participants included in the study. Informed written consent was also obtained from all the study subjects. Inclusion criteria were: Systemically healthy Subjects between 18-40 years of age with impacted mandibular third molars, American Society of Anesthesiologists (ASA) I. Exclusion criteria were: Patients with known systemic diseases, patients with periapical pathology, patients other than ASA I, patients with history of allergies, bleeding disorders, pregnant and lactating mothers, and patients with metabolic disorders.

2. Sample size estimation

A pilot study included 10 patients. Based on the outcomes of the pilot study, the sample size was calculated using the statistical software G*Power 3.1.9.7 with effect size 0.32, power 95% and 95% confidence interval. The total sample size for the present study was estimated to be 100 patients (50 in each group).

3. Blinding

In this study, double blinding was performed, with the operating surgeon and the investigator unaware of the use of intranasal calcitonin spray. The investigator was a third person who was not related to the study. The assistant surgeon instructed the procedure for administering intranasal calcitonin nasal spray to the patients. The patient and the assistant surgeon were not blinded.

4. Randomization and allocation

The patients included in this study were randomly allocated into groups through a block randomization method. Patients who chose Block A were received intranasal calcitonin spray, whereas those who chose Block B were not administered with calcitonin spray. Allocation concealment was carried out by a third person who was not involved in the study.

5. Groups

Group I included 50 patients who received intranasal salmon calcitonin spray, and 50 patients in Group II did not receive the nasal spray.

6. Surgical procedure

The procedure of third molar removal was performed under a sterile aseptic environment by a single experienced Oral surgeon. Preoperative intraoral site preparation was done using 5% povidone-iodine solution. Inferior alveolar nerve block was administered with 2% lidocaine hydrochloride and 1:80,000 adrenaline. Ward's incision was placed using a no 15 scalpel, and a full-thickness mucoperiosteal flap was raised with a periosteal elevator. Bone guttering was performed using a conventional straight hand piece and #702 tapered fissure carbide bur under copious saline irrigation. The tooth was then elevated and retrieved from the socket using forceps. The extracted sockets were then examined for remnants and irrigated well using saline. The sockets were then closed primarily with simple interrupted sutures using

3-0 silk. The patients in Group I were administered intranasal serum calcitonin spray (Calcinase; Cipla Industries). This intranasal calcitonin spray was prescribed at a dose of 200 IU (0.09 mL), delivered as 1 puff per day for 30 postoperative days. Patients in Group II were not administered calcitonin nasal spray. The postoperative instructions were given to patients of both groups and prescribed with antibiotics and analgesics (cefixime 200 mg tablet and ketorolac 10 mg tablet twice daily for three days).

7. Follow up assessments

The patients in both groups were analyzed for postoperative pain, serum osteocalcin levels and bone healing. The postoperative pain was evaluated on the 1st, 3rd and 7th days using a visual analogue scale (VAS). The serum osteocalcin levels (ng/dL) were assessed by collecting 2 mL of blood sample from participants of both groups after 30 days. Bone healing was evaluated at the 3rd month postoperatively using cone-beam computed tomography (CBCT), which was recorded in grayscale values.(Fig. 1, 2) The CBCT examination was performed using Carestream CS9300C (Carestream Dental) with 8×8 cm field of view and 180 μm voxel resolution. The region of interest selection was determined at the cervical, middle and apical regions of the newly formed bone. The measures obtained at each region were recorded and averaged. Inter-observer assessments were performed to ensure the reliability and reproducibility of results.

8. Statistical analysis

The data were entered in a Microsoft Excel 365 spreadsheet and evaluated using SPSS software (IBM SPSS Statistics ver. 20.0; IBM). The postoperative parameters, such as the pain and serum osteocalcin levels, were statistically analyzed using the Mann-Whitney U test and bone regeneration was analyzed using Friedman's two-way ANOVA test. The statistical significance was set at $P<0.05$.

III. Results

The present study included 100 patients, who required surgical removal of impacted mandibular third molars. Among 100 patients, 34 were male and 66 were female, with a mean age of 34 years. The obtained data were evaluated statistically using the Mann-Whitney U test through IBM SPSS Statistics ver. 20.0.(Table 1, Fig. 3-5)

1. Pain (VAS)

The severity of pain was less in Group I when compared to Group II with a mean difference (standard deviation [SD]) of 1.64 (1.00) on day 3 and 0.12 (0.33) on day 7 which showed a statistical significance of $P<0.05$ for Group I respectively.



Fig. 1. Cone-beam computed tomography showing bone healing evaluated at 3rd month in Group I.
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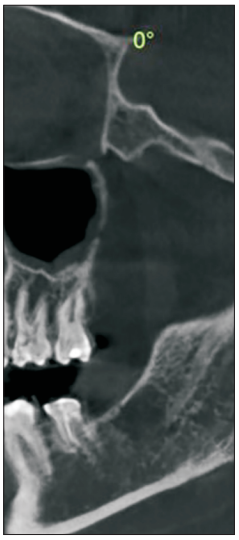


Fig. 2. Cone-beam computed tomography showing bone healing evaluated at 3rd month in Group II.
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Table 1. Mann-Whitney U test for the statistical significance of pain, serum calcitonin level and Friedman's two-way ANOVA test for Bone healing between Group I and Group II

Parameter	Mean difference (standard deviation)		*P*-value*
	Group I	Group II	
Pain, VAS			
Day 1	7.26 (1.01)	7.36 (1.27)	0.934
Day 3	1.64 (1.00)	3.04 (1.47)	0.001
Day 7	0.12 (0.33)	0.50 (0.86)	0.016
Calcitonin level (ng/dL)			
Preoperative	65.718 (8.01)	62.734 (9.45)	1.032
Postoperative	68.972 (7.48)	58.685 (6.38)	0.018
Bone healing, GSV			
Immediate	106.02 (24.07)	101.20 (20.67)	0.085
3rd month	144.60 (22.53)	126.66 (20.75)	0.008

(VAS: visual analogue scale, GSV: gray scale value)
*P<0.05 was set to be statistically significant.
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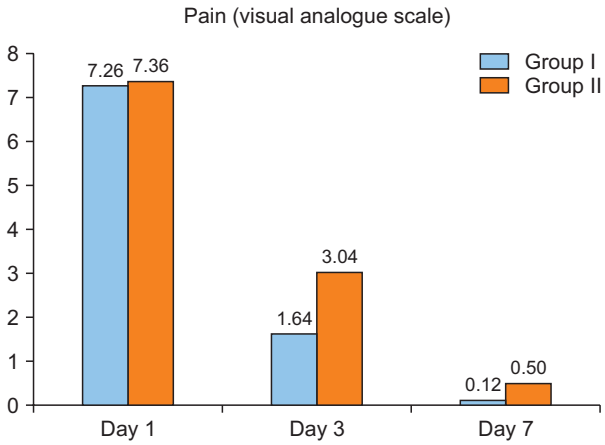


Fig. 3. Postoperative outcomes of pain evaluated at 1st, 3rd and 7th day between Group I and Group II.
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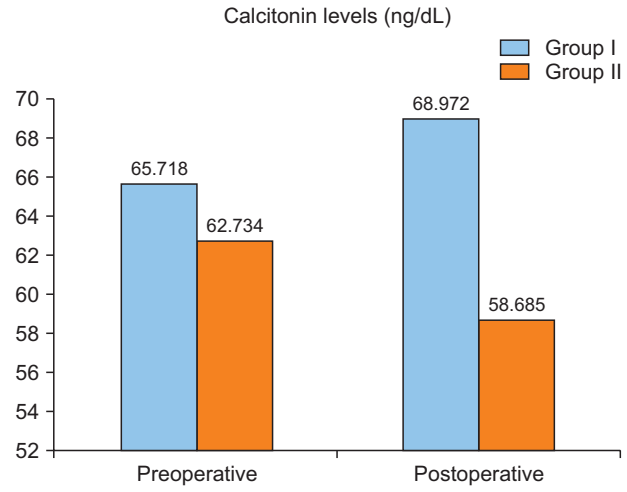


Fig. 4. Postoperative outcomes of calcitonin levels evaluated after 30 days between Group I and Group II.
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2. Calcitonin levels (ng/dL)

The postoperative serum calcitonin level in Group I was 68.972 (7.48) and 58.685 (6.38) in Group II, which showed a statistical significance of P<0.05 for Group I, respectively.

3. Bone healing (gray scale value)

The bone healing in Group I was 144.60 (22.53) and in Group II, it was 126.66 (20.75) at the 3rd month postoperatively which showed a statistical significance of P<0.05 for Group I, respectively.

IV. Discussion

The study was to evaluate the effect of salmon intranasal calcitonin nasal on postoperative outcomes, such as pain, calcitonin levels, and bone healing after mandibular third molar removal.

Third molar removal presents with various postoperative complications, which can be better assessed through inflammatory biomarkers (CRP, NLR and PLR) and managed through non-steroidal anti-inflammatory drugs (NSAIDs). Yilmaz et al.[1], emphasized that CRP, NLR and PLR values had a significant correlation with the postoperative VAS scores and analgesic consumption by the patients. However, edema and trismus had no significance with the values of bio-

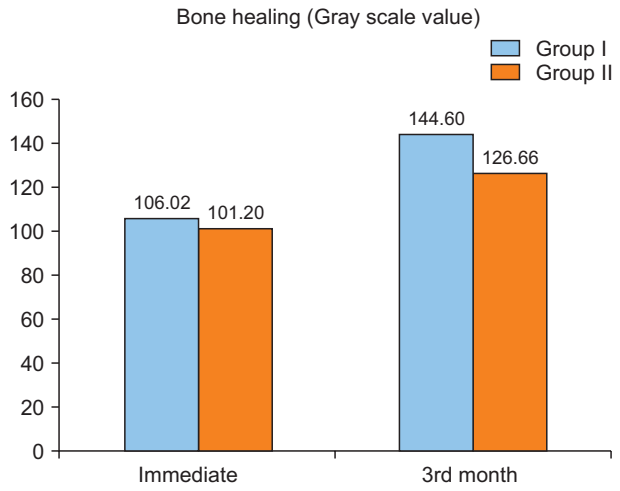


Fig. 5. Postoperative outcomes of bone healing evaluated at 3rd month between Group I and Group II.
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markers. This determines biomarkers as reliable indicators of patient comfort during healing and aids in implementing the desired postoperative care. The NSAIDs are effective in controlling pain of different intensities, which range from mild, moderate to severe[17,18]. However, NSAIDs possess numerous adverse effects, such as psychological, gastrointestinal, renal disturbances and drug-to-drug interactions[19]. These adverse effects can be altered by the utilization of intranasal calcitonin spray, which was considered superior to other available anti-inflammatory drugs[19].

Zhou et al.[20] compared the efficacy of diclofenac and calcitonin in 109 patients with type 1 Modic changes and low back pain. Sixty-two patients received 50 IU of calcitonin intramuscularly, and 47 patients were prescribed diclofenac 75 mg once daily for 4 weeks. The results suggested that the calcitonin group showed significant improvement compared with the diclofenac group in controlling type I Modic changes and low back pain. Schwartz et al.[21] investigated the effects of salmon calcitonin 100 IU per 1 mL of saline, administered 5 times a week for 6 weeks, among 13 patients presented with atypical facial pain. However, the study was withdrawn due to a high dropout rate caused by calcitonin-related side effects. The author emphasized the need for future studies on calcitonin delivered through the nasal route to reduce such adverse effects and to obtain more consistent and reliable results.

Calcitonin is synthesized in the thyroid gland by the parafollicular cells, which helps in the maintenance of bone turnover by preventing the activity of bone resorption. The normal secretion of calcitonin levels is 0.5 mg/day and 0.2 ng/mL, respectively[22]. Calcitonin can be administered safely through oral and parenteral routes[23,24], which is accompanied by several complications. Calcitonin, administered through the oral route, is degraded by the gastric acids due to its polypeptide structure, and the bioavailability of the drug is also reduced[23]. Patients with liver disturbances may not metabolize the orally administered drug because the first-pass metabolism of the drug occurs in the liver. Hence, the efficacy achieved through these supplements is minimal. These shortcomings are counteracted by administration of calcitonin through the nasal route, which is directly absorbed by the nasal mucosa and enters the bloodstream, bypassing the liver. Calcitonin reaches its maximum efficacy within one hour of administration ensuring better bioavailability.

The present study evaluated pain between groups on the 1st, 3rd and 7th postoperative days. The action of calcitonin occurs through both central and peripheral systems. Peripheral action occurs through serotoninergic and catecholaminergic receptors, and the central system is through the release of beta-endorphin, which is a neuropeptide that works on the opioid receptors as an agonist[25]. The intensity of pain in Group I was less when compared to Group II patients, which showed a statistical significance of $P<0.05$. While Yazdani and Ahmadpour[26] showed a statistical insignificant difference between the intervention and control groups. The author also stated that calcitonin nasal spray would be an effective medication in controlling pain if the required analgesic consumption is minimised. Tarantino et al.[9] emphasized that the intensity of intranasal calcitonin spray is high, and also, the duration of analgesic action is longer when compared to other routinely available analgesics.

The present study assessed calcitonin levels after 30 days and bone healing at the 3rd month postoperatively. Calcitonin implies positive bone turnover by decreasing both the action of bone resorption and the formation of new osteoclasts, angiogenesis[12]. Group I patients showed a high calcitonin level and advanced bone healing when compared to Group II patients ($P<0.05$), which had a positive association with Trovas et al.[27] and with Lucchesi and Kwok[16]. Both osteoblastic and osteoclastic activity occurs simultaneously; hence a decrease in the osteoclasts eventually decreases the osteoblasts. This signifies that calcitonin nasal spray used for a longer duration may show minor differences in the osteocalcin concentration[28].

Intranasal calcitonin spray is safer when compared to other routes of administration. However, calcitonin is associated with numerous adverse effects, which include nasal irritation, sinusitis, rhinitis, epistaxis, hypersensitivity reactions[29],

and potential for malignancy[30,31]. Ninety-seven percent had mild to moderate effects, and only 10% had severe effects with calcitonin administration[32,33]. Flushing and nausea was experienced in patients administered through parenteral or intramuscular routes[33,34]. Wells et al.[35] found no relationship between calcitonin and malignancy. In the present study, none of our patients experienced any adverse effects.

Calcitonin nasal spray must be of prime importance when compared to other available analgesics. Firstly, the patients experience complete relief of pain in situations such as post-surgical pain, neuropathies, and migraine. Secondly, the administration of intranasal calcitonin spray is simple, safer, and does not show any significant adverse effects. Thirdly, calcitonin nasal spray can be used in patients with disturbances in the liver, renal, and gastrointestinal systems to minimise the dose of required analgesics[36].

The present study had a few limitations: The sample size was small; hence, studies with larger samples would yield better results with calcitonin nasal spray. The study design was single-centred, with a relatively short follow-up period, and bone healing was assessed solely on radiological parameters. Mentally challenged and geriatric patients may have difficulty using a nasal spray, as it requires manual administration of calcitonin.

V. Conclusion

Salmon-calcitonin nasal spray is an effective and adjuvant treatment modality to other routinely available analgesics in controlling postoperative pain and advanced bone healing. The technique of nasal spray is simple and easy to administer, which can even be utilized in patients with altered systemic conditions. The results of our study delineate that Group I patients had better efficacy and excellent postoperative outcomes with calcitonin nasal spray when compared to Group II patients.

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Authors' Contributions

Study conception and design was performed by H.N. and S.C. Material preparation, data collection and analysis were performed by D.A.P., D.N., and K.K.P. The first draft of the manuscript was written by B.R. and G.S.S., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Ethical Review Board of Madha Dental College and Hospital (MDCH/IEC/2022/07). Informed consent was obtained from all individual participants included in the study.

Consent for Publishing Photographs

Written informed consent was obtained from the patients for publication of this article and accompanying images.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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