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Efficacy of Local Simvastatin in Bone Regeneration Following Surgical Extraction of Mandibular Third Molar: A Split Mouth Study

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ABSTRACT:
Background:
Surgical removal of impacted mandibular third molars is a common procedure and is often followed by postoperative pain, swelling, and alveolar bone loss. Various materials have been used to enhance socket healing, but many have limitations. Simvastatin, a widely used lipid-lowering drug, has shown osteogenic, angiogenic, and anti-inflammatory properties. This study aimed to evaluate the effect of locally delivered simvastatin on postoperative pain, swelling, and bone regeneration following mandibular third molar extraction.
Materials and Methods:
This prospective, double-blinded, split-mouth observational study was conducted on 40 patients requiring bilateral surgical extraction of impacted mandibular third molars. One extraction socket (intervention site) received 10 mg of simvastatin powder combined with gelfoam, while the contralateral socket served as the control and received gelfoam alone. Pain was assessed using the Visual Analog Scale (VAS) on the 3rd, 7th, and 14th postoperative days. Facial swelling was evaluated using tape-measuring methods at the same intervals. Radiographic bone density was assessed using cone-beam computed tomography at the 2nd, 4th, and 6th postoperative months.
Results:
Both groups showed a significant reduction in pain and swelling over time. Radiographic evaluation demonstrated a significant and progressive increase in bone density in both groups; however, the simvastatin group consistently showed significantly higher bone density values at the 2nd, 4th, and 6th months compared to the control group ($P < 0.0001$).
Conclusion:
Local application of simvastatin in mandibular third molar extraction sockets significantly enhances bone regeneration. Simvastatin appears to be a safe, effective, and economical adjunct for improving bone healing after third molar surgery, making it a promising option for socket preservation.
Key-words: *simvastatin, bone graft, osteoinduction, bone formation, extraction socket preservation*

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I. INTRODUCTION:

Tooth extraction, particularly the surgical removal of mandibular third molars, is one of the most commonly performed procedures in oral and maxillofacial surgery. Extraction is invariably followed by a cascade of biological events that result in alveolar bone resorption and dimensional alterations of the socket. It is reported that 40%–60% of the jaw bone atrophy that normally happens 2–3 years after tooth extraction and continues at a rate of 15%–25% per year until death[1]. This post-extraction bone loss can occur due to many reasons, like the absence of mechanical stimulation and disruption of local vascular supply[2], often leading to reduced ridge height and width[3]. Such events can compromise prosthetic rehabilitation, implant placement, and long-term functional and esthetic outcomes[4].

There are four distinct stages of socket healing, which can be distinguished into hemostasis and coagulation, inflammatory, proliferative, and remodeling stage[5]. Bone healing following extraction is a complex process involving osteoinduction, osteogenesis, and osteoconduction[6]. Although spontaneous healing does occur over a time period, it is often incomplete and unpredictable, also in cases of extraction socket after impacted third molar removal. In this regard, approximately 0.5 mm bone resorption has been reported[7]. To counteract these limitations, various ridge preservation and socket augmentation techniques have been proposed, including autogenous grafts, allografts, xenografts, alloplastic materials, barrier membranes, and biologically active agents[8]. However, many of these approaches are associated with certain limitations[7].

In recent years, interest has been shifted toward pharmacological agents capable of stimulating endogenous bone regeneration. Among these, statins—commonly prescribed as lipid-lowering drugs—have demonstrated significant osteopromotive properties[9]. Simvastatin, a lipophilic HMG-CoA reductase inhibitor, has been shown to enhance bone formation by upregulating bone morphogenetic protein-2 (BMP-2), vascular endothelial growth factor (VEGF), and other osteogenic markers, while simultaneously inhibiting osteoclastic activity[10]. These pleiotropic effects make simvastatin as a promising adjunct in regeneration of bone[11]. It also reduce inflammatory cytokine levels, enhance osteoblast differentiation and promote angiogenesis[12,13].

The local delivery of simvastatin directly into extraction sockets offers several advantages over systemic administration[9]. It bypasses hepatic first-pass metabolism, achieves higher local drug concentrations, minimizes systemic side effects, and provides proper healing environment. Multiple clinical studies have demonstrated enhanced bone density and accelerated osseous regeneration following local simvastatin application in mandibular third molar extraction sockets[14] . Most clinical trials have utilized simvastatin as a dosage ranges as low as 1.2mg when applied topically to 10mg/kg/day on systemic application, which appears to strike a balance between osteogenic efficacy and safety[15].

In addition to bone regeneration, postoperative morbidity—manifested as pain and swelling—remains a significant concern after third molar surgery. An ideal graft material should not only promote bone regeneration but also minimize postoperative discomfort.

Among the various socket grafting materials, including autologous blood-derived products and synthetic substitutes, it is essential to critically evaluate their relative effectiveness in terms of bone healing, soft-tissue response, pain, and swelling. This forms the basis for the present study, which aims to assess and compare the regenerative outcomes and postoperative sequelae of local simvastatin following surgical extraction of mandibular third molar.

II. SUBJECTS AND METHODS:

Study Design-

This is a observational prospective double blinded study done on 40 patients who required bilateral extraction of mandibular third molars. The study was approved by the Institutional Ethical Committee Board. The procedure was explained to all patients and informed consent was obtained.

Inclusion criteria-

1. Patients required bilateral extraction of third molars
2. Patients who were willing to participate in the study
3. Patients 20–40 years old
4. Patients having no other systemic diseases or comorbidities.

Exclusion criteria-

1. Presence of any systemic illnesses
2. Pregnant female
3. Patients who are on radiation therapy or chemotherapy to the head-and-neck region
4. Patients who are on long-term antibiotics or steroid therapy.
5. Patient with poor oral hygiene and/or generalized chronic destructive periodontitis
6. Impacted teeth interfering with the inferior alveolar canal
7. Patient with peri-apical pathosis, cystic lesions and Heavy smokers.

Laboratory Investigation-

- Complete hemogram
- Coagulation profile
- Serological screening
- Radiographs -IOPAR (Intraoral Periapical Radiograph) and CBCT (Cone Beam Computed Tomography)

Case sheet-

Information of each patient was recorded on prepared case sheet, it includes the following data: General information as name, age, gender, occupation, address. Past medical history, Past dental history, Extra oral examination, Intra oral examination, Intra operative difficulty assessment of the surgical procedure according to time and technique, Postoperative complication like wound dehiscence, dry socket, and Postoperative pain, swelling, mouth opening.

Case details-

All patients were selected subsequently diagnosed with impacted mandibular third molar bilaterally. Pre-operative CBCT(cone beam computed tomography) was done[Fig. 1]. The procedure was employed under strict aseptic conditions under local anesthesia of inferior alveolar, long buccal and lingual nerve. The study was performed using the split-mouth method. Full thickness mucoperiosteal flap elevation was done to expose the impacted tooth on one side and extraction of the tooth was done using conventional surgical handpiece and burs. Then the socket was washed with normal saline and was assigned for the placement of 10mg simvastatin powder combined with gelfoam soaked with normal saline as a carrier (study socket) [Fig. 2]. The impacted tooth from the contralateral side of the same patient was extracted in same way and placement of gelfoam soaked with normal saline entirely(control socket) was done either on the same day or with a gap of one week in some cases. Suturing of both the socket was done using 3-0 black silk suture. The study and control sites were assigned to the same patient to rule out bias due to individual variations.

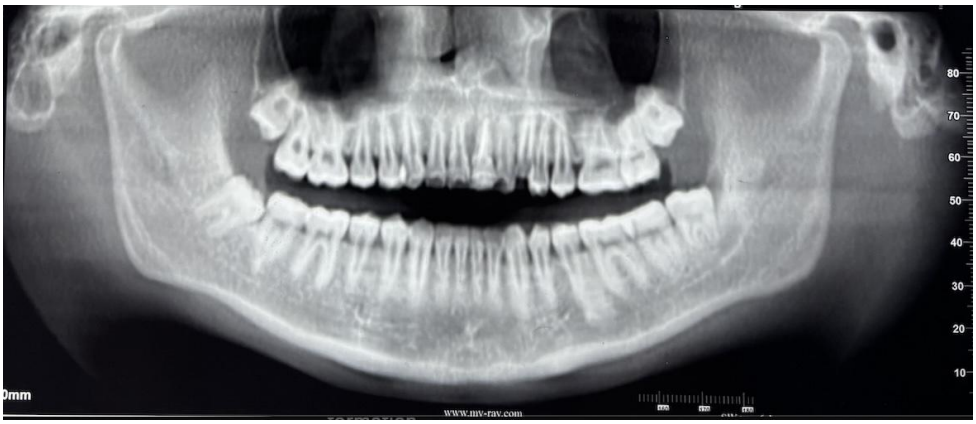

Fig. 1: Pre-operative radiograph of patient having bilateral impacted mandibular third molar

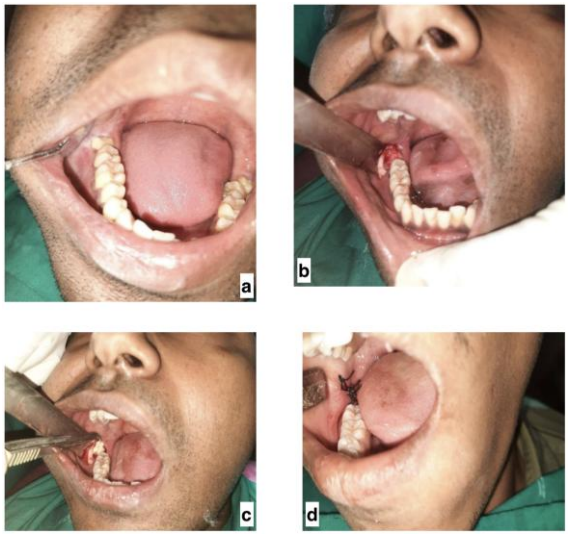

Fig. 2: Intra-operative pictures of simvastatin bone graft in third molar extraction socket

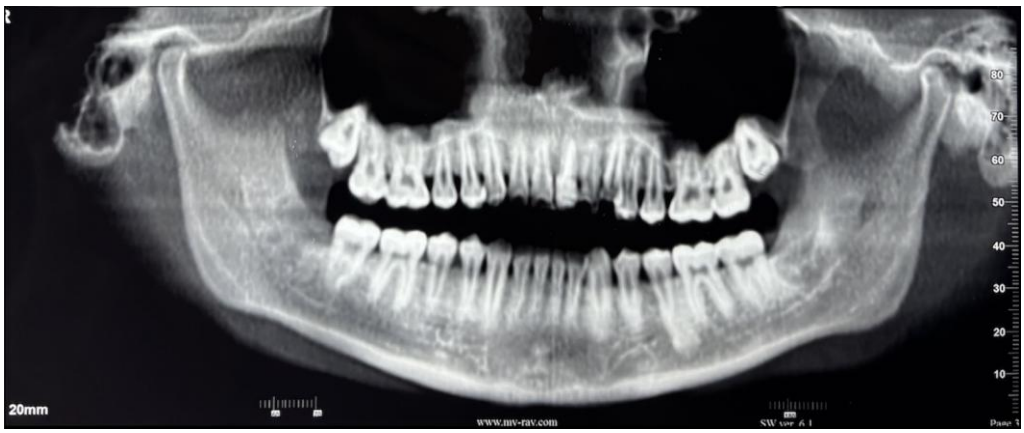

Fig. 3: Post-operative radiograph of 6th month of patient in which right side were treated with simvastatin bone graft and left side was treated as control radiograph of patient

Parameters-

- Evaluation of pain using Visual Analog Scale (VAS)
- Clinical evaluation of swelling using tape-measuring method
- Relative bone density measurement using CBCT (Cone Beam Computed Tomography) at 2 different extraction sites [Fig. 3]

III. RESULTS:

Evaluation of pain

Pain intensity was evaluated using the Visual Analog Scale (VAS) on the 3rd,7th and 14th postoperative days. The patients were asked to rate the pain on a 10-point VAS according to the intensity of the pain.

Evaluation of swelling

Preoperatively, the swelling was measured by taking a horizontal distance from the corner of the mouth to the tragus of the ear, tragus of the ear to pogonion and a vertical distance between outer canthus of the eye and gonion using measuring tape following the natural convexity of the patient's face. The procedure was repeated on the 3rd, 7th and 14th postoperative days. The swelling was compared to the nongraft side to measure whether the simvastatin causes additional swelling in the soft tissues other than the expected surgical swelling.

Bone density analysis

This was done by the digital software program "IRYS viewer" Using the preoperative radiographs

as guide, the area of the extracted molar was marked. The image parameters were standardized and applied for subsequent radiographs at the 2nd, 4th and 6th postoperative months for all patients. The mean value of the selected area was noted using histogram tool and compared.

Statistical Analysis:

The collected data was tabulated in a spreadsheet using Microsoft Excel 2024 and then statistical analysis was carried out using the GraphPad Prism for Windows, Version 10.1.2 (GraphPad Software, La Jolla California USA). A Shapiro-Wilk's test and a visual inspection of the histograms, standard Q-Q plots, and box plots showed that the collected data were approximately normally distributed for all the outcome variables except Pain scores. Descriptive statistics were used to report the quantitative variables in terms of mean/median (central tendency) and Standard deviation/inter-quartile range (measures of dispersion) and the categorical variables in terms of Frequencies and percentages. Both Parametric and non-parametric tests were carried out for inferential statistics. Repeated Measures Analysis of Variance (ANOVA) with post hoc Bonferroni's test or Friedman's test were employed for intra-group comparisons.

Paired-samples t-test/Wilcoxon's test was utilised for inter-treatment group comparisons owing to a split-mouth study design. The significance level set at $P \leq 0.05$.

Pain-

Inter-group comparisons(between the intervention group and control group) shows- At the 3rd day, no inter-group difference was observed ($P > 0.999$). By the 7th day, pain had markedly reduced in both groups; however, the inter-group comparison remained statistically non-significant ($P = 0.168$). At the 14th day, both groups demonstrated complete resolution of pain, and no inter-group difference ($P > 0.999$). [Table 1]

Within-group analysis showed a highly significant reduction in pain over time for both the Intervention and Control groups ($P < 0.0001$ for each). Pairwise comparisons demonstrated that pain scores at the 3rd day were significantly higher than both the 7th day and 14th day in each group (adjusted $P < 0.0001$). The comparison between the 7th day vs. 14th day was not statistically significant in either group (adjusted $P = 0.0877$).

Time Points/Treatment Groups	Intervention (*n*=40)		Control (*n*=40)		*P* value§
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
3rd Day	3.05 ± 1.09	3.00 (2.00–4.00)	3.05 ± 1.06	3.00 (2.00–4.00)	>0.999 (NS)
7th Day	0.85 ± 1.08	0.00 (0.00–1.75)	0.68 ± 1.14	0.00 (0.00–1.00)	0.168 (NS)
14th Day	0.08 ± 0.27	0.00 (0.00–0.00)	0.05 ± 0.22	0.00 (0.00–0.00)	>0.999 (NS)
***P* value‡**	<0.0001*		<0.0001*		-

Table 1. Descriptive statistics and comparative analysis of VAS pain scores

n: number of observations, SD: Standard deviation, IQR: inter-quartile Range, §: Inter-group comparisons(between the study groups); ‡: intra-group comparisons(between time-points within each study group), NS: not significant($P >0.05$), *: statistically significant ($P <0.05$)

Swelling-

At the 3rd day, the mean swelling measured from the tragus to the mouth corner was with no significant inter-group difference (mean difference: 0.04; $P = 0.08$). By the 7th day, swelling had reduced in both groups. The inter-group comparison at this time point remained non-significant (mean difference: 0.025; $P = 0.184$). On the 14th day, further reduction was observed, with the. The minimal difference between the groups was again not statistically significant (mean difference: 0.015; $P = 0.11$). [Table 2]

Time Points/Treatment Groups	Intervention (*n*=40)	Control (*n*=40)	Mean Difference	*P* value§
3rd Day	11.19 ± 0.668	11.23 ± 0.665	0.04	0.08 (NS)
7th Day	10.79 ± 0.695	10.81 ± 0.694	0.025	0.184 (NS)
14th Day	10.75 ± 0.685	10.77 ± 0.673	0.015	0.11 (NS)
***P* value‡**	<0.0001*	<0.0001*	-	

Table 2 : Descriptive statistics and comparative analysis of swelling (tragus–mouth corner distance) [cm]

n: number of observations, SD: Standard deviation, IQR: inter-quartile Range, §: Inter-group comparisons(between the study groups); ‡: intra-group comparisons(between time-points within each study group), NS: not significant(P >0.05), *: statistically significant (P <0.05)

At the 3rd day, the mean swelling measured from the tragus to the pogonion was virtually identical values with no significant inter-group difference (mean difference: 0.01; P = 0.76).
By the 7th day, swelling had reduced in both groups. The inter-group comparison again demonstrated no statistically significant difference (mean difference: –0.10; P = 0.36).
On the 14th day, further decrease in swelling was observed. Similar to earlier time-points, the inter-group difference remained statistically non-significant (mean difference: –0.10; P = 0.36).
[Table 3]

Time Points/Treatment Groups	Intervention (*n*=40)	Control (*n*=40)	Mean Difference	*P* value§
3rd Day	14.64 ± 0.753	14.65 ± 0.707	0.01	0.76 (NS)
7th Day	14.22 ± 0.771	14.12 ± 1.038	-0.1	0.36 (NS)
14th Day	14.18 ± 0.767	14.08 ± 1.042	-0.1	0.36 (NS)
***P* value‡**	<0.0001*	<0.0001*	-	

Table 3: Descriptive statistics and comparative analysis of swelling (tragus–pogonion distance) [cm]

n: number of observations, SD: Standard deviation, IQR: inter-quartile Range, §: Inter-group comparisons(between the study groups); ‡: intra-group comparisons(between time-points within each study group), NS: not significant(P >0.05), *: statistically significant (P <0.05)

At the 3rd day, the mean swelling measured from the outer canthus of the eye to the gonion was statistically significant (mean difference: 0.35; P = 0.0005). By the 7th day, swelling had reduced in both groups. The inter-group difference at this time point was not statistically significant (mean difference: 0.025; P = 0.18). On the 14th day, further decline was observed. Despite the minimal numerical difference, the inter-group comparison reached statistical significance (mean difference: 0.027; P = 0.0098) [Table 4].

Time Points/Treatment Groups	Intervention (*n*=40)	Control (*n*=40)	Mean Difference	*P* value§
3rd Day	10.62 ± 0.645	10.97 ± 0.497	0.35	0.0005*
7th Day	10.25 ± 0.670	10.27 ± 0.664	0.025	0.18 (NS)
14th Day	10.21 ± 0.669	10.23 ± 0.669	0.027	0.0098*
***P* value‡**	<0.0001*	<0.0001*	-	

Table 4 : Descriptive statistics and comparative analysis of swelling (Outer canthus of the eye–gonion distance) [cm]

n: number of observations, SD: Standard deviation, IQR: inter-quartile Range, §: Inter-group comparisons(between the study groups); ‡: intra-group comparisons(between time-points within each study group), NS: not significant(P >0.05), *: statistically significant (P <0.05)

Radiographic Bone Density-

At the 2nd month, the mean radiographic bone formation was significantly greater in the Intervention group (mean difference: –26.9; P < 0.0001). By the 4th month, both groups showed marked improvement; the difference remained statistically significant (mean difference: –28.18; P < 0.0001). At the 6th month, bone formation further increased, again demonstrating a significant inter-group difference favoring the Intervention group (mean difference: –57.38; P < 0.0001).
[Table 5]

Within-group analysis revealed a highly significant increase in bone density across all time points for both the Intervention and Control groups (P < 0.0001 for each). Pairwise comparisons showed substantial and statistically significant improvements from the 2nd month vs. 4th month, 2nd month vs. 6th month, and 4th month vs. 6th month for both groups (adjusted P < 0.0001 for all comparisons).

Time Points/Treatment Groups	Intervention (*n*=40)	Control (*n*=40)	Mean Difference	*P* value§
2nd Month	185.9 ± 49.18	159.0 ± 42.16	-26.9	<0.0001*
4th Month	433.6 ± 71.44	405.4 ± 68.44	-28.18	<0.0001*
6th Month	613.5 ± 69.62	556.1 ± 65.83	-57.38	<0.0001*
***P* value‡**	<0.0001*	<0.0001*	-	

Table 5 : Descriptive statistics and comparative analysis of radiographic bone formation
n: number of observations, SD: Standard deviation, IQR: inter-quartile Range, §: Inter-group comparisons(between the study groups); ‡: intra-group comparisons(between time-points within each study group), NS: not significant(P >0.05), *: statistically significant (P <0.05)

IV. DISCUSSION:

Preservation of alveolar bone following tooth extraction remains a critical challenge in oral and maxillofacial surgery. The present discussion evaluate the effectiveness of locally applied simvastatin, in promoting bone healing and modulating postoperative outcomes. Written informed consent included explicit disclosure of off-label drug use was obtained from the patient.

The Institutional Ethics Committee specifically approved the off-label local use of simvastatin. The study was non-commercial, investigator-initiated, and did not require DCGI approval, in accordance with Indian regulations.

The osteogenic potential of simvastatin has been consistently demonstrated across experimental and clinical studies. Its mechanism of action is primarily attributed to the upregulation of BMP-2, a key regulator of osteoblast differentiation and bone matrix formation. Additionally, simvastatin enhances angiogenesis through increased VEGF(vascular endothelial growth factor) expression, thereby improving vascularization within the healing socket—an essential prerequisite for effective bone regeneration[16,17,18].

Clinical trials evaluating local simvastatin application in mandibular third molar sockets have reported significantly higher bone density values in test groups compared to controls[6,19,20]. Radiographic assessments using cone-beam computed tomography consistently show accelerated and superior bone formation. These findings suggest that simvastatin not only enhances the quantity but also improves the quality of regenerated bone[11].

From a postoperative morbidity standpoint, the majority of studies report no statistically significant increase in pain or swelling associated with local simvastatin application when compared with control sockets. Pain scores, typically assessed using the Visual Analog Scale, tend to decrease rapidly within the first postoperative week, indicating that simvastatin does not exacerbate the inflammatory response . Beyond the core lipid-lowering actions, statins have pleiotropic effects on metabolic processes, the immunological system, and the lymphovascular system (endothelial-specific)[21]. This favorable soft-tissue response may be attributed to these anti-inflammatory and immunomodulatory effects of statins, which help regulate cytokine release and tissue repair[22,23].

An important clinical consideration is the choice of carrier material. Gelfoam has been widely used as a scaffold for simvastatin delivery due to its biocompatibility, hemostatic properties, and ability to retain the drug within the socket. The porous structure of gelfoam facilitates clot stabilization and provides a conducive environment for cell migration and angiogenesis. Studies employing simvastatin-gelfoam combinations consistently demonstrate superior outcomes compared to gelfoam alone[24].

V. CONCLUSION

Across all evaluated parameters, the Simvastatin group consistently demonstrated more favourable clinical and radiographic outcomes compared with the control group.

For postoperative pain, both groups showed a clear reduction over time. The improvement was smoother and more rapid in the Simvastatin group, which achieved earlier and more complete relief than the control group.

All indicators of postoperative swelling, including tragus–mouth corner distance, tragus–pogonion distance, and outer acanthus of the eye–gonion distance, showed a steady decrease at each successive time point. Although swelling reduced in both groups, the Simvastatin group demonstrated a more stable and progressive pattern of improvement, whereas the control group exhibited a comparatively slower reduction.

Radiographic assessment of bone healing revealed a continuous increase in bone formation in both groups during the follow-up period. The Simvastatin group consistently showed greater enhancement in bone density at each stage, reflecting superior early healing and a stronger regenerative response.

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