Section: Pharmacology

Original Research Article

LIPOPHILIC HMG COA REDUCTASE INHIBITOR "SIMVASTATIN" IMPACT ON ALVEOLAR BONE REMODELING POST DENTAL EXTRACTION

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ABSTRACT

Background: Healing of mandibular third molar extraction sockets often occurs by secondary intention, leading to alveolar ridge resorption. Preserving bone is crucial for long-term rehabilitation. Simvastatin, a lipophilic HMG-CoA reductase inhibitor, has shown osteoinductive effects by upregulating bone morphogenetic protein-2 (BMP-2) and other osteogenic markers. This study evaluated its local effect on bone regeneration post-extraction.

Materials and Methods: Forty patients requiring mandibular third molar extraction were randomized into two groups. The study group (n=20) received 10 mg simvastatin powder with gel foam in the socket, while the control group (n=20) received gel foam with saline. Pain was assessed on days 1 and 7 using the Visual Analog Scale (VAS). Bone regeneration was evaluated radiographically at 1, 6, and 12 weeks by mean gray-level histogram values. Statistical significance was set at $p < 0.05$.

Results: Demographic variables were comparable ($p > 0.05$). VAS scores showed no significant difference between groups (1.9 vs. 1.8 on day 1; both 0 on day 7, $p > 0.05$). Radiographic analysis demonstrated significantly higher mean gray-level values in the simvastatin group at week 1 (64.43 ± 12.42 vs. 56.61 ± 10.26), week 6 (85.46 ± 9.45 vs. 77.54 ± 6.33), and week 12 (102.05 ± 10.48 vs. 89.58 ± 8.65) ($p < 0.05$).

Conclusion: Local simvastatin did not influence postoperative pain but significantly enhanced bone density and regeneration in extraction sockets. It may serve as a cost-effective adjunct for alveolar bone preservation. Larger clinical trials are warranted to refine dosage and delivery methods.

Keywords: Lipophilic HMG CoA Reductase Inhibitor, Simvastatin, Alveolar Bone Regeneration, Bone Remodeling, Dental Extraction.

INTRODUCTION

Restoring tissue integrity after surgical or trauma-related injury continues to be a major challenge in maxillofacial reconstruction. Wound healing follows a highly coordinated but complex cascade of biological events aimed at re-establishing the structural and functional integrity of the affected tissue.[1] Tooth extraction is one of the most frequently performed procedures in maxillofacial practice, with mandibular third molar removal being particularly common due to its varied eruption patterns. Healing of extraction sockets generally occurs by secondary intention and may take up to a year for complete remodelling. During this period, bone resorption of approximately 0.5 mm has been reported.[2] As a result, maintaining or augmenting the alveolar ridge is of clinical importance. Bone regeneration is regulated by several growth factors, including bone morphogenetic protein-2 (BMP-2). A wide range of bone-inducing techniques have been explored, although each is associated with certain limitations.[2,3]

Successful bone regeneration requires three critical elements: osteoinduction, osteogenesis, and osteoconduction. Various grafting materials such as autografts, allografts, and xenografts have been employed to achieve these outcomes, but selecting the most suitable material remains a considerable challenge. Among them, autogenous bone grafts are considered the most effective, as they inherently provide all the essential components for bone regeneration, making them the benchmark material for grafting procedures.[4]

When the repair process restores tissue with the same structure and function as the original, it is considered regeneration. In contrast, when the defect is replaced with fibrous connective tissue or scar formation, the outcome is repair. Over recent decades, the integration of clinical, biological, and engineering sciences has accelerated the translation of laboratory discoveries into clinical practice. Although many findings are still limited to preclinical validation, their future clinical potential remains highly encouraging.[5]

In recent years, considerable attention has been directed toward the role of statins in bone biology. Several studies have highlighted their ability to activate genes associated with osteogenesis, indicating significant potential for use in craniofacial bone grafting. The osteoinductive properties of statins were notably emphasized in the work of Gutierrez GE et al.[2,6] Simvastatin, a non-hygroscopic white crystalline compound, has demonstrated multiple biological effects beyond its lipid-lowering action, including properties that promote bone formation.[7] The present study was undertaken to evaluate the osteotrophic potential of simvastatin by examining its influence on the rate of bone regeneration and bone density at different stages of the healing process.

MATERIALS AND METHODS

A total of 40 patients requiring mandibular third molar extractions were enrolled from central India. Of these, 20 patients received simvastatin (10 mg) powder combined with gel foam moistened in normal saline as the test intervention, while the other 20 patients received gel foam soaked in saline alone, serving as controls. Eligible participants were between 18 and 40 years of age, required third molar extraction, and were free of systemic diseases or comorbidities. Patients with systemic illnesses, those undergoing radiation or chemotherapy in the head-and-neck region, or those receiving long-term antibiotics or steroid therapy were excluded.

All procedures were performed under strict aseptic precautions and local anesthesia. Following preparation of the surgical site with 5% povidone-iodine, inferior alveolar, lingual, and buccal nerve blocks were administered using 2% lidocaine with adrenaline. A standard surgical technique was adopted for all cases, wherein Ward's incision was made, a mucoperiosteal flap was reflected, and bone removal was carried out with a surgical drill under saline irrigation. The tooth was elevated and extracted, and postoperative dressing was placed. In the test group, a 10-mg simvastatin tablet was crushed in to fine powder suspended in 2 mL of 0.9% normal saline and soaked with gel foam was inserted into the extraction socket, while in the control group, gel foam with saline alone was used. Closure was achieved using simple interrupted sutures. All patients were prescribed amoxicillin 500 mg thrice daily for three days and a combination of aceclofenac (100 mg) with paracetamol (325 mg) twice daily for three days, along with routine postoperative instructions. Patients were reviewed on the first and seventh postoperative days for assessment of pain and swelling.

Pain intensity was recorded using a 5-point Visual Analog Scale (VAS), where 0 represented no pain and 4 represented very severe pain. Bone density was evaluated with standardized intraoral periapical radiographs taken at baseline, and at the 1st, 6th, and 12th postoperative weeks. The mean gray-level histogram values were calculated using Adobe Photoshop version 7.0. For radiographic analysis, the extraction socket area was delineated on the digitalized radiographs using the Photoshop, and the histogram function was used to obtain mean density values for comparison over time.

Osseous regeneration was quantified by comparing the sequential radiographs, and statistical analysis was performed using a paired t-test, with significance set at $p < 0.05$.

RESULTS

The demographic analysis of the study population showed that the mean age of participants in the study group was 27.45 ± 5.2 years, while in the control group it was 26.57 ± 4.9 years. The age distribution between the two groups was comparable, with no statistically significant difference ($p > 0.05$). Gender distribution was also balanced, with males comprising 56% of the study group and 58% of the control group, while females accounted for 44% and 42%, respectively. These findings indicate that both groups were demographically similar, minimizing the risk of confounding due to age or gender differences.

Postoperative pain assessment using the Visual Analog Scale (VAS) revealed similar outcomes in both groups. On the first postoperative day, the mean VAS score was 1.9 in the study group and 1.8 in the control group. By the seventh postoperative day, all participants in both groups reported complete resolution of pain, with a mean VAS score of 0. The difference between the two groups at both time intervals was statistically non-significant ($p > 0.05$), suggesting that the placement of simvastatin did not significantly influence the subjective pain experience compared to the control.

Radiographic evaluation of bone healing through mean gray-level histogram analysis demonstrated notable differences between the groups. At the end of

the first postoperative week, the study group exhibited a mean gray-level value of 64.43 ± 12.42, whereas the control group showed a lower value of 56.61 ± 10.26. This trend continued in the subsequent follow-ups, with the study group achieving mean values of 85.46 ± 9.45 at the sixth week and 102.05 ± 10.48 at the twelfth week. In comparison, the control group recorded mean values of 77.54 ± 6.33 and 89.58 ± 8.65 at the sixth and twelfth weeks, respectively. The differences observed at all three time points were statistically significant ($p < 0.05$).

These results clearly suggest that while simvastatin placement did not have a significant impact on postoperative pain, however, it contributed to enhanced bone regeneration in extraction sockets. The higher mean gray-level histogram values observed in the study group consistently across follow-ups indicate superior bone density and osseous healing when compared with the control group.

Table 1: Age and gender wise distribution among the study participants

Demographic variables		Study group	Control group	P value
Mean Age		27.45±5.2 years	26.57±4.9 years	>0.05 Not significant
Gender	Male	56%	58%	>0.05 Not significant
	Female	46%	42%	

Table 2: Comparison of VAS scores post extraction day1 and day 7

	Day 1	Day 7	P value
Study group	1.9	0	>0.05
Control group	1.8	0	>0.05

Table 3: Comparison of mean values of mean gray level histographic values post extraction at 1st week, 6th week and 12th week

Groups	1st week	6th week	12th week
Study group	64.43±12.42	85.46±9.45	102.05±10.48
Control group	56.61±10.26	77.54±6.33	89.58±8.65
P value	<0.05	<0.05	<0.05

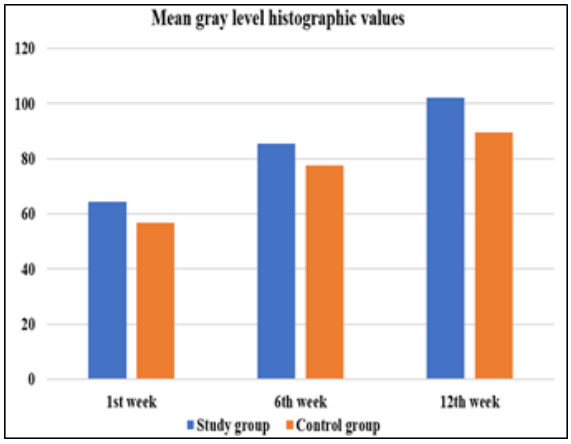

Figure 1: Comparison of mean values of mean gray level histographic values post extraction at 1st week, 6th week and 12th week

DISCUSSION

Simvastatin, widely prescribed as an antihyperlipidemic agent since the 1980s, has gained attention for its osteoinductive potential following the pioneering work of Mundy et al,8 who demonstrated its ability to upregulate bone morphogenetic protein-2 (BMP-2) expression and promote osteogenesis. The mechanism involves induction of heat shock protein 27, enhanced mRNA expression of BMP-2, alkaline phosphatase (ALP), osteocalcin, and vascular endothelial growth factor (VEGF), mediated through inhibition of Rho-associated kinase activity in osteoblasts, bone marrow cells, and stem cells both in vitro and in vivo.[8,9] These findings provide a biological rationale for exploring the local application of simvastatin in bone regeneration.

The present study demonstrated that while simvastatin placement did not significantly reduce postoperative pain compared to the control group, it significantly enhanced bone regeneration in extraction sockets. Demographic parameters such as age and gender distribution were comparable across groups, reducing confounding. Pain assessment through VAS scores indicated no difference between groups, which is consistent with findings by Stein et al,[10] where reduction in inflammatory response was observed only at specific doses. However, radiographic assessment through mean gray-level histogram analysis revealed significantly higher values in the study group at the first, sixth, and twelfth postoperative weeks, indicating superior bone density and healing.

These results align closely with the findings of Harsha G et al,[11] and Degala S et al,[12] both of whom reported significantly greater gray-level histogram values and CBCT-based bone density in simvastatin-treated sockets compared to controls. Similarly, Velavan K et al,[13] emphasized the cost-effectiveness and efficacy of locally applied simvastatin in early bone regeneration, further supporting the present observations. Experimental studies, such as those by Nyan et al,[14] also reported substantial bone regeneration when simvastatin was combined with calcium sulfate, although accompanied by soft tissue inflammation, suggesting that formulation and delivery methods may influence clinical outcomes.

The current findings also corroborate the observations of Seto H et al,[15] who reported beneficial effects of simvastatin delivered as a 2.5% topical gel in periodontal pockets. Collectively, these studies strengthen the evidence base supporting the local application of simvastatin in promoting alveolar bone regeneration following minor oral surgical procedures.

Contrasting results, however, have also been reported. Pauly et al,[16] observed impaired osseointegration of simvastatin-coated intramedullary titanium implants in rat femurs after 8 weeks, while Lima et al,[17] found that combining simvastatin with demineralized bovine bone matrix produced undesirable healing outcomes in rat calvarial defects. Such inconsistencies highlight that simvastatin's osteoinductive potential may be highly dependent on the delivery method, dosage, carrier material, and host factors. Furthermore, systemic administration of statins has shown limited effectiveness in bone healing due to rapid metabolism, short half-life, and potential systemic side effects at higher doses.[9] This emphasizes the importance of localized, controlled delivery strategies to harness simvastatin's regenerative potential safely and effectively.

CONCLUSION

The present study demonstrated that local application of simvastatin in mandibular third molar extraction sockets did not significantly affect postoperative pain but significantly enhanced bone regeneration, as evidenced by higher radiographic bone density values at multiple follow-up intervals. These findings are in agreement with several experimental and clinical studies supporting the osteoinductive role of simvastatin in craniofacial bone healing. However, contrasting evidence in the literature indicates that the efficacy of simvastatin may vary with dosage, formulation, and delivery method. Within the limitations of this study, local application of simvastatin appears to be a promising, cost-effective adjunct for enhancing alveolar bone regeneration following tooth extraction. Further large-scale randomized controlled clinical trials are warranted to optimize dosage, carrier systems, and long-term clinical outcomes.

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